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Bibliografia

AOUN, S.G.; BENDOK, B.R.; RAHME, R.J.; DACEY, R.G. Jr.; BATJER H.H. Standardizing the evaluation of scientific and academic performance in neurosurgery – critical review of the "h" index and its variants. **World Neurosurgery**, 2012 jan 31 [epub ahead of print].

ASKEHAVE, I.; SWALES, J.M. Genre identification and communicative purpose: a problem and a possible solution. **Apllied Linguistics**, v. 22, n. 2, p. 195-212, 2002.

AYERS, G. The evolutionary nature of genre: An investigation of the short texts accompanying research articles in the scientific journal *Nature*. **English for Specific Purposes**, v. 27, p. 22–41, 2008.

BAKHTIN, M. Os gêneros do discurso. In: **Estética da criação verbal**. Trad: Paulo Bezerra. São Paulo: Martins Fontes, 2003.

BAZERMAN, C. **Shaping written knowledge:** The genre and activity of the experimental article in science. Madison: University of Wisconsin Press, 1988.

_____. The life of genre, the life in the classroom. In: BISHOP, W. e OSTRUM, H. (eds.) **Genre and writing:** issues, arguments, alternatives. Portsmouth: Boynton/Cook, 1997, p.19-26.

_____. Atos de fala, gêneros textuais e sistemas de atividades: como os textos organizam atividades e pessoas. In: DIONÍSIO, A. e HOFFNAGEL, J.C. (orgs.) **Gêneros textuais, tipificação e interação**. São Paulo: Cortez, 2004.

BERNARDINO, C.G. **Depoimento de alcoólicos anônimos: um estudo do gênero textual**. 2000. Dissertação (Mestrado em Linguística) – Universidade Federal do Ceará, Fortalza.

BHATIA, V.K. **Analysing genre:** language use in professional settings. London: Longman, 1993.

_____. Methodological issues in genre analysis. **Hermes, Journal of Linguistics**, v. 16, p. 39-59, 1996.

_____. Integrating research methods. In: **Worlds of Written Discourse**. London: Continuum, 2004.

BIASI-RODRIGUES, B. **Estratégias de condução de informações em resumos de dissertações**. 1998. Tese (Doutorado em Linguística) – Universidade Federal de Santa Catarina, Florianópolis.

BIASI-RODRIGUES, B.B.; ARAÚJO, J.C.; SOUZA S.C. (Orgs.) **Gêneros textuais e comunidades discursivas:** um diálogo com John Swales. Belo Horizonte: Autêntica, 2009.

BIBER, D.; JOHANSSON, S.; LEECH, G.; CONRAD, S.; FINEGAN, E. **Longman Grammar of Spoken and Written English.** London: Longman, 1999.

BIGNALL, J.; HORTON, R. Learning from stories – *The Lancet*'s Case Reports. **The Lancet**, v. 346, p. 1246, 1995.

BIGNALL, J. 3 years of *Lancet* case reports. **The Lancet**, v. 352, p. 1570, 1998.

BOURDIEU, P. **O poder simbólico.** Lisboa: Difel, 1989.

_____. **Os usos sociais da ciência:** por uma sociologia clínica do campo científico. São Paulo: Unesp, 2004.

BRITISH MEDICAL ASSOCIATION. **Reference styles**. Disponível em: http://www.bma.org.uk/library_services/ask_for_help/libraryreferencestyles.jsp. Acesso em: 20/01/2012.

BRUCE, I. Cognitive genre structures in methods sections of research articles: a corpus study. **English for Specific Purposes**, v. 27, p. 38–54, 2008.

CARAMELLI, B. O título – arauto da comunicação científica. **Revista da Associação Médica Brasileira**, v. 57, n. 4, p. 359, 2011.

CARVALHO, G. de. Gênero como ação social em Miller e Bazerman: o conceito, uma sugestão metodológica e um exemplo de aplicação. In: MEURER, J.L.; BONINI, A.; ROTH, D.M. (orgs.) **Gêneros:** teorias, métodos, debates. São Paulo: Parábola Editorial, 2005.

CELCE-MURCIA, M.; LARSEN-FREEMAN, D. **The grammar book:** An ESL/EFL teacher`s course. Rowley, MA: Newbury House Publishers, 1983.

CHALMERS, A.F. **O que é ciência afinal?** Tradução Raul Fiker. São Paulo: Brasiliense, 1993.

CHELVARAJAH, R.; BYCROFT, J. Writing and publishing case reports: the road to success. **Acta neurochirurgica**, v. 146, n. 3, p. 313–6, 2004.

COCCIA, C.T.; AUSMAN, J.I. Is case report an anecdote? **Surgical Neurology**, v. 28, p. 111-3, 1987.

COLMAN, E. The first English medical journal: *Medicina Curiosa*. **Lancet**, v. 354, p. 324-326, 1999.

CONSELHO FEDERAL DE MEDICINA. **Resolução CFM nº 1638/2002.** Define prontuário médico e torna obrigatória a criação da Comissão de Revisão de Prontuários nas instituições de saúde. Disponível em: http://www.portalmedico.org.br/resolucoes/cfm/2002/1638_2002.htm. Acesso em: 20/12/2011.

CORACINI, M.J. **Um fazer persuasivo:** o discurso subjetivo da ciência. São Paulo: Pontes Educ, 1991.

DEBAKEY, L; DEBAKEY, S. The title. What`s in a name? **International Journal of Cardiology**, v. 2, p. 401-406, 1983.

_____. The case report. I. Guidelines for preparation. **International Journal of Cardiology**, v. 4, p. 357-364, 1983.

_____. The case report. II. Style and form. **International Journal of Cardiology**, v. 6, p. 247-254, 1984.

DEL SAZ RUBIO, M.M. A pragmatic approach to the macro-structure and metadiscoursal features of research article introductions in the field of Agricultural Sciences. **English for Specific Purposes**, v. 30, p. 258-71, 2011.

DEVITT, A.J. A theory of genre. In: **Writing genres**. Carbondale: Southern Illinois University Press, 2004, p. 1-32.

DING, H. Genre analysis of personal statements: Analysis of moves in application essays to medical and dental schools. **English for Specific Purposes,** v. 26, p. 368–392, 2007.

FENTON, J.E.; KHOO, S.G.; AHMED, I.; ULLAH, I.; SHAIKH, M. Tackling the case report. **Auris Nasus Larynx**, v. 31, p. 505-207, 2004.

FERGUSON, G. The global spread of English, scientific communication and ESP: questions of equity, access and domain loss. **Ibérica**, v. 13, p. 7-38, 2007.

FLOWERDEW, J.; DUDLEY-EVANS, T. Genre analysis of editorial letters to international journal contributors. Applied Linguistics, v. 23, n. 4, p.463–489, 2002.

GIDDENS, A. **The constitution of society:** outline of the theory of structuration. California: University of California Press, 1984.

GOTTSCHLICH, M. Writing basics: elements of the case study. **Journal of the American Dietetic Association**, v. 100, n. 1, p. 1293-1295, 2000.

GREEN, B.N.; JOHNSON, C.D. How to write a case report for publication. **Journal of Chiropractic Medicine**, v. 5, n. 2, p. 72-82, 2006.

GUNNARSSON, B-L. Medical discourse: sociohistorical construction. **Encyclopedia of Language & Linguistics (Second Edition)**, p. 709-717, 2006.

GUTHRIE, D. **A history of Medicine**. London: Nelson, 1945.

HEMAIS, B.; BIASI-RODRIGUES, B. A proposta sociorretórica de John M. Swales para o estudo de gêneros textuais. In: MEURER, J.L.; BONINI, A.; ROTH, D.M. (orgs.) **Gêneros:** teorias, métodos, debates. São Paulo: Parábola Editorial, 2005.

HIRSCH, J.E. An index to quantify an individual's scientific research output. **Proceedings of the National Academy of Sciences**, v. 102, n. 46, p.16569-16572, 2005.

HOLMES, R. Genre analysis, and the social sciences: an investigation of the structure of research article discussion sections in three disciplines. **English for Specific Purposes,** v. 16, n. 4, p. 321–337, 1997.

HYLAND, K. Researching writing. In: PALTRIDGE, B.; PHAKITI, A. (eds.). **Continuum companion to research methods in Applied Linguistics**. Nova York: Continuum, 2010. p. 191-204.

HYON, S. Genre in three traditions: implications for ESL. **TESOL Quarterly**, v. 30, n. 4, p. 693-722, 1996.

ILES, R.L.; PIEPHO, R.W. Presenting and publishing case reports. **The Journal of Clinical Pharmacology**, v. 36, p. 573-9, 1996.

JAMJOOM, A.A.B.; NIKKAR-ESFAHANI, A.; FITZGERALD, J.E.F. Writing a medical case report. **Student BMJ**, v. 17, p. 5274, 2009.

KANG, S. Anecdotes in medicine – 15 years of *Lancet* Case Reports. **The Lancet**, v. 376, p. 1448-1449, 2010.

KANOKSILAPATHAM, B. Rhetorical structure of biochemistry research articles. **English for Specific Purposes,** v. 24, p. 269-292, 2005.

KRESS, G.; van LEEUWEN, T. **Reading images: the grammar of visual design**. London: Routledge, 1996.

KOCH, I. Gêneros textuais. In: **Ler e compreender os sentidos do texto.** São Paulo: Contexto, 2006, p.101-122.

LANCET, THE. **Information for authors**. Disponível em: http://www.thelancet.com/lancet-information-for-authors/article-types-manuscript-requirements. Acessado em 13 de dezembro de 2011.

LANG, T. Medical writing: where it's been, where it's going. **American Medical Writers Association Journal**, v.15, n.2, 2000.

LATOUR, B.; WOOLGAR, S. **Laboratory life:** the construction of scientific facts. Princeton, NJ: Princeton University Press, 1979.

LAVE, J.; WENGER, E. **Communities of practice:** learning, meaning, and identity. Cambridge: Cambridge University Press, 1998.

LEMKE, J.L. Metamedia literacy: transforming meanings and media. In: REINKING, D.; LABBO, L.; MCKENNA, M e KIEFER, R. (eds.), **Handbook of Literacy and Technology: transformations in a post-typographic world**. Hillsdale, NJ: Erlbaum, 1998, pp.283-301. [disponível em: http://www-personal.umich.edu/~jaylemke/jll-new.htm]

_____. Multiplying meaning: visual and verbal semiotics in scientific text. In: MARTIN, J. e VEEL, R. (eds.),**Reading Science**. Londres, Routledge, 1998, p. 87-113.

MARCONDES, D. **A pragmática na filosofia contemporânea**. Rio de Janeiro: Zahar, 2005.

MARCUSCHI, L.A. Gêneros textuais: definição e funcionalidade. In: DIONÍSIO, A.P., MACHADO, A.R., BEZERRA, M. A. (Orgs.) **Gêneros textuais & ensino.** Rio de Janeiro: Lucerna, 2005.p.19-36.

MARTYN, C. Case reports, case series and systematic reviews. **Quaterly Journal of Medicine**, v. 95, p. 197–8, 2002.

MASON, R.A. The case report – an endangered species? **Anesthesia**, v. 56, p. 99-102, 2001.

MCCARTHY, L.H; REILLY, K.E.H. How to write a case report. **Family Medicine**, v. 32, n. 3, p.190-195, 2000.

MERTON, R.K. Structural analysis in Sociology. In: BLAU, P.M. (Ed.). **Approaches to the Study of Social Structure**. London: Open Books, 1975, p.21-52.

MEURER, J. L.; BONINI, A.; MOTTA-ROTH, D. (orgs).**Gêneros:** teorias, métodos, debates. São Paulo: Parábola, 2005.

MILLER, C.R. Genre as social action. **Quaterly Journal of Speech**, v. 70, p. 151-167, 1984.

_____. Rhetorical community: the cultural basis of genre. In: FREEDMAN, A. e MEDWAY, P. (eds.) **Genre and the New Rhetoric.** London: Taylor & Francis, 1994, p.67-78.

MILLER, T. Visual persuasion: a comparison of visuals in academic texts and the popular press. **English for Especific Purposes**, v. 17, n. 1, p. 29-46, 1998.

MOED, H.F.; VAN LEEUWEN, T.N. Improving the accuracy of institute for scientific information's journal impact factors. **Journal of the American Society for Information Science**, v. 46, p. 461–467, 1995.

MORGAN, P.P. Why case reports? **Canadian Medical Association Journal**, v. 133, p. 353, 1985.

MOTTA-ROTH, D. **Rhetorical features and disciplinary cultures**: a genre-based study of academic book reviews in linguistics, chemistry and economics. Tese (Doutorado em Linguística) – Florianópolis: Universidade Federal de Santa Catarina, 1995.

MUELLER, S.P.M. O periódico científico. In: CAMPELLO, B.S.; CENDÓN, B.V.; KREMER, J.M. (Org.). **Fontes de informação para pesquisadores e profissionais**. Belo Horizonte: Editora UFMG, 2000. p. 73-95.

MYERS, G. **Writing biology:** texts in the social construction of scientific knowledge. Madison, WI: University of Wisconsin Press, 1990.

NEVES, M.H. de M. **Texto e gramática**. São Paulo: Contexto, 2006.

NWOGU, K.N. **Discourse variation in medical texts: schema, theme and cohesion in professional and journalistic accounts**. Monographs in Systemic Linguistics, vol. 2. Nottingham: University of Nottingham, 1990.

_____. Structure of science popularization: a genre-analysis approach to the schema of popularized medical texts. **English for Specific Purposes**, v. 10, p. 111-123, 1991.

_____. The medical research paper: structure and functions. **English for Specific Purposes**, v. 16, p. 119-138, 1997.

OLIVA, O. **Filosofia da ciência**. Rio de Janeiro: Zahar, 2010.

PARÉ, A.; SMART, G. Observing genres in action: towards a research methodology. In: FREEDMAN, A.; MEDWAY, F. (eds.) **Genre and the New Rhetoric**. Londres: Taylor & Francis, 1994. pp. 146-154.

PEACOCK, M. Communicative moves in the discussion section of research articles. **System**, v. 30, p. 479–497, 2002.

PERELMAN, C.; OLBRECHTS-TYTECA, L. **Traité de l'argumentation:** la nouvelle rhétorique. Bruxelles: Editions de L'Universite de Bruxelles, 1958.

PEIRCE, C.S. **Semiótica**. 2ª ed., São Paulo: Perspectiva, 1995.

PIERSON, D.J. Case reports in respiratory care. **Respiratory Care**, v. 49, p. 1186–94, 2004.

PIQUÉ-ANGORDANS, J.; POSTEGUILLO, S. Medical discourse and academic genres. **Encyclopedia of Language & Linguistics (Second Edition)**, p. 649-57, 2006.

POYNTER, F.N.L. The first medical journal. **British Medical Journal**, p. 307-8, 1948.

RIGUEIRA, A.M. **Texto sobre cinema:** organização retórica e avaliação em resenhas de filme. Tese (Doutorado em Letras) – Rio de Janeiro: PUC-Rio, 2010.

ROWLEY-JOLIVET, E. Image as text. Aspects of the shared visual language of scientific conference participants. **ASp**, p. 133-154, 2000.

_____. Visual discourse in scientific conference papers – A genre-based study. **English for Specific Purposes**, v. 21, n. 1, p. 19–40, 2002.

SALAGER-MEYER, F. Hedges and textual communicative function in medical English written discourse. **English for Specific Purposes**, v. 13, n. 2, p. 149–170, 1994.

_____. Referential behavior in scientific writing: a diachronic study (1810±1995). **English for Specific Purposes**, v. 18, n. 3, p. 279–305, 1999.

_____. Rhetorical evolution of oppositional discourse in French academic writing – oppositional discourse in academic writing. **Hermes**, v. 25, p. 23-48, 2000.

_____. The scimitar, the dagger and the glove: intercultural differences in the rhetoric of criticism in Spanish, French and English Medical Discourse (1930–1995). **English for Specific Purposes**, v. 22, n. 3, p. 223-247, 2003.

_____. Scientific publishing in developing countries: challenges for the future. **Journal of English for Academic Purposes**, v. 7, n. 2, p. 121–132, 2008.

SALAGER-MEYER, F.; DEFIVES, G.; HAMELINSCK, M. Epistemic modality in 19th and 20th century medical English written discourse: a principal component analysis. **Interface. Journal of Applied Linguistics**, v. 10, n. 2, p. 163-199, 1996.

SAMRAJ, B. Introductions in research articles: variations across disciplines. **English for Specific Purposes,** v. 21, p. 1–17, 2002.

SOLER-MONREAL, C.; CARBONELL-OLIVARES, M.; GIL-SALOM, L. A contrastive study of the rhetorical organization of English and Spanish PhD thesis introductions. **English for Specific Purposes**, v. 30, p. 4-17, 2011.

SOLLACI, L.B.; PEREIRA, M.G. The introduction, methods, results, and discussion (IMRAD) structure: a fifty-year survey. **Journal of the Medical Library Association**, v. 92, n. 3, p.364–371, 2004.

SORINOLA, O.; OLUFOWOBI, O.; COOMARASAMY, A.; KHAN, K.S. Instructions to authors for case reporting are limited: a review of a core journal list. **BMC Medical Education**, v.4, n.4, 2004.

SQUIRES, B.P. Case reports: What editors want from authors and peer reviewers. **Canadian Medical Association Journal**, v. 141, p. 379-380, 1989.

SWALES, J.M. Discourse communities, genres and English as an international language. **World Englishes**, v. 7, n. 2, p. 211-220, 1988.

_____. **Genre analysis:** English in academic and research settings. Cambridge: Cambridge University Press, 1990.

_____. Re-thinking genre: another look at a discourse community effects. In: **Re-thinking Genre Colloquium.** Otawa: Carleton University, 1992.

_____. **Other floors, other voices:** a textography of a small university building. Mahwah, N.J.: Lawrence Erlbaum, 1998.

_____. **Research genres:** exploration and applications. Cambridge: Cambridge University Press, 2004.

TODOROV, T.; BERRONG, R.M. The origin of genres. **New Literary History**, v. 8, n. 1, p.159–170.

TREASURE, T. What is the place of the clinical case report in medical publishing? **Journal of the Royal Society of Medicine**, v. 88, p. 279, 1995.

VAN DIJK, T.A. Discourse as interaction in society. In: **Discourse as Social Interaction.** London: Sage, 1997, p. 133-41.

VANDENBROUCKE, J.P. Case reports in an evidence-based world. **Journal of the Royal Society of Medicine**, v. 92, n. 4, p. 159-163, 1999.

_____. In defense of case reports and case series. **Annals of Internal Medicine**, v. 134, n. 4, p. 330-334, 2001.

WALSH, B. **Ciência e Linguagem:** integrando discurso e contexto sociohistórico na análise de seções de conclusão de artigos experimentais do periódico "Memórias do Instituto Oswaldo Cruz" (1909 a 1919 e 1980 a 1989). Tese (Doutorado em Letras) – Universidade Federal Fluminense, Niterói, 2010.

WALTER, G.; REY, J.M.; DEKKER, F. The humble case report. **Australian and New Zealand Journal of Psychiatry**, v. 35, p. 240-245, 2001.

WHEELER, H. The semiosis of Francis Bacon's scientific empiricism. **Semiotica – Journal of the International Association for Semiotic Studies/ Revue de l'Association Internationale de Sémiotique**, v. 133, p. 45–67, 2001.

WHITE, A. Writing case reports: author guidelines for Acupuncture in Medicine. **Acupuncture in Medicine**, v. 22, p. 83–6, 2004.

WRIGHT, S.M.; KOUROUKIS, C. Capturing zebras: what to do with a reportable case. **Canadian Medical Association Journal**, v. 163, p. 429–31, 2000.

ZEN, A.M.D. A comunicação científica como literatura: o lugar do sujeito na construção do conhecimento. **Em Questão**, Porto Alegre, v. 10, n. 1, p. 11-12, 2004.

8
Apêndice

8.1. Apêndice 1: A relação dos relatos de caso

RC#1: ABDULLA, K.M.; DAVIDSON, N.M. A woman who collapsed after painting her soles. **The Lancet**, v. 348, n. 9028, p. 658, 1996.

RC#2: GASBARRINI, G.; MINGRONE, G.; GRECO, A.V.; CASTAGNETO, M. An 18-year-old woman with familial chylomicronaemia who would not stick to a diet. **The Lancet**, v. 348, n. 9030, p. 794, 1996.

RC#3: MARQUET, P.; FRANÇOIS, B.; VIGNON, P.; LACHÂTRE. A soldier who had seizures after drinking quarter of a litre of wine. **The Lancet**, v. 348, n. 9034, p. 1070, 1996.

RC#4: METKUS, A.P.; TRABULSY, P.P.; SCHLOBOHM, R.S.; HICKEY, M.S. A firefighter with pancreatitis. **The Lancet**, v. 348, n. 9043, p. 1702, 1996.

RC#5: ADZICK, N.S.; CROMBLEHOLME, T.M.; MORGAN, M.A.; QUINN, T.M. A rapidly growing fetal teratoma. **The Lancet**, v. 349, n. 9051, p. 538, 1997.

RC#6: DELSYS, J.P.; LASMÉZAS, C.I.; STREICHENBERGER, N.; HILL, A.; COLLINGE, J.; DORMONT, D.; KOPP, N. New variant Creutzfeldt-Jakob disease in France. **The Lancet**, v. 349, n. 9044, p. 30-31, 1997.

RC#7: VISSER, L.; STRICKER, B.; HOOGENDOORN, M.; VINKS, A. Do not give paraffin to packers. **The Lancet**, v. 352, n. 9137, p. 1352, 1998.

RC#8: SHETTY, A.K.; STEELE, R.W.; SILAS, V.; DEHNE, R. A boy with a limp. **The Lancet**, v. 351, n. 9097, p. 182, 1998.

RC#9: STIRLING, C.M.; BOULTON-JONES, J.M.; SIMPSON, K. Progressive oedema in a 30-year-old. **The Lancet**, v. 352, n. 9126, p. 450, 1998.

RC#10: RABUSIN, M.; LEPORE, L.; COSTANTINES, F.; BUSSANI, R. A child with severe asthma. **The Lancet**, v. 351, n. 9095, p. 32, 1998.

RC#11: TEICHMAN, D.; GROBUSCH, M.P.; WESSELMAN, H.; TEMMESFELT-WOLLBRÜCK, B.; BREUER, T.; DIETEL, M.; EMMERICH, P.; SCMITZ, H.; SUTTORP, N.A haemorrhagic fever from the Côte d'lvoire. **The Lancet**, v. 354, n. 9190, p. 1608, 1999.

RC#12: DENAYS, R.; COLLIER, A.; RUBINSTEIN, M.; ATSAMA, P. A 51-year-old woman with disorientation and amnesia. **The Lancet**, v. 354, n. 9192, p. 1786, 1999.

RC#13: MURAKAMI, T. OGURA, E.W.; TANAKA, Y.; YAMAMOTO, M. High blood pressure lowered by pregnancy. **The Lancet**, v. 356, n. 9246, p. 1980, 2000.

RC#14: CARBY, M.; SMITH, S.R. A hazard of paint spraying. **The Lancet**, v. 355, n. 9207, p. 896, 2000.

RC#15: de GANS, J.; van WESTRUM, S.S.; KUIJIPER, E.; SCHAAP, G.R. Earache and back pain. **The Lancet**, v. 355, n. 9202, p. 464, 2000.

RC#16: VEGA, M.; RIVERO, J.C.; RUÍZ, L.; SUÁREZ, S. A fish bone in the liver. **The Lancet**, v. 358, n. 9286, p. 982, 2001.

RC#17: WATKINS, E.J.; BROOKSBY, P.; SCHWEIGER, M.S.; ENRIGHT, S.M. Septicaemia in a pig-farm worker. **The Lancet**, v. 357, n. 9249, p. 38, 2001.

RC#18: SPRINGER,J.; CHOLLET, A. A traumatic car crash. **The Lancet**, v. 357, n. 9271, p. 1848, 2001.

RC#19: HARITOGLOU, C.; DOTSE, S.D.; RUDOLPH, G.; STEPHAN, C.M.; THURAU, S.R.; KLAUSS, V. A tourist with dengue fever and visual loss. **The Lancet**, v. 360, n. 9339, p. 1070, 2002.

RC#20: VIETH, R.; PINTO, T.R.; REEN, B.S.; WONG, M.M. Vitamin D poisoning by table sugar. **The Lancet**, v. 359, n. 9307, p. 672, 2002.

RC#21: AFZAL, N.A.; ALBERT, D; THOMAS, A.L.; THOMSON, M. A child with oesophageal strictures. **The Lancet**, v. 359, n. 9311, p. 1032, 2002.

RC#22: SANDER, H.W.; MAGDA, P.; CHIN, R.L.C.; WU, A.; BRANNAGAN III, T.H.; GREEN, P.H.R.; LATOV, N. Cerebellar ataxia and coeliac disease. **The Lancet**, v. 362, n. 9395, p. 1548, 2003.

RC#23: CLAYTON, P.T.; SURTEES, R.A.H.; DEVILLE, C.; HYLAND, K.; HEALES, S.J.R. Neonatal epileptic encephalopathy. **The Lancet**, v. 361, n. 9369, p. 1614, 2003.

RC#24: SCHOTT, J.M.; HARKNESS, K.; BARNES, J.; ROCCHETTA, A.I.; VINCENT, A.; ROSSOR, M.N. Amnesia, cerebral atrophy, and autoimmunity. **The Lancet**, v. 361, n. 9365, p. 1266, 2003.

RC#25: ROWSHANI, A.T.; SCHOT, L.J.; ten BERGE, J.M. c-ANCA as a serological pitfall. **The Lancet**, v. 363, n. 9411, p. 782, 2004.

RC#26: ROMI, N.S.; KRÄNKE, B.; ABERER, W. A silver man. **The Lancet**, v. 363, n. 9408, p. 532, 2004.

RC#27: WHITE, J.M.L.; BARKER, R.D.; SALISBURY, J.R.; FIFE, A.J.; LUCAS, S.B.; WARCHURST, D.C.; HIGGINS, E.M. Granulomatous amoebic encephalitis. **The Lancet**, v. 364, n. 9429, p. 220, 2004.

RC#28: RADCLIFFE, M.; SCADDING, G.; BROWN, H.M. Lupin flour anaphylaxis. **The Lancet**, v. 365, n. 9467, p. 1360, 2005.

RC#29: PALMIERI, C.; FISHER, R.A.; SEBIRE, N.J.; LINDSAY, I.; SMITH, J.R.; McCLUGGAGE, W.G.; SAVAGE, P.; SECKL, M.J. Placental site trophoblastic tumour arising from a partial hydatidiform mole. **The Lancet**, v. 366, n. 9486, p. 688, 2005.

RC#30: PAVLU, J.; HARRINGTON, D.J.; VOONG, K.; SAVIDGE, G.F.; JAN-MOHAMED, R.; KACZMARSKI, R. Superwarfarin poisoning. **The Lancet**, v. 365, n. 9459, p. 628, 2005.

RC#31: KOREN, G.; CAIRNS, J.; CHIAYAT, D.; GAEDIGK, A.; LEEDER, S.J. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. **The Lancet**, v. 368, n. 9536, p. 704, 2006.

RC#32: BODENMANN, P.; GENTON, B. Chikungunya: an epidemic in real time. **The Lancet**, v. 368, n. 9531, p. 258, 2006.

RC#33: YU, H.; SHU, Y.; Hu, S.; ZHANG, H.; GAO, Z.; CHEN, H.; DONG, J.; XU, C.; ZHANG, Y.; XIANG, N.; WANG, M.; GUO, Y.; COX, N.; LIM, W.; LI, D.; WANG, Y.; YANG, W. The first confirmed human case of avian influenza A (H5N1) in Mainland China. **The Lancet**, v. 367, n. 9504, p. 84, 2006.

RC#34: WOOD, D.M.; DARGAN, P.I.; BUTTON, J.; HOLT, D.W.; OVASKA, H.; RAMSEY, J.; JONES, A.L. Collapse, reported seizure—and an unexpected pill. **The Lancet**, v. 369, n. 9571, p. 1490, 2007.

RC#35: LEUNG, W.K.; BJARNASON, I.; WONG, V.W.S.; SUNG, J.J.Y.; CHAN, F.K.L. Small bowel enteropathy associated with chronic low-dose aspirin therapy. **The Lancet**, v. 369, n. 9561, p. 614, 2007.

RC#36: SCHRAUDER, A.; HENKE-GENDO, C.; SEIDEMANN, K.; SASSE, M.; CARIO, G.; MOERICKE, A.; SCHRAPPE, M.; HEIM, A.; WESSEL, A. Varicella vaccination in a child with acute lymphoblastic leukaemia. **The Lancet**, v. 369, n. 9568, p. 1232, 2007.

RC#37: RUSSELL, K.; BROADBRIDGE, C.; MURRAY, S.; WAGHORN, D.; MAHONEY, A. Gardening can seriously damage your health. **The Lancet**, v. 371, n. 9629, p. 2056, 2008.

RC#38: ANDERSSON, M.I.; HUGHES, J.; GRDON, F.H.; IJAZ, S.; DONATI, M. Of pigs and pregnancy. **The Lancet**, v. 372, n. 9644, p. 1192, 2008.

RC#39: FLEMING, J.D.; McSORLEY, A.; BATES, K.M. Blood, semen, and an innocent man. **The Lancet**, v. 371, n. 9616, p. 958, 2008.

RC#40: PETER, J.V.; PRABHAKAR, A.T.; PICHAMUTU, K. In-laws, insecticide—and a mimic of brain death. **The Lancet**, v. 371, n. 9612, p. 622, 2008.

RC#41: KIDD, I.M.; DOWN, J.; NASTOULI, E.; SCHULMAN, R.; GRANT, P.R.; HOWELL, D.C.J.; SINGER, M. H1N1 pneumonitis treated with intravenous zanamivir. **The Lancet**, v. 374, n. 9694, p. 1036, 2009.

RC#42: KASKI, D.; MEAD, S.; HYARE, H.; COPER, S.; JAMPANA, R.; OVERELL, J.; KNIGHT, R.; COLLINGE, J.; RUDGE, P. Variant CJD in an individual heterozygous for PRNP codon 129. **The Lancet**, v. 374, n. 9707, p. 2128, 2009.

RC#43: KHOSROSHAHI, A.; STONE, J.R.; PRATT, D.S.; DESHPANDE, V.; STONE, J.H. Painless jaundice with serial multi-organ dysfunction. **The Lancet**, v. 373, n. 9673, p. 1494, 2004.

RC#44: GLOCKER, E-O.; FREDE, N.; PERRO, M.; SEBIRE, N.; ELAWAD, M.; SHAH, N.; GRIMBACHER, B. Infant colitis—it's in the genes. **The Lancet**, v. 376, n. 9748, p. 1272, 2010.

RC#45: MURAKAMI, H.; TAMASAWA, N.; YAMASHITA, M.; TAKAYASU, S.; NIGAWARA, T.; MATSUI, J.; SUDA, T. Altered pain perception in schizophrenia. **The Lancet**, v. 375, n. 9717, p. 864, 2010.

RC#46: SAMMLER, E.M.; FOLEY, P.L.; LAUDER, G.D.; WILSON, S.J.; GOUDIE, A.R.; O`RIORDAN, J.I. A harmless high?. **The Lancet**, v. 376, n. 9742, p. 742, 2010.

RC#47: SCHEMBRI, G.; SCHOBER, P. Killing two birds with one stone. **The Lancet**, v. 377, n. 9759, p. 96, 2011.

RC#48: ABERER, E.; FINGERLE, V.; WUTTE, N.; FINK-PUCHES, R.; CERRONI, L. Within European margins. **The Lancet**, v. 377, n. 9760, p. 178, 2011.

RC#49: PRASAD, N.; GHIYA, B.C.; BUMB, R.A.; KAUSHAL, H.; SABOSKAR, A.A.; LEZAMA-DAVILA, C.M.; SALOTRA, P.; SATOSKAR, A.R. Heat, Oriental sore, and HIV. **The Lancet**, v. 377, n. 9765, p. 610, 2011.

9
Anexos

9.1. Anexo 1: Os relatos de caso

RC#1 – ABDULLA, K.M.; DAVIDSON, N.M. A woman who collapsed after painting her soles. **The Lancet**, v. 348, n. 9028, p. 658, 1996.

THE LANCET

Case report

A woman who collapsed after painting her soles

Kamil A Abdulla, Neil McD Davidson

In December, 1993, a 40-year-old Saudi Arabian woman who had been well during the day, suddenly became breathless in the evening, and was taken to a local clinic. She had to have an endotracheal tube inserted in the ambulance during transfer to hospital, where she was still severely hypoxic despite high-flow oxygen. There were fine crepitations bilaterally up to the mid-zones, and profuse, clear, frothy sputum requiring repeated suction, but no evidence of cardiac failure, angio-oedema, or bronchospasm. A chest radiograph showed patchy bilateral basal consolidation without cardiomegaly. She was admitted to intensive care, ventilated, and treated for pulmonary oedema of unknown cause. All routine investigations were normal. Her chest radiograph became normal within 24 hours, and her endotracheal tube was removed within 48 hours.

Questioning then revealed that after dinner on the evening of admission she had applied henna to her feet (figure), and had begun to apply it to her left palm and it was then that she had suddenly become breathless. She had often used henna before, but had never experienced any similar episodes. On this occasion, she used a henna hair-dye mixture prepared by a neighbour, who told her that it was a special preparation, but it proved impossible to obtain exact details of the constituents. She recovered fully and went home 2 days later.

Henna has been used for centuries by women throughout Africa and Asia to beautify their hair and hands. It is applied to hands and feet using an icing bag or syringe to trace intricate patterns. Sometimes a second dye, para-phenylenediamine (pPD, "para" in the trade), is added to henna to speed up dyeing,[1] and to improve pattern definition. In some countries, such as the Sudan, pPD is readily available in local markets, but ingestion produces such severe toxic effects[2] (angio-oedema, respiratory distress, rhabdomyolysis,[3] and renal failure[4]) that it is commonly used in attempted suicide. pPD is banned in some countries, and its concentration in hair dyes is controlled in others, including Saudi Arabia. Although there is no proof that pPD caused this patient's near-fatal pulmonary oedema, the circumstantial evidence is strong, including the refusal of the neighbour to give full details of the henna mixture, and the acute presentation with one hand painted and the other not. The patient had no abrasions on her skin, but hair-dye ingredients can penetrate intact skin and cause systemic toxicity.[5] Previous accounts ascribe respiratory distress from pPD to angio-oedema,[2] and asthma,[5] but acute pulmonary oedema is probably equally important. Although such reactions are well known where pPD is used freely, they are normally unknown where pPD is used after controls are sometimes frustrated by illicit importation. Many expatriates in Saudi Arabia will have previously used pPD at home, and some probably bring it in from time to time (as powder[2] or as black stony lumps[3]).

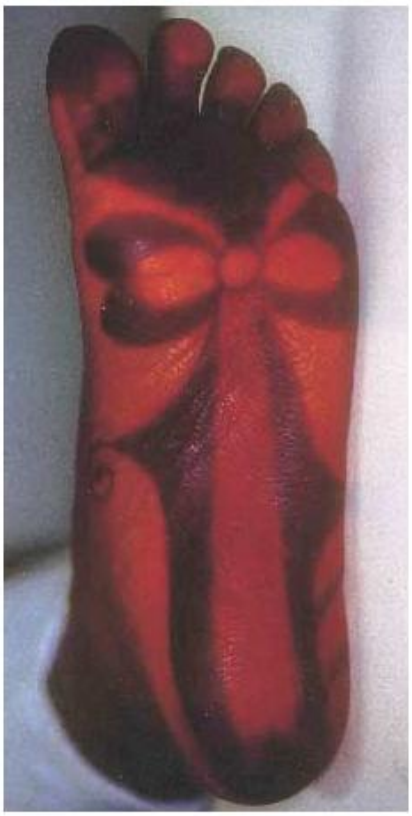

Figure: Painted left foot

We thank Obed Haylor, National Guard Hospital, Riyadh.

References

1 D'Arcy PF. Fatalities with the use of a henna dye. *Pharmacy Int* 1982: 217–18.
2 El-Ansary EH, Ahmed MEK, Clague HW. Systemic toxicity of para-phenylenediamine. *Lancet* 1983; i: 1341.
3 Baud F, Bismuth C, Galliot M, Garnier R, Peralma A. Rhabdomyolysis in para-phenylenediamine intoxication. *Lancet* 1983; ii: 514.
4 Chugh KS, Malik GH, Singhal PC. Acute renal failure following paraphenylene diamine (hair dye) poisoning: Report of two cases. *J Med* 1982; 13: 131–37.
5 Gosselin RE, Smith RP, Hodge HC, Braddock JE. Clinical toxicology of commercial products. 5th ed. Baltimore: Williams and Wilkins, 1984; section 2:210.

Lancet 1996; **348**: 658

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RC#2 – GASBARRINI, G.; MINGRONE, G.; GRECO, A.V.; CASTAGNETO, M. An 18-year-old woman with familial chylomicronaemia who would not stick to a diet. **The Lancet**, v. 348, n. 9030, p. 794, 1996.

Case report

An 18-year-old woman with familial chylomicronaemia who would not stick to a diet

Giovanni Gasbarrini, Geltrude Mingrone, Aldo V Greco, Marco Castagneto

After having tried diets and other treatments, an 18-year-old white woman came to our department at the Catholic University, Rome (GG). She had been well until aged 12, when she developed cutaneous xanthomas over most of her body. She also complained of recurrent episodes of abdominal pain which were associated with increased plasma amylase. Abdominal ultrasonography showed enlargement of liver and spleen, consistent with steatosis. Plasma triglycerides and free fatty acids were respectively 45·0 g/L and 0·99 g/L; plasma cholesterol was 13·05 mmol/L. Lipoprotein lipase activity, measured in heparinised plasma was low (0·0015 μmol mL^{-1} min^{-1}); apolipoprotein C-II was normal. 2 years later, insulin-resistant diabetes mellitus ensued; it was unresponsive to metformin (2250 mg/day) and required up to 150 U of insulin daily to maintain blood glucose concentrations around 14 mmol/L.

An oral diet rich in medium-chain triglycerides (MCT) (6270 kJ/day, 14·5% proteins, 42·4% lipids [87% MCT], and 43·0% carbohydrates) and low-lipid (about 10%), low-calorie (<6270 kJ/day) parenteral nutrition failed to bring triglycerides back to normal, or to correct hyperglycaemia. A euglycaemic hyperinsulinaemic clamp showed a whole-body glucose uptake normalised to fat mass of 0·012 mmol kg^{-1} min^{-1}. She refused to follow a life-long MCT-rich, low-calorie diet. We suggested a modified Scopinaro's biliopancreatic diversion,[1] which leads to almost complete malabsorption of lipids. The operation was agreed to and done on July 20, 1995. The operation differed from the one currently used for the treatment of morbid obesity in that a larger part of stomach was retained and the tract of absorbing intestine was half the length of the small bowel. 2 weeks after the operation her daily dose of insulin was reduced to 20 U with good glycaemic control (glycaemia <6·7 mmol/L throughout the day). 3 weeks after the operation, insulin was discontinued. Plasma triglycerides were 2·5–4·5 g/L. Plasma cholesterol was less than 3·9 mmol/L. 3 months after the operation, glucose uptake returned to normal (0·025 mmol kg^{-1} min^{-1}). When last seen, on June 24, 1996, she had gained 1·5–2·0 kg in weight, blood glucose was normal with a glycated haemoglobin of 4·2%, cholesterol 3·6 mmol/L, and triglycerides 3·8 g/L. Skin eruptions had disappeared on her palms, soles, and elbows (figure); on the other parts of her body only hyperpigmented spotty areas due to sun exposure were left. She continues to receive fat-soluble vitamins, calcium, iron, and folate supplements.

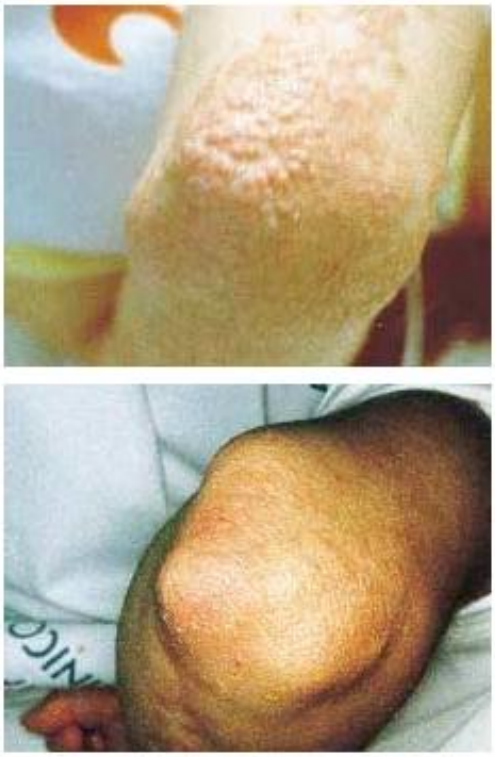

Figure: Elbow before (top) and after (bottom) treatment

The favourable early outcome for this patient indicates that a surgical approach is effective for conditions in which severe hypertriglyceridaemia is present. The patient's syndrome is linked to a high risk of early atherosclerotic cardiovascular disease. Another important consequence of the operation was the reversibility of insulin-resistant diabetes mellitus. It seems likely that insulin resistance observed in this case was due to the presence of high plasma FFA concentrations involved in Randle's cycle.[2] Insulin resistance proved to be reversible after the operation, which allowed a decrease of triglyceride and FFA plasma concentrations with normal oral glucose absorption.[3,4] We believe that further evaluation of the proposed approach to the treatment of severe chylomicronaemia is warranted.

Lancet **1996; 348:** 794

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References

1 Scopinaro N, Gianetta E, Adami GF, et al. Biliо-pancreatic diversion for obesity at eighteen years. *Surgery* 1996; **119**: 261–68.
2 Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty acid cycle and diabetes mellitus. Ciba Foundation, Colloquia on endocrinology 15, Aetiology of diabetes mellitus and its complications. London: Churchill Ltd, 1964: 192–216.
3 Tataranni PA, Mingrone G, Greco AV, et al. Glucose-induced thermogenesis in post-obese women who have undergone biliо-pancreatic diversion. *Am J Clin Nutr* 1994; **60**: 320–26.
4 Castagneto M, DeGaetano A, Mingrone G, et al. Normalization of insulin-sensitivity in the obese patients after stable weight reduction with biliо-pancreatic diversion. *Obesity Surgery* 1994; **4**: 161–68.

RC#3 – MARQUET, P.; FRANÇOIS, B.; VIGNON, P.; LACHÂTRE. A soldier who had seizures after drinking quarter of a litre of wine. **The Lancet**, v. 348, n. 9034, p. 1070, 1996.

THE LANCET

Case report

A soldier who had seizures after drinking quarter of a litre of wine

P Marquet, B François, P Vignon, G Lachâtre

During a party to celebrate his initiation into an artillery regiment, in September, 1994, a healthy 19-year-old white man drank 250 mL of wine which had flowed through the barrel of a 155 mm gun after several shots had been fired, as was the regimental custom. 15 min later he began to have seizures which lasted for 25 min until they were stopped by intravenous diazepam. He was transferred to a teaching hospital in Limoges. On physical examination (BF), he was unconscious and did not react to any stimuli. Neurological examination was otherwise unremarkable. Blood pressure was 125/80 mm Hg; heart rate was regular at 85 min. There were no heart murmurs. He was breathing slowly without cyanosis, and his lungs were clear on auscultation. Abdominal examination was normal. Central temperature was 37·2°C. Initial management was tracheal intubation to enable mechanical ventilation. Laboratory findings at the time of admission are shown in the table. Computed tomography and magnetic resonance imaging of the brain as well as cerebrospinal fluid examination were unremarkable. Electroencephalographic tracings showed high-voltage slow waves without evidence of paroxysmal or focal electric activity. Blood ethanol concentration was 0·31 g/L. Repeated toxicological screening failed to find any common intoxicant or drug in the patient's serum. Specific assays for cyanide, mercury, and lead were negative.

Inductively coupled plasma (ICP) emission spectometry showed high concentrations of tungsten in all biological samples measured: 5 mg/L in serum (normal 0·0023–0·0093 mg/L in non-exposed people[1]); 101 mg/L in urine (accepted safety values <0·5 mg/24 h for exposed workers[2]); and 8 mg/L in gastric contents. A high concentration of tungsten was found in the wine the patient drank (1540 mg/L; dose ingested approximately 385 mg). On his second day in hospital, he spontaneously recovered consciousness and was extubated. Onset of acute anuric renal failure required haemodialysis on day 3. Serum creatine phosphokinase concentrations reached a peak on day 2 (992 IU/L) and returned to normal by day 5. An ultrasound-guided renal biopsy showed extensive tubular necrosis without associated glomerular injury. Haemodialysis was maintained until day 9 and diuresis resumed on day 12. He was discharged from hospital on day 35 fully recovered. Despite haemodialysis, high concentrations of tungsten were still found in the patient's serum and urine until day 12 and 33, respectively. Tungsten was undetectable in the patient's hair and nails during his hospital admission, but high concentrations were measured 2 months after the accident (4·26 µg/g and 3·81 µg/g, respectively). He was last seen in February, 1995, and was well.

	Value	Normal range
Sodium (mmol/L)	142	135–145
Potassium (mmol/L)	5·6	3·5–5·0
Chloride (mmol/L)	106	95–110
Calcium (mmol/L)	2·00	2·10–2·70
Blood urea nitrogen (mmol/L)	6·4	3·2–7·5
Creatinine (µmol/L)	160	65–120
Glucose (mmol/L)	4·2	3·9–5·5
White blood cell count (×10⁹/L)	22·7	4–9
Haemoglobin (g/dL)	15	14–18
Packed-cell volume (%)	44	40–50
Platelet count (×10⁹/L)	249	150–400
Creatine phosphokinase (IU/L)	485	31–210
Lactate dehydrogenase (IU/L)	940	300–800

Table: **Laboratory results on admission**

Tungsten is a heavy metal that may cause lung fibrosis or dermatitis in chronically exposed workers. In such people, mean metal concentrations in blood, urine, toenails, and pubic hairs are higher than those in non-exposed normal individuals.[3] However, to the best of our knowledge, this is the first report of acute tungsten intoxication in a human being. Acute toxicity of orally ingested tungsten has been studied in pregnant mice.[4] After rapid intestinal absorption, tungsten was found in the spleen, bones, and kidneys and appeared to be eliminated by glomerular filtration. Urine tungsten concentration was initially high in our patient and persisted for more than 30 days despite haemodialysis. Non-specific tubular necrosis was attributed to tungsten toxicity, because no other causes were identified. As with animal experiments, the clinical presentation of our patient was with neurological signs, consisting of seizures accompanied by slow waves on the electroencephalogram.[5] We found that the composition of gun barrels had recently changed, with the inclusion of tungsten to harden the steel. The other recruits who had attended the party vomited immediately after having drunk the contaminated wine. Since this accident, such dangerous celebrations have been forbidden in the French Army.

We thank G Nedelec (Department of Nephrology and Hemodialysis, The Val-de-Grâce Army Instruction Hospital, Paris, France).

Lancet 1996; **348**: 1070

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References

1 Wester PO. Trace elements in serum and urine from hypertensive patients before and during treatment with chlorthalidone. *Acta Med Scand* 1973; **194**: 505–12.

2 Barboník M. Excretion of cobalt and tungsten in workers in the production of hard metals. II—the daily excretion of tungsten in urine. The influence of $CaNa_2$ EDTA and penicillamine on its excretion. *Pracov Lek* 1972; **24**: 295–97.

3 Nicolaou G, Pietra R, Sabbioni E, Mosconi G, Cassina G, Seghizzi P. Multielement determination of metals in biological specimens of hard metal workers: a study carried out by neutron activation analysis. *J Trace Elem Electrolyte Health Dis* 1987; **1**: 73–77.

4 Wide M, Danielsson BRG, Dencker L. Distribution of tungsten in pregnant mice and effects on embryonic cells in vitro. *Environ Res* 1986; **40**: 487–98.

5 Takahashi S, Yamauchi T, Hirabayashi Y. Experimental seizures produced by tungstic acid gel in rats. *Life Sci* 1972; **11**: 1011–20.

RC#4 – METKUS, A.P.; TRABULSY, P.P.; SCHLOBOHM, R.S.; HICKEY, M.S. A firefighter with pancreatitis. **The Lancet**, v. 348, n. 9043, p. 1702, 1996.

THE LANCET

Case report

A firefighter with pancreatitis

Andrea P Metkus, Philip P Trabulsy, Richard S Schlobohm, Michael S Hickey

A 34-year-old previously healthy woman firefighter was admitted to San Francisco General Hospital on March 9, 1995, with a severe inhalation injury and 40% partial thickness burns involving her face, neck, abdomen, and legs. She had been trapped in a closed space and inhaled gas fumes at an estimated temperature of 1650°C, but had no associated blunt trauma. She had no history of alcohol abuse, biliary-tract disease, or lipid disorders. In the emergency department her blood pressure was 150/80 mm Hg. She had a tachycardia of 110/min, tachypnoea, and inspiratory stridor. She was intubated, mechanical ventilation was started, and she was transferred to the Burns Intensive Care Unit. Carboxyhaemoglobin was 15·0%. Flexible fibreoptic bronchoscopy showed carbonaceous sputum and erythema and oedema of the tracheobronchial mucosa. On hospital day 6, her ventilatory failure decompensated to severe respiratory failure requiring oxygen (FiO_2=1·0) and positive end-respiratory pressure 18 cm H_2O). Vecuronium was needed to achieve oxygenation saturation above 90%. Propofol (30–140 μg kg^{-1} min^{-1}) was added to her continuous infusions of morphine sulphate and lorazepam. During the next 9 weeks of mechanical ventilation, she developed severe hypertriglyceridaemia that directly corresponded to her propofol dose. Her maximum serum triglyceride level was 48·3 μmol/L. She received nutrition by mouth, did not have cardiovascular instability or sepsis, and never received pressors. On her 69th day in hospital, she developed a fever of 39°C and diffuse abdominal tenderness. Her white blood cell count was 18·6×10^9/L, amylase was 31 IU/L (normal 30–126 IU/L), and lipase 148 IU/L (normal 10–180 IU/L). A computed tomography scan of her abdomen suggested peripancreatic fat stranding and oedema (figure).

A laparotomy revealed necrotising pancreatitis with fluid in the lesser sac. After drainage of the fluid, propofol infusion was discontinued. Pancreatitis resolved over 2–3 weeks. She was eventually discharged from hospital and was living independently when last seen in April, 1996.

Propofol (Diprivan, Zeneca Pharmaceuticals, Wilmington, DE, USA) is a sedative-hypnotic agent used predominantly for the induction of general anaesthesia. Increasingly, propofol has been used in the intensive care unit for sedation. Provided in a continuous infusion, propofol allows rapidly controllable periods of sedation due to its half-life of 2–8 min. Propofol is one of the alkyphenol group of oils; it is highly lipid soluble and is

Lancet **1996; 348:** 1702

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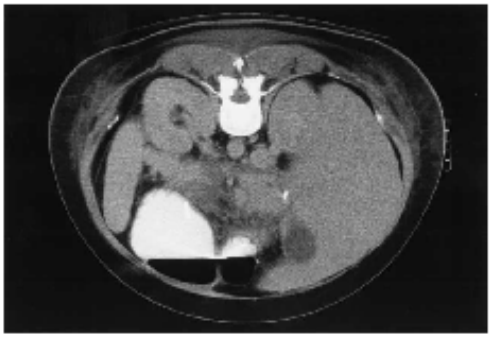


Figure: **Computed tomography scan of patient's abdomen**

prepared in a solution similar to 10% Intralipid.[1] The association between hypertriglyceridaemia and pancreatitis is well known among patients with primary or secondary hypertriglyceridaemia, who are prone to develop episodes of acute pancreatitis when their serum triglycerides are uncontrolled. Patients with severe hypertriglyceridaemia usually have a normal serum amylase (lipaemic serum interferes with the amylase assay), and the associated pancreatitis is often necrotising. There is conflicting evidence on the effect of short-term propofol use on serum lipids. Gottardis et al[2] found no significant difference in serum lipid concentrations between patients in intensive care who received a continuous propofol infusion for 3 days and those who received conventional sedation. Others have found that propofol induces hypertriglyceridaemia with short-term and long-term (>7 days) use; the hypertriglyceridaemia returns to normal when the propofol is discontinued.[3] Boyle et al[4] found that serum lipids increased when the rate of infusion exceeded 100 μg kg^{-1} min^{-1} for prolonged periods. Propofol has many advantages over other more commonly used sedatives in intensive care, although prolonged infusions at high rates can raise serum lipid concentrations. Propofol has been implicated in a few sporadic cases of postoperative pancreatitis, but it is unlikely that intraoperative bolus doses would either raise serum lipids or induce pancreatitis, as argued by Leisure et al.[5] Propofol-induced hypertriglyceridaemia is the most likely cause of necrotising pancreatitis in this patient. Despite high serum triglycerides, the infusion was continued to allow life-saving mechanical ventilation. Prolonged continuous propofol infusion in the intensive care unit should be discontinued, if possible, in the presence of hypertriglyceridaemia, to prevent pancreatitis.

References

1 Levine RL. Pharmacology of intravenous sedatives and opioids in critically ill patients. *Crit Care Clin* 1994; **10:** 709–31.
2 Gottardis M, Khuni-Brady KS, Koller W, et al. Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations. *Br J Anaesthesia* 1989; **62:** 393–96.
3 Carrasco G, Molina R, Costa J, et al. Propofol vs midazolam in short-, medium-, and long-term sedation of critically ill patients. *Chest* 1993; **103:** 557–64.
4 Boyle WA, Shear JM, White PF, et al. Tolerance and hyperlipidemia during long-term sedation with propofol. *Anesthesiology* 1990; **73** (suppl): A245.
5 Leisure GS, O'Flaherty J, Green L, et al. Propofol and postoperative pancreatitis. *Anesthesiology* 1996; **84:** 224–27.

RC#5 – ADZICK, N.S.; CROMBLEHOLME, T.M.; MORGAN, M.A.; QUINN, T.M. A rapidly growing fetal teratoma. **The Lancet**, v. 349, n. 9051, p. 538, 1997.

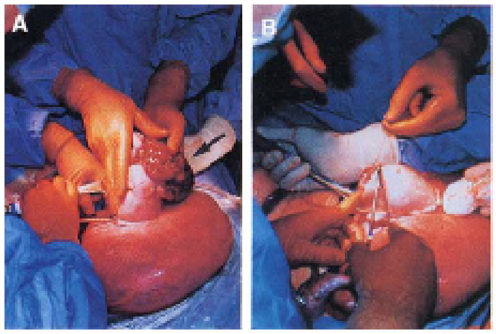
THE LANCET

A rapidly growing fetal teratoma

N Scott Adzick, Timothy M Crombleholme, Mark A Morgan, Theresa M Quinn

In June, 1996, a 25-year-old woman was referred for assessment of a fetus (25 weeks' gestation) with a sacrococcygeal teratoma. The teratoma was first detected at a routine 20-week ultrasound scan. The tumour grew rapidly thereafter to become nearly the size of the fetus. By 25 weeks, polyhydramnios and placentomegaly had developed. Fetal echocardiography showed that a large portion of the fetal cardiac output perfused the teratoma. Placental thickness increased from 40 mm to 60 mm (normal 25 mm) in 1 week, and maternal tachycardia and proteinuria suggested impending maternal mirror syndrome.

After maternal general anaesthesia provided fetal anaesthesia and uterine relaxation for open fetal surgery, a low transverse maternal laparotomy and vertical hysterotomy were done.[1] The fetal rectum was dissected away from the teratoma, which measured 14 cm by 10 cm by 8 cm. A tourniquet was applied to the base of the tumour to constrict the blood flow. Sterile intraoperative ultrasound demonstrated no fetal haemodynamic compromise. The tumour was resected with a 90 mm thick tissue stapler (US Surgical Co, Norwalk, CT, USA) (figure). The fetal sacral wound was closed, amniotic fluid was replaced with warm lactated Ringer's solution and the uterine and laparotomy wounds were closed. Postoperatively, the fetus showed marked skin oedema and ascites and the mother developed vulval oedema; both resolved after maternal fluid restriction and frusemide diuresis. Tocolysis was maintained with magnesium sulphate intravenous infusion and indomethacin rectal suppositories, followed by terbutaline given by subcutaneous pump. By 10 days after fetal surgery, the fetal hydrops and placentomegaly had regressed and the mother was discharged. Pathology of the 400 g teratoma showed a grade III immature teratoma without evidence of malignancy. At 29 weeks' gestation, preterm labour led to the caesarean-section delivery of a 1·13 kg baby girl who required a short period of ventilatory support. The mother recovered uneventfully. The baby underwent a second operation to resect the coccyx and surrounding tissue at 2 months of age; no residual tumour was found. She has met all developmental milestones at 7 months of age.



Fetal surgery
A: exposure of 25-week fetus through hysterotomy revealing sacrococcygeal teratoma (arrow).
B: closure of skin flaps after resection.

Most sacrococcygeal teratomas diagnosed in neonates have low malignant potential and a good prognosis after resection.[2] However, prenatally diagnosed sacrococcygeal teratoma associated with fetal hydrops can be rapidly fatal in utero or lead to polyhydramnios and premature delivery.[3] The high-output cardiac failure is related to a "vascular steal" from the high blood flow through the tumour.[4,5] Fetal hydrops and placentomegaly may also jeopardise maternal health through the maternal mirror syndrome, in which the maternal condition begins to "mirror" that of the sick fetus. In this case we considered that resection of the tumour in utero might prevent the maternal mirror syndrome and fetal death. Previous attempts at resection of sacrococcygeal teratomas have failed because of advanced fetal hydrops and placentomegaly. This case demonstrates that resection earlier in the disease course can have a successful outcome.

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1 Adzick NS, Harrison MR. Fetal surgical therapy. *Lancet* 1994; 343: 897–902.
2 Altman RP, Randolph JG, Lilly JR. Sacrococcygeal teratoma. *J Pediatr Surg* 1974; 9: 389–98.
3 Flake AW, Harrison MR, Adzick NS, Laberge JM, Warsof SL. Fetal sacrococcygeal teratoma. *J Pediatr Surg* 1986; 21: 563–66.
4 Langer JC, Harrison MR, Schmidt KG, et al. Fetal hydrops and death from sacrococcygeal teratoma: rationale for fetal surgery. *Am J Obstet Gynecol* 1989; 160: 1145–50.
5 Flake AW. Fetal sacrococcygeal teratoma. *Sem Pediatr Surg* 1993; 2: 113–20.

RC#6 – DELSYS, J.P.; LASMÉZAS, C.I.; STREICHENBERGER, N.; HILL, A.; COLLINGE, J.; DORMONT, D.; KOPP, N. New variant Creutzfeldt-Jakob disease in France. **The Lancet**, v. 349, n. 9044, p. 30-31, 1997.

In October, 1994, she wished to start a family but had severe anxiety about any treatment with hormone preparations derived from human sources, because of her fears of Creutzfeld-Jakob disease. Pelvic ultrasound showed a small uterus and small polycystic ovaries. Serum gonadotropin and oestradiol concentrations were very low. Treatment with pulsatile LHRH was again attempted but there was no response after 6 weeks. Supplies of recombinant FSH (Gonal-F) and LH (LHadt) to induce follicular growth, and of recombinant hCG (Ovidrel) to induce ovulation and stimulate the corpus luteum, were provided by Serono Laboratories (UK) on a compassionate and named-patient basis. The patient's first treatment cycle was initiated with 75 IU of Gonal-F and 75 IU of LHadt by subcutaneous injection. The dose was titrated to the patient's response. A single dose of Ovidrel (500 µg, 10 000 IU) was administered subcutaneously to induce ovulation and maintain the corpus luteum. The cycle was ovulatory but the patient did not conceive. In a second treatment cycle, with the same doses of Gonal-F and LHadt, the patient over-responded and treatment with Ovidrel was withheld. A third treatment cycle was commenced in June, 1996, and the patient conceived. 7 days after Ovidrel injection, ultrasound showed seven ovarian cysts of 14 to 30 mm diameter on each ovary. 1 week later she had a positive urine pregnancy test, a serum oestradiol concentration of 6908 pmol/L, and a serum concentration of vascular endothelial growth factor[4] of 5-8 ng/mL (normal range 1·3–2·5 ng per mL). She subsequently developed abdominal distension and tightness in the chest. Ultrasound examination confirmed the presence of bilaterally enlarged ovaries, multiple ovarian cysts, moderate ascites, and bilateral small pleural effusions. A diagnosis of severe ovarian hyperstimulation was made and the patient admitted for observation. Her condition rapidly improved without intervention and she now has a 26 weeks' singleton pregnancy.

To our knowledge, this is the first pregnancy recorded after use of recombinant LH, FSH, and hCG but we may anticipate that biosynthetic preparations will soon replace all preparations derived from human urine currently in use. Notwithstanding differences of recombinant LH and FSH from gonadotropins derived from pituitary and urine, it is clear from the published research and our case report that these monohormonal preparations are effective and potent. Our patient tended to over-respond despite low-dose treatment and, indeed, in her cycle of conception she developed severe ovarian hyperstimulation syndrome, which fortunately settled quickly on conservative treatment. Management of patients with polycystic ovaries carries the risk of excessive response to gonadotropin stimulation.[5] Physicians are cautioned to undertake careful monitoring and surveillance of ovulation-induction regimens as these potent biosynthetic monohormonal preparations are introduced into clinical practice.

1 Germond M, Dessole S, Senn A, Loumaye E, Howles C, Beltrami V. Successful in-vitro fertilisation and embryo transfer after treatment with recombinant human FSH. *Lancet* 1992; **339**: 1170.

2 Hull M, Corrigan E, Plazzi A, Loumaye E. Recombinant human luteinising hormone: an effective new gonadotropin preparation. *Lancet* 1994; **344**: 334–35.

3 Imthurn B, Plazzi A, Loumaye E. Recombinant human luteinising hormone to mimic mid-cycle LH surge. *Lancet* 1996; **348**: 332–33.

4 McClure N, Healy DL, Rogers PAW, et al. Vascular endothelial growth factor as capillary permeability agent in ovarian hyperstimulation syndrome. *Lancet* 1994; **344**: 235–36.

5 MacDougal MJ, Tan SL, Balen AH, Jacobs HS. A controlled study comparing patients with and without polycystic ovaries undergoing in vitro fertilisation. *Hum Reprod* 1993; **8**: 233–37.

Division of Reproductive Endocrinology, Department of Medicine, UCL Medical School, The Middlesex Hospital, London W1N 8AF, UK (H S Jacobs); **and Serono Laboratories (UK) Ltd, Welwyn Garden City**

New variant Creutzfeldt-Jakob disease in France

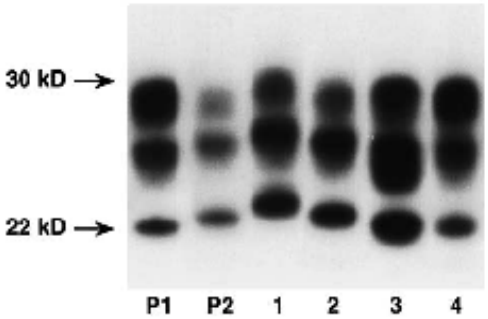
J-P Deslys, C I Lasmezas, N Streichenberger, A Hill, J Collinge, D Dormont, N Kopp

All ten cases of the new variant of Creutzfeldt-Jakob disease (nvCJD) studied in the UK share a specific electrophoretic pattern of PrP-Pres,[1] the abnormal isoform of the prion protein (PrP), which is partially resistant to protease digestion and accumulates in the brain of patients during the disease. The PrP protein has two possible sites of glycosylation and the electrophoretic pattern shows three bands (corresponding to the di-, mono-, and unglycosylated forms). Under mild conditions of treatment by proteinase K, normal PrP is completely hydrolysed while only the N-terminal extremity of PrP-Pres is cleaved. The molecular weight of PrP-Pres after proteolysis is lower in nvCJD than in sporadic CJD and there is a higher proportion of the di-glycosylated form. Thus, a type of PrP-Pres has been defined according to these two parameters and appears to be specific for nvCJD.

The first patient suffering from nvCJD described in France was a 26-year-old man, homozygous for methionine at codon 129 of the PrP gene and without any known risk factor.[2] All currently known cases of nvCJD have been homozygous for methionine at codon129.[3] Pathological examination showed typical florid plaques and the PrP immunostaining pattern seen in nvCJD in the UK. We report that he also had an indistinguishable electrophoretic pattern to UK cases (type 4, figure). This result confirms the apparent great homogeneity of the nvCJD group.

Florid plaques were also found in a brain specimen of another French patient who was a methionine homozygote at codon 129.[4] This patient has been reported as a possible case of nvCJD even though the history of this 52-year-old woman included a dura-mater graft 11 years before. As seen in the figure, the electrophoretic pattern of this case is not a type 4 but a type 2 pattern similar to that described in an iatrogenic dura-mater linked CJD case.[1]

These findings suggest that this second French case is not nvCJD but most likely an iatrogenic case linked to the dura-mater graft. These findings indicate that the observation of a few florid plaques is insufficient for the diagnosis of nvCJD which should take into account the criteria described by Will et al as a whole, that is the clinical history, the presence of florid plaques, and the pattern of PrP-Pres deposition



Western blot detection of PrPSc in brains from patients with CJD using PrP monoclonal antibody 3F4.
P1 patient 1 (type 4 pattern, nvCJD); P2 patient 2 (type 2 pattern); 1 sporadic CJD (type 1 pattern); 2 sporadic CJD (type 2 pattern); 3 iatrogenic CJD linked to growth hormone (type 3 pattern); 4 nvCJD from UK (type 4 pattern). All patients presented here were methionine homozygotes at codon 129 of the PrP gene except type 3 who was a valine homozygote (details of the protocol are available from the authors).

RC#7 – VISSER, L.; STRICKER, B.; HOOGENDOORN, M.; VINKS, A. Do not give paraffin to packers. **The Lancet**, v. 352, n. 9137, p. 1352, 1998.

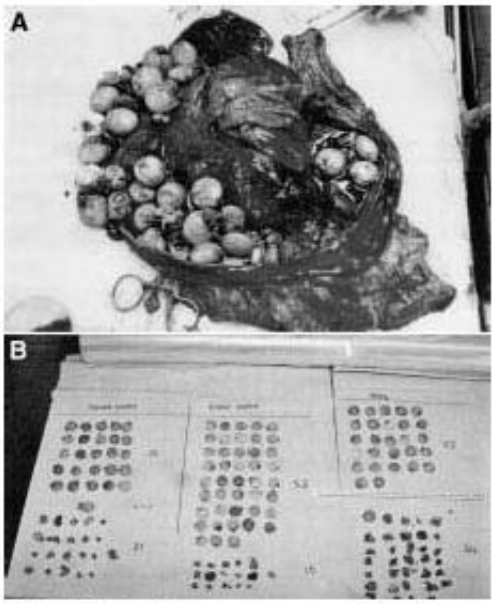
Case report

Do not give paraffin to packers

Loes Visser, Bruno Stricker, Mels Hoogendoorn, Alexander Vinks

A 49-year-old man with a history of appendicectomy and three myocardial infarctions became unwell, in January, 1998, during a flight from the Dutch Antilles to Amsterdam, Netherlands. During his flight he had not taken any food or drink. On arrival at the airport he was unable to stand, was perspiring, had abdominal pain, was agitated and hallucinating. He had no psychiatric history. Because the authorities suspected he was a body-packer, he was arrested. Owing to the severity of the symptoms, however, he was taken to the emergency clinic of the nearest university hospital. Here, he said that he had ingested 102 latex packages each containing 5 g cocaine, together with 20 tablets of 125 mg activated charcoal. He was a regular nasal user of cocaine. On admission he had a distended and painful abdomen, a blood pressure of 160/112 mm Hg, and a tachycardia of 117/min. He had a dilated left pupil; his right eye was blind. Abdominal radiography showed a large number of spherical packages in his gastrointestinal tract. There were no gas haloes or other signs of leakage from the packages. Because his cardiovascular, respiratory, and neurological status was stable, he was transferred to the prison hospital. During his transfer he had a convulsion and was taken to the emergency clinic of Bronovo Hospital in The Hague. On admission, he was treated with 200 mg phenytoin and 30 mg diazepam intravenously, later followed by 4 mg lorazepam, 100 mg metroprolol, and 90 mL lactulose. He had a good diuresis but some of his laboratory tests were abnormal: serum creatine kinase 684 U/L (normal <200), γ-glutamyltranspeptidase 53 U/L (normal <50), glucose 9·4 mmol/L (normal <8·8), and lactate dehydrogenase 486 U/L (normal <450). Electrolytes, serum amniotransferase, and serum creatinine concentrations were within the normal range. Analysis of his urine was strongly positive for cocaine, with a concentration of more than 3 mg/L. Serum concentration of cocaine was 1·95 mg/L on high-performance liquid chromatography. Since his condition remained stable, he had no further convulsions, and he had not defaecated, he was given liquid paraffin.

During the next 24 h, he remained agitated and disoriented. His pH decreased to 6·7, serum creatinine increased to 141 μmol/L (normal <125), and pCO_2 increased to 111 mm Hg (normal 35–45). His serum cocaine increased to 2·2 mg/L, and he was prepared for operation, but he developed untreatable ventricular arrhythmia and fibrillation. Necropsy showed his upper gastrointestinal tract filled with cocaine packages (figure, A), of which 71 were ruptured, and 95 were still intact (figure, B). Postmortem gas chromatography mass spectrometry serum concentrations of cocaine and benzoylecgonine were 7·7 mg/L and 11·8 mg/L, respectively.



Contents of stomach

This patient died as a result of cardiovascular and respiratory failure due to cocaine intoxication. The lethal oral dose of cocaine is 1–3 g,[1] dependent on individual factors such as tolerance from repeated use. This patient had ingested more than 150 packages of 5 g each of cocaine—a total of almost 1 kg. The usual treatment of a body-packer is with laxatives such as sorbitol or lactulose with activated charcoal. Surgery should be considered if there are symptoms of intoxication.[2] In this case, the patient was treated with a mineral oil which may have contributed to rupture of the packages because mineral oil dissolves latex. Exposure of latex to mineral oil causes a decrease in strength and flexibility within 15 min.[3] Despite this, older handbooks on clinical toxicology advise the use of paraffin. Since a package generally contains more than 3 g of cocaine, the rupture of one package may be fatal.[1] Liquid paraffin should not be used as a laxative for body-packers.

We thank Peter Zwelpfenning for the postmortem serum measurements and Rob Visser for the necropsy photographs.

Lancet 1998; **352**: 1352

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References

1 Lancashire MJR, Legg PK, Lowe M, Davidson SM, Ellis HW. Surgical aspects of international drug smuggling. *BMJ* 1988; 296: 1035–37.

2 Ellenhorn MJ, Schonwald S, Ordog G, Wassenberger J. Ellenhorn's medical toxicology: diagnosis and treatment of human poisoning. Baltimore: Williams & Wilkins, 1997: 380.

3 White N, Taylor K, Lyszkowski A, Tullett J, Morris C. Dangers of lubricants used with condoms. *Nature* 1988; 335: 19.

RC#8 – SHETTY, A.K.; STEELE, R.W.; SILAS, V.; DEHNE, R. A boy with a limp. **The Lancet**, v. 351, n. 9097, p. 182, 1998.

Case Report

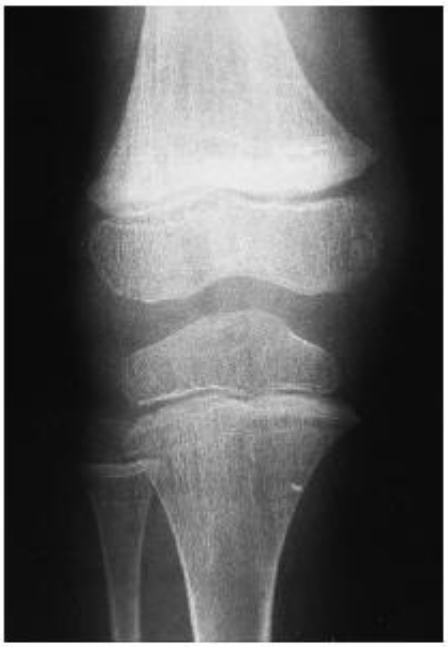
A boy with a limp

Avinash K Shetty, Russell W Steele, Victoria Silas, Robert Dehne

A 6-year-old white boy was referred to the Children's Hospital in New Orleans, Louisiana, USA, in December, 1996, for evaluation of hip pain and a limp for 6 weeks. There was no history of trauma, fever, or weight loss. The pain had worsened progressively until, the day before, he had become unable to walk. He had had intermittent bleeding from his gums over the past month. There was a 4-year history of autism with developmental delay. On physical examination he was apprehensive, but did not speak. His weight was 16·7 kg (less than 5th centile) and height 113 cm (10th centile). His gums were swollen and friable, and one of his upper incisors was loose. Proximal leg muscles were tender bilaterally. Skin and joint examination was normal. His haemoglobin was 11·8 g/dL; mean corpuscular volume 74 fL, platelet count 415×10^9/L; and white-cell count $5·7\times10^9$/L, with 54% segmented neutrophils, 37% lymphocytes, 8% monocytes, and 1% atypical lymphocytes. ESR was 44 mm/h. Antinuclear antibody and rheumatoid factor were negative. Coagulation tests were normal. Radiographs of his legs showed diffuse osteopenia (figure). A ^{99m}technetium bone scan showed hyperactivity in the right tibiofibular joint. Magnetic resonance imaging of the pelvis and hips was normal. Acute leukaemia was the first diagnosis considered; however, a bone marrow smear and biopsy specimen showed only nonspecific changes.

At this point, clinical and radiographic findings were reassessed. Scurvy was suspected. A further history from his parents revealed that his diet had consisted of cookies, yogurt, whole milk, biscuits, and water for the past 12 months. He did not eat any fruit, vegetables, meat, or fish. A leucocyte ascorbic acid concentration of less than 0·6 mg/dL (normal 0·6–2·0 mg/dL) confirmed the diagnosis of scurvy. He was treated with ascorbic acid (200 mg orally) for 10 days and a balanced diet. The response was rapid, with resolution of gingival bleeding and resumption of weight bearing within 2 weeks. When last seen in July, 1997, he was well.

Ascorbic acid is essential for human health. Its absence in the diet can be life threatening. In industrialised countries, scurvy has become a rare disease. Only the oldest paediatricians in the developed world will have ever seen a child with scurvy, unless they have done so when visiting a developing country. In his 1753 monograph, Sir James Lind described the natural history of scurvy and its prevention by dietary means.[1] Scurvy in childhood was thought to be a complication of acute rickets until Thomas Barlow of London identified it as a separate entity in 1893, and as being no different from adult scurvy.[2] Scurvy is still found intermittently in developed countries, especially among food faddists, alcoholics, the elderly, and men who live alone. Infants fed exclusively cows' milk formula, and children with neurodevelopment disabilities and psychomotor retardation are at additional risk.[3] The diagnosis of scurvy can often be made by the presence of characteristic clinical findings and a history of a diet inadequate in ascorbic acid. Scurvy can mimic many other medical diseases such as vasculitis,[4] blood dyscrasias, deep vein thrombosis, and rheumatic disorders.[5] Patients with scurvy are often extensively investigated for other systemic disorders, including leukaemia, as in the present case. Presentation with tenderness of the limbs and the pain elicited by movement can often lead to the erroneous diagnosis of arthritis. The present case clearly shows that despite advances in medicine, living conditions, and nutrition, scurvy still can occur and highlights the need for continued medical awareness of this potentially life-threatening disease by all health professionals.



Radiograph of right knee

Lancet 1998; **351:** 182

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References

1 Lind J. A treatise on the scurvy. Stewart CP, Cuthrie D, eds. Edinburgh: Edinburgh University Press, 1753.
2 Barlow T. On cases described as "acute rickets" which are possibly a combination of rickets and scurvy, the scurvy being essential and the rickets being variable. *Medico-Chirurgical Transactions* 1883; 66: 159–220.
3 Garty B, Danon Y, Grunebaum M, Nitzan M. Scurvy in children with severe psychomotor retardation. *Int Pediatr* 1989; 4: 280–82.
4 Scully RE, Mark EJ, McNeely BU. Case records of the Massachusetts General Hospital, Case 33-1986. *N Engl J Med* 1986; 315: 503–08.
5 Shetty AK, Buckingham RB, Killian PJ, Girdany D, Meyerowitz R. Hemarthrosis and femoral head destruction in an adult diet faddist with scurvy. *J Rheumatol* 1988; 15: 1878–80.

RC#9 – STIRLING, C.M.; BOULTON-JONES, J.M.; SIMPSON, K. Progressive oedema in a 30-year-old. **The Lancet**, v. 352, n. 9126, p. 450, 1998.

Case report

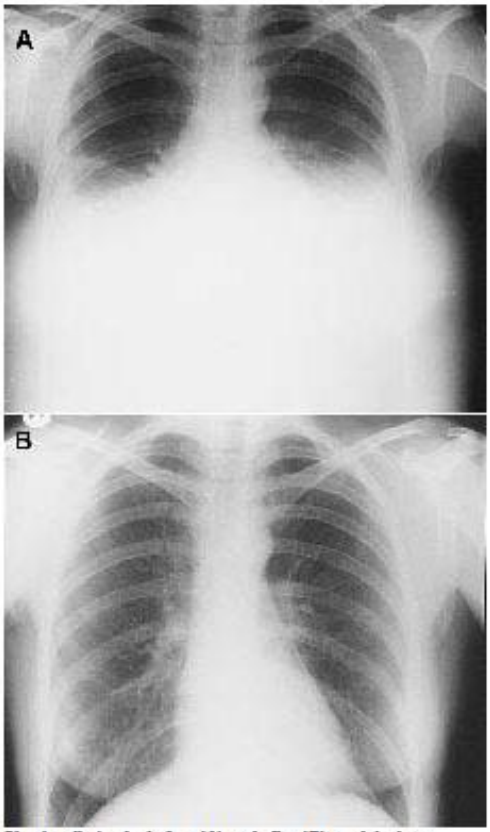
Progressive oedema in a 30-year-old

C M Stirling, J M Boulton-Jones, K Simpson

A woman aged 30 years came to the renal unit in October, 1996, with an 8-week history of progressive generalised oedema and weight gain of 12 kg. Her serum albumin was 28 g/L; albuminuria was 5 mg/24 h. She had no evidence of heart failure, renal failure, or a protein-losing enteropathy, and no abnormalities of liver function. Anti-nuclear antibody was positive at a titre of 1:2560. Rheumatoid factor was positive at 77 IU/mL and C4 was decreased. Antibodies to DNA and extractable nuclear antigens were negative and complement studies, including C3, C1 inhibitor, C1-inhibitor antibody, and C1q and C1q precipitins, were also negative. She did not fulfil the diagnostic criteria for systemic lupus erythematosus.[1] Concentrations of peripheral-blood renin and aldosterone were slightly raised but cortisol was normal. Her blood pressure was 114/68 mm Hg. Eosinophil count and C-reactive protein were normal. Viral titres were negative. Skin biopsy was normal. Serum protein electrophoresis showed oligoclonal banding, consisting of an 8·2 g/L IgG κ band and two small IgG λ bands. Bone-marrow aspiration and trephine specimens were normal and there was no Bence-Jones protein in her urine.

Capillary permeability, as determined by cuff capillary-filtration coefficient,[2] was raised and a diagnosis of systemic capillary leak was made. She was treated with daily plasma exchange and then with high-dose human immunoglobulin (2 g/kg) for 5 days without any clinical improvement. Oral prednisolone 1 mg/kg was then given which resulted in improvement within 24 h, accompanied by a large diuresis (figure). She lost 12 kg over the next 10 days. Repeat capillary permeability testing, 6 weeks after starting steroids, was normal. Prednisolone was decreased over the next year and she was in remission 18 months later, in May, 1998.

Systemic capillary-leak syndrome (SCLS) was described by Clarkson in 1960[3] and is characterised by episodic attacks (usually lasting 24–48 h) of unexplained increased capillary permeability. This permeability leads to plasma protein and fluid extravasation, hypovolaemia, and hypotension, which can be life threatening. Secondary hyperaldosteronism leads to water retention and oedema. The underlying cause is not known and there have been fewer than 40 cases reported. It is associated with an IgG paraprotein band, although it is unclear whether this is causative or a marker of disease. It affects people aged 30–40 years and has a high mortality, with only six of 25 patients surviving for more than 5 years.[4] Different treatments have been tried, including plasmapheresis, steroids, epoprostenol, salbutamol, and *Ginkgo biloba* extract with success in some cases.[4] This case was unique in that the onset was slow and the response to steroids striking. Other illnesses thought to be due to leaky capillaries are idiopathic acute respiratory distress (ARDS) and minimal-change nephropathy (MCN). MCN is thought to involve a circulating vascular permeability factor (VPF) produced by lymphocytes that causes glomerular capillary leakage. A circulating component may cause SCLS, possibly via production of interleukin 2.[5] Until we know more about the pathophysiology of this disorder, treatment will remain empirical. We recommend that steroid therapy be considered early.



Chest radiographs before (A) and after (B) prednisolone

We thank Alan Jaap for the measurement of capillary-filtration coefficient and Alex Farrell for his advice.

Lancet 1998; 352: 450

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References

1 Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus nephritis. *Arthritis Rheum* 1982; **25**: 1271–77.
2 Jaap AJ, Shore AC, Gartside IB, Gamble J, Tooke TJ. Increased microvascular fluid permeability in young type I diabetic patients. *Diabetologia* 1993; **37** (7): 648–52.
3 Clarkson B, Thompson D, Horwith M, Luckey EH. Cyclical edema and shock due to increased capillary permeability. *Am J Med* 1960; **29**: 193–216.
4 Teelucksingh S, Padfield PL, Edwards CRW. Systemic capillary leak syndrome. *Q J Med* 1990; **75**: 515–24.
5 Cicardi M, Gardinali M, Bisiani G, et al. The systemic capillary leak syndrome: appearance of interleukin-2-receptor positive cells during attacks. *Ann Intern Med* 1990; **113**: 475–77.

RC#10 – RABUSIN, M.; LEPORE, L.; COSTANTINES, F.; BUSSANI, R. A child with severe asthma. **The Lancet**, v. 351, n. 9095, p. 32, 1998.

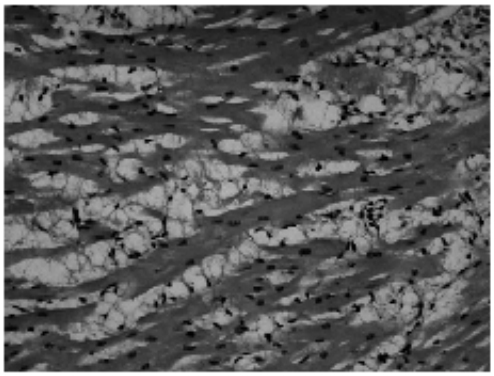
Case Report

A child with severe asthma

Marco Rabusin, Loredana Lepore, Fulvio Costantinides, Rossana Bussani

A 2-year-old boy was admitted to our Department for a very severe acute asthma attack in June, 1996. He was restless and had pronounced dyspnoea and cyanosis. His heart rate was 135 bpm; on auscultation, wheezing was clearly evident bilaterally. Oxygen saturation was 70%. During the previous 12 h, he had been treated at home with nebulised salbutamol (ten doses, 2 mg/dose) without any improvement. He had a history of extensive atopic dermatitis (with eosinophilia [4×10^9/L] and high IgE), recurrent asthma attacks (eight episodes from 6 months of age; three necessitated hospital admission) and two episodes of urticaria and angioedema after ingestion of horse-meat and cottage cheese. A chest radiograph at 12 months was normal. The atopic dermatitis was treated with intermittent local steroidal drugs and avoidance of foods to which he had shown positive skinprick-test responses. The parents would not accept systemic or nebulised steroid therapy for the asthma. On admission, the child received oxygen (5 L/min), intravenous salbutamol (up to 0·4 $\mu g\ kg^{-1}\ min^{-1}$) and subcutaneous epinephrine (0·2 mg). As on previous occasions, the parents refused steroid therapy. The child was transferred to the intensive-care unit, where he was intubated and ventilated. Oxygen saturation improved to 100%, but there was progressively worsening bradycardia, which led to cardiac arrest; resuscitation procedures were unsuccessful.

The necropsy showed signs of very severe interstitial and perivascular myocarditis, very probably the ultimate cause of death, with the presence of eosinophils and mastocytes. There were also signs of chronic fibrosis, probably due to previous episodes of myocarditis (figure). During life the child had shown no cardiac disorders so had not undergone cardiac investigations. The skin biopsy sample showed extravascular infiltration with eosinophils and plasma cells in the derma and hypoderma; in the lungs there was widespread infiltration of eosinophils in alveolar and interstitial tissues, bronchial epithelium, and peribronchial tissues. Eosinophilic myocarditis is a rare feature observed in various clinical situations; it can be isolated and idiopathic, or induced by drugs (such as antibiotics and carbamazepine).[1] By contrast, the association of eosinophilic myocarditis with severe bronchial asthma, an eosinophil count of more than 10%, and history of severe food allergy, combined with the described histological features, meets the diagnostic criteria for Churg-Strauss syndrome.[2]



Myocardium of left ventricle
Multiple areas of interstitial fibrosis and multicentric infiltration of lymphocytes, eosinophils, and mastocytes visible; there is severe atrophy of myocytes. Haematoxylin and eosin; reduced by 40% from ×40.

Churg-Strauss syndrome is a necrotising vasculitis of medium and small vessels, with or without granuloma, characterised by asthma and hypereosinophilia.[3] It is slightly more common among females than males, and the mean age at onset is usually about 30–40 years;[4] the syndrome is very rare in children. Our patient, to our knowledge, is the youngest reported so far. The history of severe asthma and food allergy with hypereosinophilia in this case should have suggested the diagnosis of Churg-Strauss syndrome earlier. Computed tomography of the thorax, skin biopsy, electrocardiography, and echocardiography would have confirmed the diagnosis. In the presence of cardiomyopathy, a poor prognostic factor, steroids alone or with cyclophosphamide are strongly indicated.[5]

Lancet 1998; **351:** 32

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References

1 Gravanis MB, Hertzler G, Franch RH, et al. Hypersensitivity myocarditis in heart transplant candidates. *J Heart Lung Transplant* 1991; **10:** 688–97.
2 Churg J, Strauss L. Allergic granulomatosis, allergic angiitis and periarteritis nodosa. *Am J Pathol* 1951; **27:** 277–301.
3 Masi A, Hunder G, Lie JT, Michel B, et al. The American College of Rheumatology 1990: criteria for the classification of Churg-Strauss syndrome. *Arthritis Rheum* 1990; **33:** 1094–101.
4 Lhote F, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome: clinical aspect and treatment. *Rheum Dis Clin North Am* 1995; **21:** 911–47.
5 Guillevin L, Lhote F, Gayraud M, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome: a prospective study in 342 patients. *Medicine Bal* 1996; **75:** 17–28.

RC#11 – TEICHMAN, D.; GROBUSCH, M.P.; WESSELMAN, H.; TEMMESFELT-WOLLBRÜCK, B.; BREUER, T.; DIETEL, M.; EMMERICH, P.; SCMITZ, H.; SUTTORP, N.A haemorrhagic fever from the Côte d'Ivoire. **The Lancet**, v. 354, n. 9190, p. 1608, 1999.

Case report

A haemorrhagic fever from the Côte d'Ivoire

Dieter Teichmann, Martin P Grobusch, Hans Wesselmann, Bettina Temmesfeld-Wollbrück, Thomas Breuer, Manfred Dietel, Petra Emmerich, Herbert Schmitz, Norbert Suttorp

A 39-year-old freelance cameraman returned to Germany on Aug 1, 1999, from Abidjan, Côte d'Ivoire, where he had spent 2 weeks working in Comoé National Park in the northeast of the country. He started feeling unwell on the final part of his journey and went to a hospital in Frankfurt/Oder the same day. He had a sudden onset of fever with a temperature over 39°C and chills, general malaise, and weakness. Subsequently, he had muscle and joint pains, headache, abdominal discomfort, nausea, and one bout of haematemesis. Laboratory results showed impaired coagulation status with thrombocytopenia (107×10^9/L), low prothrombin (25%), and prolonged partial thromboplastin time (PTT; 44 s). Initially, renal function was unaffected and electrolytes were normal. Haemoglobin, leucocyte count, and erythrocyte sedimentation rate were normal. C-reactive protein was 2·8 mg/L. Aspartate and alanine aminotransferase concentrations were raised (22 538 U/L, 8732 U/L) and so was bilirubin (45 μmol/L), suggesting acute liver failure. Ultrasonography of the liver showed a hyperdense, slightly enlarged organ with signs of fatty degeneration. A chest radiograph on admission was normal. He was suspected to have a viral haemorrhagic fever and was air-lifted to a specialised infectious diseases unit on the third day of his illness. On arrival at the unit, his symptoms were worse. He was fully oriented, febrile (39·2°C), had enanthema of his palate, conjunctival injection with discrete jaundice, petechiae on both arms with multiple sites of mosquito bites, and an enlarged liver without splenomegaly. His previous medical history was unremarkable. He had taken mefloquine for malaria prophylaxis. During his stay in the Côte d'Ivoire he was well. He stated that he had been immunised against yellow fever in 1993. Because of his travel history, clinical features, and laboratory results, he was diagnosed as having a viral haemorrhagic fever, possibly highly contagious, and transferred to a negative-air-pressure isolation unit.[1] The patient's wife and another man travelling with him were quarantined at home and in hospital respectively. People who had close contact with him were identified and all possible contacts on his airline flights were traced. Malaria was excluded by repeated blood smears. Piperacillin/tazobactam, ciprofloxacin, and ribavirin were started. Fluid and clotting-factor replacement and balanced nutrient supply were given intravenously. His coagulation status deteriorated (prothrombin below 10% and PTT 94 s), he had a thrombocytopenia of 39×10^9/L, and impaired renal function resulting in complete anuria. His consciousness deteriorated gradually, he fell into a coma and died 5 days after the onset of his illness. Necropsy showed features of acute viral haemorrhagic fever with evidence of acute liver and kidney failure (tubular necrosis) and cerebral oedema. Blood samples were analysed in a biosafety level 4 laboratory. Aerobic and anaerobic cultures remained sterile. No antibodies were found to HBc antigen but antibodies to HBs antigen and to HCV were found. There was no evidence of Lassa virus, Marburg virus, various Ebola virus strains (Zaire, Sudan, Côte d'Ivoire, and Gabon), dengue viruses (1–4), or Crimean-Congo or Rift Valley viruses in the patient's blood by RT-PCR with fluorochrome-labelled probes[2] or agarose-gel electrophoresis.

Yellow-fever RT-PCR targeting the NS5/3′ non-coding region yielded a clear band of the same size as obtained with the 17D vaccine strain.[3] 48 h after inoculation yellow-fever virus was detected in both vero and C6/36 insect cells up to a serum dilution of 10^{-4} by indirect immunofluorescence with a yellow-fever-specific monoclonal antibody. The sequence of the 675 bp PCR product showed closest homology of the isolated virus with the French viscerotropic strain originating from Senegal (97% identity); the virus probably belonged to the West African strains characterised by Lepiniec et al.[4]

There is evidence that yellow-fever virus has moved out of the West African sylvatic cycle to cause urban outbreaks in West Africa and the Americas. The overall incidence of viral haemorrhagic fevers imported to non-endemic areas is low; in the majority of cases, travellers were not immunised. The patient confirmed several times that he had received yellow-fever vaccination 6 years previously. Yellow-fever vaccination (D17 strain) failure is rare.[5] Despite prompt efforts, we could not immediately get hold of his vaccination certificate. Once the certificate was checked there was no evidence of vaccination. The patient was suspected of having mixed up the terms "Gelbsucht" (German for hepatitis) and "Gelbfieber" (German for yellow fever) for previous vaccinations. This notion is supported by his positive hepatitis B vaccination status. Specific treatments for yellow fever do not exist. Prevention by vaccination is highly efficient and safe and should be advocated for travellers to areas endemic for yellow fever.

Lancet 1999; **354:** 1608

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References

1 Centers for Disease Control. Management of patients with suspected viral hemorrhagic fever. *MMWR Morb Mortal Wkly Rep* 1988; **37** (suppl S-3): 1–15.

2 Laue T, Emmerich P, Schmitz H. Detection of dengue virus RNA in patients after primary or secondary Dengue infection by using the TaqMan automated amplification system. *J Clin Microbiol* 1999; **37**: 2543–47.

3 Tanaka M. Rapid identification of flaviviruses using the polymerase chain reaction. *J Virol Methods* 1993; **41**: 311–12.

4 Lepiniec L, Dalgarno L, Huong VT, Monath TP, Digoutte JP, Deubel V. Geographic distribution and evolution of yellow fever viruses based on sequencing of genomic cDNA fragments. *J Gen Virol* 1994; **75**: 417–23.

5 Nolla-Salas J, Sabalis-Radresa J, Bada JL. Imported yellow fever in a vaccinated tourist. *Lancet* 1989; **ii**: 1275.

RC#12 – DENAYS, R.; COLLIER, A.; RUBINSTEIN, M.; ATSAMA, P. A 51-year-old woman with disorientation and amnesia. **The Lancet**, v. 354, n. 9192, p. 1786, 1999.

Case report

A 51-year-old woman with disorientation and amnesia

Roger Denays, Andrea Collier, Michel Rubinstein, Patricia Atsama

A previously healthy 51-year-old woman was admitted to hospital in April, 1999, with acute disorientation and amnesia. Physical examination was normal, except for a fresh right parietal scalp wound. On neurological examination, she was found to have severe verbal memory impairment. There were no signs of meningeal irritation. Creatinine phosphokinase was 2200 IU/L, C-reactive protein was 3·1 mg/dL. Computed tomography of her head was normal. Cerebrospinal fluid (CSF) was clear, with 0·46 g/L protein, 23 white cells/mm³ (80% lymphocytes), 39 red cells/mm³, normal glucose, lactate 24·9 mg/dL. Electroencephalogram (EEG) showed discontinuous pseudoperiodic paroxysmal discharges affecting mainly the left temporal lobe. It was considered that she may have had an epileptic seizure due to herpes simplex virus (HSV) encephalitis. Intravenous acyclovir (30 mg/kg daily) and oral valproate (600 mg daily) were given. Intravenous amoxicillin 6 g daily was also given to prevent infection of her head wound. Our confidence in the diagnosis of HSV encephalitis was reinforced by the results of magnetic resonance imaging (MRI) showing bilateral mesiotemporal lesions, predominant on the left side (figure) and by the demonstration of a left temporal focus of increased uptake on the Tc-99m HMPAO brain single-photon emission computed tomography (SPECT). Assay of CSF for HSV 1 and HSV 2 DNA by PCR was negative, which prompted us to consider an alternative diagnosis of lymphocytic meningoencephalitis. We looked for a rise in CSF antibody titre for HSV.

All tests were negative, with the exception of high serum *Treponema pallidum* haemagglutination test (1/40960) and fluorescent treponemal antibody (1/12800) titres. The diagnosis of neurosyphilis was strengthened by the demonstration of intrathecal production of antibodies against *T pallidum*. Penicillin G (20 million IU daily) was substituted for amoxicillin and given intravenously for 10 days. Before her discharge there was a marked improvement of memory, partial return to normal of CSF (protein 0·39 g/L, white cells 20/mm³ [lymphocytes 90%], red cells 10/mm³, normal glucose and lactate), resolution of EEG and SPECT anomalies, and regression of MRI lesions in T1-weighted sequences. When last seen in July 1999, she had resumed work.

HSV-like encephalitis is, an uncommon presentation of syphilis.[1] There was no case of syphilis in a series of 432 patients who underwent brain biopsy for presumptive HSV encephalitis between 1973 and 1988.[2] Conversely, in a

Lancet 1999; **354:** 1786

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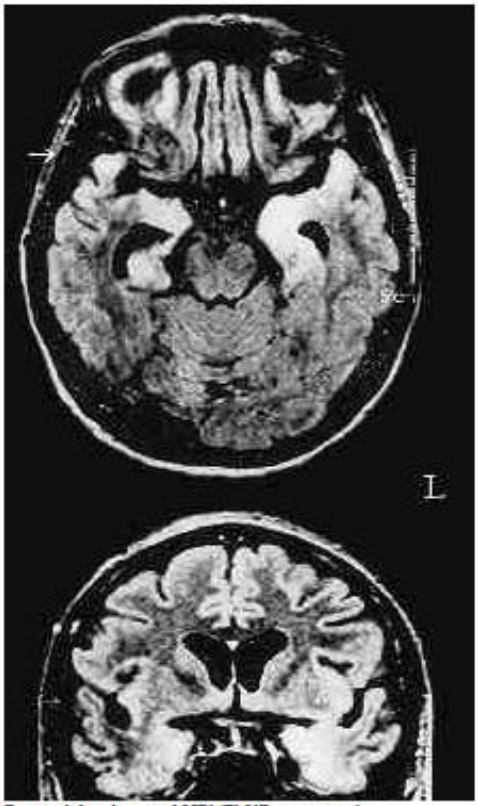


Transaxial and coronal MRI (FLAIR sequences)
There are asymmetrical, predominantly left denser signals in mesiotemporal areas.

MEDLINE search of the literature since 1970, we found only one patient with syphilis who presented with confusion, aphasia, and left mesiotemporal lesions on MRI suggesting HSV encephalitis.[3] In our patient, in addition to the EEG and MRI anomalies suggestive of HSV encephalitis, there was focal temporal increased uptake of Tc-99m HMPAO on SPECT, a finding which may be specific for HSV encephalitis.[4] In the preparalytic phase of neurosyphilis, frontal and temporal parenchymas are usually involved, producing impairment of intellect and memory, and causing personality changes.[5] Seizures may also occur. In the early stages, as suggested by the present case, adequate treatment may not only prevent further progression of the disease but also allow complete recovery. This case underlines the importance of considering the diagnosis of neurosyphilis in all patients with unexplained encephalitis.

References

1 Hooshmand H, Escobar MR, Kopf SW. Neurosyphilis. A study of 241 patients. *JAMA* 1972; **219:** 726–29.
2 Whitley RJ, Cobbs CG, Alford CA, et al. Diseases that mimic herpes simplex encephalitis. *JAMA* 1989; **262:** 234–39.
3 Angus F, Maysuria H, Bryan CS. Neurosyphilis mimicking herpes simplex encephalitis. *J S C Med Assoc* 1998; **94:** 315–17.
4 Launes J, Nikkinen P, Lindroth L, et al. Diagnosis of acute herpes simplex encephalitis by brain perfusion single photon emission computed tomography. *Lancet* 1988; **i:** 1188–91.
5 Bharucha NE, Bharucha EP. Infections of the nervous system. In: Bradley WG, et al. Neurology in clinical practice. Butterworth-Heinemann: Stoneham, 1992: 1049–131.

RC#13 – MURAKAMI, T. OGURA, E.W.; TANAKA, Y.; YAMAMOTO, M. High blood pressure lowered by pregnancy. **The Lancet**, v. 356, n. 9246, p. 1980, 2000.

Case report

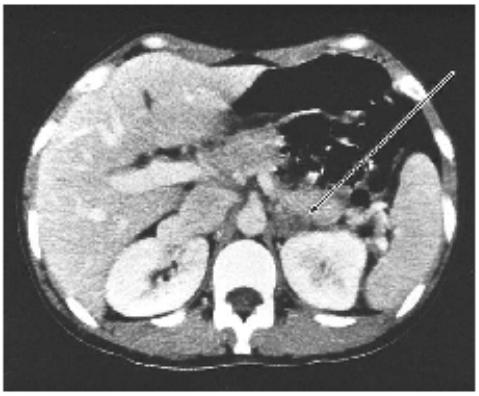
High blood pressure lowered by pregnancy

Takehiko Murakami, Eriko Watanabe Ogura, Yuji Tanaka, Michiko Yamamoto

A 30-year-old woman was referred to our department from a local hospital in June, 1999, for investigation of hypertension which had improved during pregnancy. Her hypertension was first noted shortly after the delivery of her first child in June, 1995. Since then she had had sustained hypertension (150–160/90–100 mm Hg by self-monitoring at home) until early 1997, when her blood pressure fell after she became pregnant for the second time. She was normotensive (110–130/70–80 mm Hg) throughout the pregnancy, as she had been with her first pregnancy. After the birth of her second child in November, 1997, her blood pressure rose again to around 160–100 mm Hg and she began to have carpal spasms and perioral numbness. In early 1999, headache and nocturia developed. She had had no investigations done in the past 4 years although she had consulted her general practitioner several times. Her postpartum hypertension and related symptoms had been attributed to the stresses of bringing up a baby. When seen in our department, her blood pressure was 178/106 mm Hg. Trousseau's sign was negative but carpal spasm was readily induced by hyperventilation.

There was hypokalaemia (2·3 mmol/L), suppressed renin activity (<0·1 μg/L/s), and raised plasma aldosterone concentration (1496 pmol/L; normal range, 100–665). Urine catecholamines, plasma corticotropin, cortisol, and calcium concentrations were all within the normal range. A diagnosis of primary aldosteronism was made and computed tomography showed a left adrenal tumour (figure). After laparoscopic resection of an aldosterone-producing adenoma (weighing 8 g) in August, 1999, she became normotensive, normokalaemic, and symptom-free, and had remained so when she was last seen in July, 2000.

Hypertension and pre-eclampsia is a well known complication of pregnancy. Non-obstetricians often have a misconception that blood pressure usually increases during pregnancy. Presumably, the doctors this patient had seen previously considered that she had no serious underlying diseases to cause hypertension based on the fact that her blood pressure had been normal throughout gestation. However, blood pressure tends to fall during pregnancy in both normotensive and chronically hypertensive women,[1,2] and pre-existing hypertension often gets worse after delivery. The history of this patient reminded us that we have to investigate the development of hypertension not only during pregnancy, but also in the puerperium. Pregnant women usually remain normotensive despite striking expansion of blood volume and activation of the renin-angiotensin-aldosterone system. This physiological adaptation is mediated through many mechanisms,



Contrast-enhanced computed tomogram. There is a heterogeneous, low-density tumour, about 2 cm diameter, in the left adrenal region (arrow).

including the antagonising action of progesterone on aldosterone and the peripheral vasodilatation caused by various vasorelaxation factors including prostaglandins. However, it is not well understood how blood pressure changes when patients with primary aldosteronism become pregnant. We found three reports of amelioration of hypertension during pregnancy,[3–5] whereas there were more reports of women presenting mid-gestation with severe hypertension. One possible explanation for the different clinical presentation is that pregnant women with primary aldosteronism remain normotensive when their plasma aldosterone concentrations are within the pregnancy range and excessive aldosterone action is antagonised by raised progesterone, as is the case with normotensive pregnant women. Hypertension might develop when their aldosterone concentrations exceed the normal pregnancy range, that is several-fold to ten-fold higher than the non-pregnant value,[1] even if various antihypertensive mechanisms are operating during pregnancy. Although this explanation needs to be tested in other patients, we speculate that significant amelioration of pre-existing hypertension during pregnancy, as seen in our patient, could be a characteristic of primary aldosteronism of mild to moderate severity.

Lancet 2000; **356**: 1980

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References

1 Wilson M, Morganti AA, Zervoudakis J, et al. Blood pressure, the renin-aldosterone system and sex steroids throughout normal pregnancy. *Am J Med* 1980; **68**: 104.
2 August P, Lenz T, Ales KL, et al. Longitudinal study of the renin-angiotensin-aldosterone system in hypertensive pregnant women: deviations related to the development of superimposed preeclampsia. *Am J Obstet Gynecol* 1990; **163**: 1612–21.
3 Biglieri EG, Slaton PE Jr. Pregnancy and primary aldosteronism. *J Clin Endocr* 1967; **27**: 1628–32.
4 Aoi W, Doi Y, Tasaki S, et al. Primary aldosteronism aggravated during peripartum period. *Jpn Heart J* 1978; **19**: 946–53.
5 Gordon RD, Tunny TJ. Aldosterone-producing adenoma (A-P-A): effect of pregnancy. *Clin Exp Hypertens* 1982; **4**: 1685–93.

RC#14 – CARBY, M.; SMITH, S.R. A hazard of paint spraying. **The Lancet**, v. 355, n. 9207, p. 896, 2000.

Case report

A hazard of paint spraying

Martin Carby, S Rolf Smith

A 42-year-old man was referred from his general practitioner in December, 1995. He smoked 15 cigarettes per day, had no other medical history and was on no medication. He complained of 4 weeks of dry cough, myalgia, sweats, and anorexia with about 6 kg of weight loss. In the 2 weeks before presentation his cough had become productive of white sputum and he had had increasing breathlessness. There had been no response to antibiotics.

On examination his temperature was 37·7 C, he was breathless at rest, centrally cyanosed, and had clubbed fingernails. His heart rate was 90 beats/min, he was normotensive, and heart sounds revealed a right ventricular gallop. Harsh, coarse, high pitched squeaks and fine crackles were present throughout both lung fields. Arterial blood gases showed a pO_2 of 5·3 kPa, a pCO_2 of 5·0 kPa, and oxygen saturations of 70% on air. Full blood count, creatinine, and electrolytes were normal. Spirometry showed an FEV$_1$ of 1·92 and an FVC of 2·33 (expected values of 3·63 and 4·42, respectively). Chest radiography showed extensive pulmonary infiltrates.

Rapidly progressive pulmonary fibrosis was diagnosed and he was started on 60 mg of prednisolone daily. Further questioning revealed that he worked as a paint sprayer. He wore a protective space suit at work but over recent weeks had noticed a rancid taste while wearing the suit. An examination of his sputum revealed alveolar macrophages containing fat droplets. An investigation at his work place found that an inlet for air pumped to the space suit was adjacent to a leaking oil mist generator. Oil mist was used as a lubricant in another part of the factory. Filters and condensation traps along the piped air supply were found to contain oil (figure). A diagnosis of lipoid pneumonitis due to accidental inhalation of mineral oil was made. He was discharged on oral prednisolone greatly improved.

One month later, breathlessness had improved and his chest signs had resolved. Spirometry had improved with an FEV$_1$ of 2·3 and an FVC of 2·7. He was informed that although he had made some recovery, he had a remaining respiratory deficit which was unlikely to resolve. He then made an inquiry regarding compensation for industrial injury through his union. The case was settled when he was promoted to a senior managerial position within the company.

Lancet 2000; 355: 896

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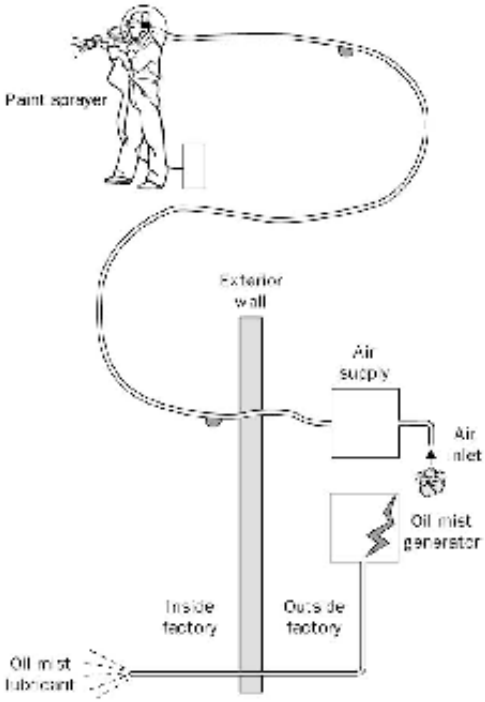

Diagram of workplace

Lipid inhalation is uncommon in the population at large but may be seen commonly within certain subgroups, especially those with impaired swallowing and recurrent aspiration. It occurs most frequently in the elderly using paraffin as oil-based nose drops or as a laxative[1] or children in whom mineral oil is often used to treat chronic constipation.[2] The oil is not irritating to the trachea, so is deposited in the lungs without stimulating a cough and without any immediate effects. Oil is usually fairly inert within the lungs, but it is difficult for the body to clear. Patients can present with a productive cough, low-grade fever, and breathlessness or be symptom free and present with coincidental findings on the chest radiograph.

Our patient was exposed to a particularly high concentration of inspired mineral oil droplets and presented with severe respiratory failure. He was wearing protective respiratory apparatus that was designed to prevent occupational lung disease associated with inhalation of isocyanate pain sprays. Ironically this was the means by which he was accidentally exposed to another toxic agent via the inhaled route.

References

1 Stern EJ. Chronic progressive, bibasilar infiltrates in a woman with constipation. *Chest* 1992; **102**: 263–65.

2 Hart PR. Lipoid pneumonia: a silent complication of mineral oil aspiration. *Paediatrics* 1999; **103**: E19.

RC#15 – de GANS, J.; van WESTRUM, S.S.; KUIJIPER, E.; SCHAAP, G.R. Earache and back pain. **The Lancet**, v. 355, n. 9202, p. 464, 2000.

Case report

Earache and back pain

J de Gans, S Schade van Westrum, E Kuijper, G R Schaap

A 53-year-old woman, a native of Surinam, was admitted in April, 1999, complaining of severe low back pain with radiation to her right lower leg. The pain started in January, 1999, while she was returning from a visit to Surinam. She had previously been well, apart from two episodes of ear pain in December, 1998, diagnosed as otitis media by her general practitioner. She received amoxicillin for 7 days and then co-amoxyclav for 7 days. Neurological examination elsewhere in January, 1999, showed an L5 root radiculopathy; a computed tomogram (CT) of the lumbar spine (figure, A) showed a soft-tissue mass at the L4–5 level on the right side. A diagnosis of lumbar disc herniation was made and she was given non-steroidal anti-inflammatory drugs and physiotherapy. However, her pain worsened and she became bedridden. When examined in April, 1999, she was in pain but otherwise appeared well. Her temperature was 37°C, but rose to 38·6°C 3 days later. Muscle strength was diminished in her right anterior tibial and extensor hallucis muscles. Sensation to pinprick was impaired on the dorsum of her right foot. Deep-tendon reflexes were decreased but equal in both legs. Straight-leg raising provoked severe back pain with radiation down her right leg. Investigations showed haemoglobin 55 g/L, leucocyte count $8{\cdot}4\times10^9$/L, and erythrocyte sedimentation rate (ESR) 136 mm/h. C-reactive protein (CRP) was 40 mg/L rising to 151 mg/L over the next 2 weeks.

A contrast magnetic resonance image (MRI) (figure, B), showed an L4–5 hypointense ring-enhancing lesion extending within the spinal canal on T_1-weighted images, suggesting an abscess. A bone scan (technetium-99m phosphate) showed increased radioisotope uptake at the L4–5 level. Cerebrospinal fluid (CSF) obtained by suboccipital puncture was normal and CSF cultures were sterile. Microscopic examination of a CT-guided needle biopsy specimen of the L4–5 mass showed no organisms and no malignant cells; stains for acid-fast bacteria and bacterial cultures were also negative. A second biopsy specimen yielded the same results on microscopy but after 3 days of incubation the culture grew *Fusobacterium varium*. Treatment with co-amoxyclav 1200 mg six times daily, was started. The strain subsequently produced

Lancet 2000; **355**: 464

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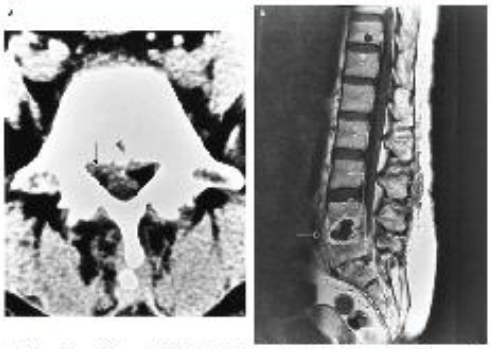

A: Disc herniation at L4–5 level on the right side (black arrow) on CT of lumbar spine. B: L4–5 hypointense ring-enhancing lesion on T_1-weighted MRI images

β-lactamase but was susceptible to co-amoxyclav, clindamycin, and metronidazole. ESR and CRP subsequently decreased. At surgery by an anterior approach necrotic tissue was removed and her spine stabilised with bone from her iliac spine. Culture of the specimen obtained at operation yielded no growth. The patient received antibiotic therapy for 8 weeks. Both her back pain and leg weakness improved. The presumed source of infection was the preceding otitis media in December, 1998. When last seen in September, 1999, she was well.

Pyogenic spondylodiscitis is uncommon, especially in previously healthy people. Causative micro-organisms are usually *Staphylococcus aureus* or aerobic gram-negative bacteria.[1] Anaerobic spinal infections are even more rare, accounting for only 5% of all non-postoperative cases of spondylodiscitis.[2] The predominant anaerobic pathogens are *Bacteroides* spp. Vertebral osteomyelitis usually presents with increasing back pain, occasionally with root compression; systemic signs of acute infection are often absent.[2] MRI is the most useful diagnostic tool.[3] Diagnosis needs to be confirmed by isolation of the micro-organism from biopsy specimens. As in our patient, there is often delay in establishing the diagnosis.[1] A search of Current Contents, MEDLINE, and Embase found no other reports of spondylodiscitis caused by *Fusobacterium varium*, although other *Fusobacterium* species have been reported including *F necrophorum*, the causative agent of Lemierre's syndrome.[4]

We thank M H Godfried and F J H Huismans for helpful discussions and contributions to diagnosis.

References

1 Jiménez-Mejías ME, de Dios Colmenero J, Sánchez-Lora FJ, et al. Postoperative spondylodiscitis: etiology, clinical findings, prognosis, and comparison with nonoperative pyogenic spondylodiscitis. *Clin Infect Dis* 1992; 29: 339–45.

2 Torda AJ, Gottlieb T, Bradbury R. Pyogenic vertebral osteomyelitis: analysis of 20 cases and review. *Clin Infect Dis* 1995; 20: 320–28.

3 Frank AM, Trappe AE. The role of magnetic resonance imaging (MRI) in the diagnosis of spondylodiscitis. *Neurosurg Rev* 1990; 13: 279–83.

4 Bytyn SJ. Necrobacillosis. *Scand J Infect Dis* 1989; suppl 62: 41–46.

RC#16 – VEGA, M.; RIVERO, J.C.; RUÍZ, L.; SUÁREZ, S. A fish bone in the liver. **The Lancet**, v. 358, n. 9286, p. 982, 2001.

Case report

A fish bone in the liver

María de la Vega, José Carlos Rivero, Luis Ruíz, Saturnino Suárez

An 86-year-old woman presented in May, 1999, with abdominal pain, nausea, and vomiting. She had a history of hypertension, diabetes, chronic obstructive pulmonary disease, spondyloarthropathy, and dementia. She had just finished a 15 day course of cefuroxime and fluconazole, prescribed for recurrent urinary tract infections. On examination, she was febrile and tachycardic. Her abdomen was soft and tender to palpation, and there were no signs of peritoneal irritation. She was hyperglycaemic (11·9 mmol/L) and had raised creatinine (128 µmol/L) and leucocytosis. Urine dipstick was positive for blood and leukocytes. Plain chest and abdominal radiographs showed no abnormalities other than those consistent with chronic obstructive pulmonary disease and spondlyoarthritis, and were unchanged from films obtained 10 years previously. We diagnosed sepsis, secondary to urinary tract infection. A few hours later, the patient deteriorated and died.

At necropsy, there was no pus in the peritoneal cavity, but the liver was large (2120 g), with a smooth surface. A multiloculated abscess (13×8×8 cm) was found in the right lobe (figure 1). We extracted a slightly curved and vitreous foreign body of about 2·5 cm in length, from the abscess cavity (figure 2). The structure was macroscopically and microscopically compatible with a fish bone. After sectioning the liver we could see that the abscess had not breached the hepatic capsule. As the patient had no record of abdominal surgery, biliary catherisation or trauma, we had to consider a gastrointestinal source. We thoroughly examined the oesophagus, stomach, and bowel, but could find no evidence of perforation. Microscopically, the liver showed moderate steatosis, and the stomach showed atrophic gastritis with intestinal metaplasia.

People frequently swallow foreign bodies and these usually pass through the gastrointestinal tract without complications. However, intestinal perforations or abscesses can occur. The first case of hepatic abscess as a result of a gastrointestinal perforation caused by foreign body was published by Lambert in 1898.[1] Symptoms are usually due to obstruction or perforation which can be complicated by peritonitis or abscesses. Frequently, patients do not remember swallowing the foreign body and signs may appear months or even years later.[2,3] The cause of the symptoms can be impossible to determine even with meticulous clinical and radiological evaluations. The classic presentation of hepatic abscesses; fever, abdominal pain, and jaundice, appears in a small number of patients, and is almost always associated with cholangitis. Most patients have non-specific symptoms such as anorexia, vomiting, or

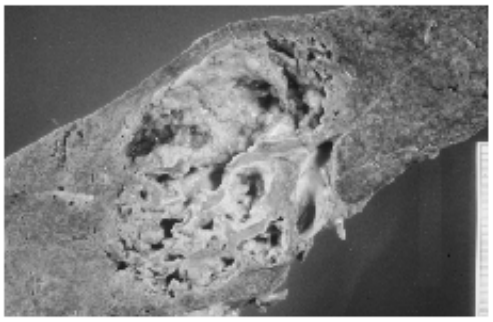

Figure 1: **Hepatic abscess**

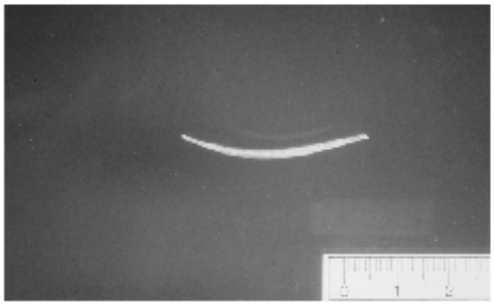

Figure 2: **Fish bone extracted from the abscess**

weight loss, with leukocytosis, or increased transaminases, bilirubin or alkaline phosphatase. Our patient had moderate leukocytosis, but we did not measure liver function or have time to do abdominal ultrasonography. Radiography may not detect intrabdominal abcesses, but ultrasonography and computed tomography have good sensitivity and specificity.[4,5] This case is a good reminder that intraparenchymal abscesses should be included in the differential diagnosis of sepsis, and that these may have been caused by long-forgotten difficulties with a fish dinner.

Lancet 2001; **358:** 982

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References

1 Lambert A. Abscess of the liver of unusual origin. *NY Med J* 1898; February: 177–78.
2 Dugger K, Leby T, Brus M, Sahgal S, Lefkin JB. Hepatic abcess resulting from gastric perforation of a foreing object. *Am J Emerg Med* 1990; 8: 323–25.
3 Bloom RR, Nakano PH, Gray SW, et al. Foreign bodies of the gastrointestinal tract. *Am Surg* 1986; 52: 618–21.
4 Broome CJ, Peck RJ. Hepatic abscess complicating foreign body perforation of the gastric antrum: an ultrasound diagnosis. *Clin Radiol* 2000; 55: 242–43.
5 Horii K, Yamazaki O, Matsuyama M, Higaki I, Kawai S, Sakane Y. Successful treatment of a hepatic abscess that formed secondary to fish bone penetration by percutaneous transhepatic removal of the foreign body: report of a case. *Surg Today* 1999; 29: 922–26

RC#17 – WATKINS, E.J.; BROOKSBY, P.; SCHWEIGER, M.S.; ENRIGHT, S.M. Septicaemia in a pig-farm worker. **The Lancet**, v. 357, n. 9249, p. 38, 2001.

CASE REPORT

Case report

Septicaemia in a pig-farm worker

E J Watkins, P Brooksby, M S Schweiger, S M Enright

A 30-year-old pig-farm worker, presented in August, 1999, with a 16 h history of general malaise, fever, shortness of breath, and headache. Earlier that day his primary care practitioner had visited him at home and prescribed amoxycillin for a presumed chest infection. He had had a splenectomy after trauma 3 years previously. On admission he was feverish and drowsy with no signs of meningism. He was hypotensive, tachycardic, hypoxic, and oliguric with a symmetrical purpuric rash on his feet which rapidly became generalised over his limbs and torso. He had a minor abrasion on his foot. He had a metabolic acidosis, disseminated intravascular coagulopathy, and acute renal failure (urea 12·6 mmol/L, creatinine 311 μmol/L). A diagnosis of severe sepsis with shock, multiple organ failure, and associated purpura fulminans was made. He was treated with intravenous cefotaxime 2 g, benzylpenicillin 1·2 g, and aggressive fluid resuscitation, but required increasing intotropic support. He developed acute respiratory distress syndrome that rapidly deteriorated despite ventilatory support and nebulised prostacyclin. His oliguria persisted despite dopexamine, a bumetanide infusion, and mannitol. Refractory shock and irreversible hypoxaemia led to his death 12 h after admission. *Streptococcus suis* type 14 was cultured subsequently from blood.

He had been employed at the pig farm for 3 weeks before his death. His main occupation was painting the outside of the pig sheds, and once a week he pressure-hosed the weaning pens. An outbreak of lameness amongst the pigs at his place of work was being investigated by veterinary surgeons and *S suis* type 14 was identified as the cause in these animals. He had an abrasion on his foot and it is possible contaminated water had soaked into his boot. Alternative possibilities are either inhalation of contaminated water spray or transfer of bacteria from his hands to his mouth as he smoked cigarettes during his rest periods.

S suis is a Gram positive, catalase negative, encapsulated coccus that causes a wide range of clinical disease syndromes in pigs and other domestic animals. It occurs mainly in Northern Europe and Southeast Asia. Little is known about the pathogenesis of *S suis* infection in human beings, but the entry site is probably most commonly a minor occupational wound.[1] *S suis* infections in human beings were reviewed in 1988 by Arends and Zanen.[1] Many serotypes of *S suis* have been identified. Type 2 causes most human infections, almost exclusively in people exposed to pigs or unprocessed pig meat.[2] It usually causes purulent meningitis[3] and is the commonest cause of bacterial meningitis in Hong Kong. Septic shock is a rare complication but is commonly fulminant and fatal. *S suis* type 14 has been reported in one human being previously, and we believe that our case is the first reported isolation of this serotype from a human being in the UK.[1,4] Purpura fulminans has been associated with *S suis* in only one reported case previously, and this was with the more commonly pathogenic serotype 2.[3] Serious infections, frequently with encapsulated bacteria (*S pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*), are more common within 5 years of splenectomy and especially during the first year. UK Department of Health guidelines *Information about splenectomy for patients* (May, 1999) recommended several prophylactic measures against infection. They advise prophylactic antibiotics after splenectomy as "essential in the first few years . . . and for children up to the age of 16 years". No prophylactic regimen can be totally effective but the sensitivity of this *S suis* isolate to penicillin suggests that penicillin prophylaxis would have been effective. *S suis* infection is an important occupational disease in humans. People in daily contact with pigs or pig meat should use protective gloves and work practices in the meat and farming industries should keep skin trauma to a minimum.[5] We suggest that people without a spleen should be advised not to work with pigs or in the meat trade and that pig farmers should be advised not to employ such people.

We thank J Haynes for comments.

Lancet 2001; **357:** 38

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References

1 Arends JP, Zanen HC. Meningitis caused by *Streptococcus suis* in humans. *Rev Infect Dis* 1988; **10:** 131–17.
2 Robertson ID, Blackmore DK. Occupational exposure to *Streptococcus suis* type 2. *Epidemiol Infect* 1989; **101:** 1102–05.
3 Tanbyah PA, Kumarasinghe G, Chan HL, Lee KO. *Streptococcus suis* infections complicated by purpura fulminans and rhabdomyolysis: case report and review. *Clin Infect Dis* 1997; **24:** 710–12.
4 Gottschalk M, Higgins R, Jacques M, Mittal KR, Henrichsen J. Description of 14 new capsular types of *Streptococcus suis*. *J Clin Microbiol* 1989; **27:** 2633–36.
5 Clarke D, Almeyda J, Ramsay I, Drabu YJ. Primary prevention of *Streptococcus suis* meningitis. *Lancet* 1991; **338:** 1147–48.

RC#18 – SPRINGER,J.; CHOLLET, A. A traumatic car crash. **The Lancet**, v. 357, n. 9271, p. 1848, 2001.

Case report

A traumatic car crash

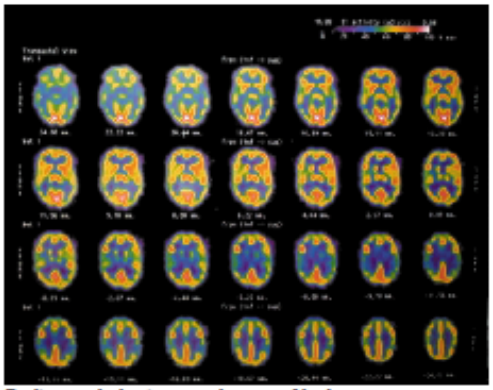
Jackie Springer, Annette Chollet,

A healthy 47-year-old man sustained head and multiple skeletal injuries in a motor vehicle accident in January, 1998. The patient's car was struck three times. In the emergency room, the patient was treated for lumbar, rib, and sternum fractures. Neurological examination was normal. The patient did not recall losing consciousness and had no complaints of double or blurred vision.

2 months after the accident, the patient and his family noticed severe cognitive impairment characterised by his inability to process simple information. He complained of severe headaches and decreased peripheral vision. He was examined neurologically 8 months after the accident. A positron emission tomography (PET) scan showed right versus left cortical asymmetry with large areas of hypometabolism in the right frontal lobe (figure). In a neuropsychological examination, the patient scored in the borderline or extremely low range in all of nine psychological tests. These included the Derogatis Symptom Checklist, Grooved Pegboard Test; Trail Making Tests A & B, Digit Vigilance Test, Ammons Quick Test, Hooper Visual Organization Test, Wechsler Memory Scale-III (partial), Wechsler Adult Intelligence Scale-III, and the Wide Range Achievement Test-Rev. Post-traumatic dementia was diagnosed.

The patient was referred to our office 2 years after his accident for an endocrinology consultation. He had a flat affect and physical examination showed a complete absence of all body hair except for the scalp. He had difficulty with his memory and all information had to be repeated several times. A stimulation test for human growth hormone showed peak growth hormone concentration was less than 0·5 mIU/L (normal greater than 9·0).[1] Testosterone concentration was 10·6 nmol/L (normal range 10–35) and cortisol concentrations were 176·6 nmol/L in the morning (140–690) and 46·9nmol/L in the afternoon (80–330). IGFBP-3 was 1800 ng/L (2000–4000). The patient started initial treatment with testosterone, cortisol, and thyroxine. As early as 2 weeks following initiation of recombinant human growth hormone, the patient's family reported an improvement in his affect and his cognitive abilities. When last seen in March, 2001, his cognitive abilities had improved further.

Pituitary failure is rarely considered in patients involved in motor-vehicle accidents. The Center for Disease Control estimates that each year approximately 80 000 Americans sustain head injury and are left with a related disability.[2] A recent survey reported only 367 cases of hypopituitarism due to head trauma of differing causes.[3] Another study estimated that hypopituitarism occurs in 40% of patients with moderate or severe head injury, with growth hormone and gonadotropin deficiencies being most common.[4] Our case demonstrates the importance of investigating the endocrine status of trauma patients with or without head injuries. If serum testing is limited only to pituitary hormones, pituitary failure may be missed. In the presence of pituitary failure, the serum levels of pituitary hormones will appear normal, as the pituitary is unable to respond to low end organ hormone production. It is important to investigate patients with possible pituitary failure with with other tests such as Insulin-like Growth Factor (IGF-1) or a growth hormone stimulation test. Current therapies including rehabilitation are costly and often do not completely mitigate the negative effects of a traumatic brain injury.[2,5] Physicians most often in a position to recognise and refer head-injured and trauma patients for endocrinological investigation include emergency care specialists, family practitioners, internists, geriatricians, neurologists, and psychiatrists. In view of the 5·3 million Americans currently living with a traumatic brain injury related disability,[2] neuroendocrine hormone replacement therapy is an area of endocrinology that clearly warrants additional research.



Positron emission tomography scan of brain

Lancet 2001; **357**: 1848

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We thank Richardson K Noback for critical review and helpful comments on the manuscript and S Mehr for interpretation of the PET scan.

References

1 Growth Hormone Task Force. The American Association of Clinical Endocrinologists. AACE Clinical Practice Guidelines for Growth Hormone Use in Adults and Children. 1998. http://www.aace.com/clin/guides/ghg/lab-diag.htm, (accessed Dec 2, 2000).
2 Centers for Disease Control and Prevention. Epidemiology of Traumatic Brain Injury in the United States. 1996–1997. http://www.cdc.gov/ncipc/dacrrdp/tbi.htm (accessed Dec 2, 2000).
3 Benvenga S, Campenni A, Ruggeri R, et al. Hypopituitarism secondary to head trauma. *J Clin Endocrinol and Metab* 2000; 85: 1353–61.
4 Kelly DF, Gonzalo IT, Cohan P, Berman N, Swerdloff R, Wang CI. Hypopituitarism following traumatic brain injury and aneurismal subarachnoid hemorrhage: a preliminary report. *J Neurosurg* 2000; 93: 743–52.
5 Salazar A, Warden DL, Schwab K, et al. Cognitive rehabilitation for traumatic brain injury: A Randomized Trial. *JAMA* 2000; 283: 3075–81.

RC#19 – HARITOGLOU, C.; DOTSE, S.D.; RUDOLPH, G.; STEPHAN, C.M.; THURAU, S.R.; KLAUSS, V. A tourist with dengue fever and visual loss. **The Lancet**, v. 360, n. 9339, p. 1070, 2002.

Case report

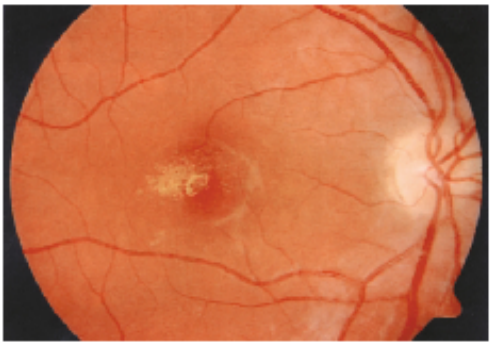
A tourist with dengue fever and visual loss

Christos Haritoglou, Sarah D Dotse, Günther Rudolph, C M Stephan, S R Thurau, Volker Klauß

A 25-year-old woman was in holiday in Thailand in April, 2002. 2 days before her planned return flight to Germany, she developed a high fever, aching muscles, and decreased visual acuity. She did not seek medical care in Thailand, but upon arriving in Germany, she was immediately seen by a general physician who referred her to the Department of Tropical Diseases. 3 days after onset of symptoms, we examined her and found that she was still febrile, and had maculopapulous exanthema of the limbs, hepato-splenomegaly, thrombocytopenia (69 000/µL) and elevated liver enzymes (GOT 146 U/L, GPT 118 U/L, gamma GT 80 U/L). We suspected that she had contracted dengue fever, and measured serum titres of specific IgM antibodies. IgM 1:640. On ophthalmological examination, we found that her visual acuity was reduced to 20/500 bilaterally. Electrophysiological examination showed prolonged latencies (138 and 128 msec) and reduced amplitudes (4 microV) of visually evoked cortical responses and a mild, bilateral reduction of amplitudes in the multifocal electroretinogram. The Arden Color Contrast Test showed that her colour vision was severely affected.

We examined the fundus and observed bilateral exudative maculopathy and small haemorrhages located in the nerve fibre layer. We decided not to give any treatment at this stage. The patient was followed in 2-week intervals. At the first follow-up visit, she presented in a better physical condition, with marked regression of her generalised symptoms. Visual acuity remained at the level of 20/250 in both eyes. 8 weeks after initial presentation, when last seen in June, 2002, visual acuity had increased to 20/100 in the right and 20/32 in the left eye without treatment. The reduction in the right eye was due to intraretinal lipid deposits as a sequale of exudation observed initially (figure).

Dengue fever is a viral disease transmitted by *Aedes aegypti* mosquitos. It is endemic in the Americas, southeast Asia, western Pacific, Africa, and the eastern Mediterranean. The disease is divided into four stages: stage 1 dengue fever is characterised by high fever, headache, vomiting, myalgia, arthralgia, retro-orbital pain, maculopapular rash, and thrombocytopenia; bleeding complications such as epistaxis, gingival bleeding, gastrointestinal bleeding, and haematuria can develop in stages 2 to 3.[1] Patients who have stage 4 dengue fever, (also known as dengue shock syndrome) present with a rapid and weak pulse, narrow pulse pressure or hypotension, cold clammy skin, and altered mental status.[1] Tourists are



6 weeks after initial presentation, intraretinal lipid deposits were present in the macula

seldom effected by dengue fever,[2,3] although it is a major endemic disease, affecting millions of people worldwide. Ocular manifestations of dengue fever in tourists have been described.[4,5] The opthalmological findings mainly included retinal haemorrhages as a sign of increased vascular permeability and breakdown of the inner blood retinal barrier and cotton-wool spots representing microinfarctions of the nerve fibre layer due to occlusion of precapillary arterioles. Hypoperfusion is also confirmed by delayed choroidal filling during fluorescein angiography. In our patient, the results of the electrophysiological evaluation as well as colour vision impairment are consistent with optic neuritis as a symptom of central nervous system involvement. There is no specific antiviral treatment or commercially available vaccine. Generally, dengue fever has a favourable prognosis.[1] Usually, the ocular alterations resolve without specific treatment within a short period of time.[4] In cases with severe exudative maculopathy, visual recovery may be prolonged or patients may remain visually impaired, as described in this report. The only empirical treatment option is the systemic application of steroids, which is contraindicated during viraemia. Although dengue fever and its ocular manifestation is a rare condition among the European populations, we will be increasingly confronted with this tropical disease, as a consequence of growing tourism in endemic regions.

Lancet 2002; **360**: 1070

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References

1 Guzman MG, Kouri G. Dengue: an update. *Lancet Infect Dis* 2001; 2: 33–42.
2 Schwartz TF, Jager G, Gilch S. Imported dengue virus infections in German tourists. *Zentralbl Bakteriol* 1995; 282: 333–36.
3 Jelinek T, Dobler G, Holscher M, Loscher T, Nothdurft HD. Prevalence of infections with dengue virus among international travelers. *Arch Intern Med* 1997; 157: 2367–70.
4 Haritoglou C, Scholz F, Bialasiewicz A, Klauß V. Okuläre Manifestation bei Dengue-Fieber. *Ophthalmologe* 2000; 97: 433–36.
5 Spitznas M. Makulablutung bei Dengue-Fieber. *Klin Mbl Augenheilkd* 1978; 172: 105–07.

RC#20 – VIETH, R.; PINTO, T.R.; REEN, B.S.; WONG, M.M. Vitamin D poisoning by table sugar. **The Lancet**, v. 359, n. 9307, p. 672, 2002.

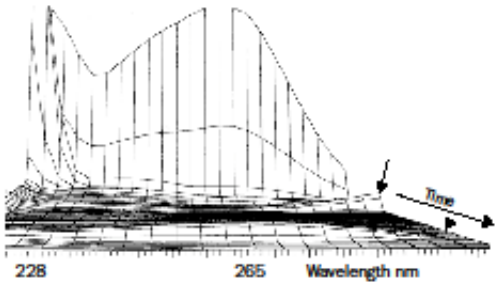
Case report

Vitamin D poisoning by table sugar

Reinhold Vieth, Tanya R Pinto, Bajinder S Reen, Min M Wong

In June 1999, a 29-year-old man came to the emergency department with right-sided flank pain, conjunctivitis, anorexia, fever, chills, increased thirst, and vomiting. He had lost 5 kg in weight, and was in acute renal failure. He was treated with steroids and discharged. In October, 1999, his 63-year-old father came to the emergency department with similar complaints. He was also in acute renal failure and denied a history of renal stones. His serum creatinine was 442 µmol/L (NR, 60–120 µmol/L); calcium, 3·82 mmol/L (2·20–2·65 mmol/L), PTH <1 pmol/L (1·3–7·6 pmol/L); 25-hydroxyvitamin D [25(OH)D], 1555 nmol/L (20–80 nmol/L) and serum 1,25(OH)$_2$D, 131 pmol/L (30–140 pmol/L). More complete biochemical testing on the son in October, 1999, showed the same biochemical profile. Kidney biopsies of both patients showed severe nephrocalcinosis. The similarities initially suggested a genetic abnormality, or a granulomatous disease, but the 25(OH)D results showed severe vitamin D intoxication. The patients continued to be treated with prednisone. Both denied taking any nutritional supplements. In December, 1999, the son was readmitted with extreme pain, nausea, and dehydration. Serum 1,25(OH)$_2$D was 266 pmol/L; calcium, 4·39 mmol/L. The serum 25(OH)D was now 3700 nmol/L by radioimmunoassay, but chromatography revealed a huge excess of vitamin D3 (figure 1). The patient was given intravenous hydrocortisone, sodium phosphate, and pamidronic acid.

We tested various foods from the household, including white table sugar sampled in December, 1999, after the son fell sick from drinking sweetened tea. One gram of sugar contained 21·4 mg vitamin D3, measured after extraction into ethanol. When the sugar was dissolved in water, the distinctive, long, white crystals of vitamin D3 floated up when centrifuged, and we did high performance liquid chromatography which confirmed their composition. A second sugar sample in January, 2000, contained 3·2 mg of vitamin D per gram of sugar. Assuming an average of 12·6 mg vitamin D3 per gram of sugar, and a conservative usage of 100 g sugar per month, the patient and his father had consumed more than 1·3 g of vitamin D3 per month, or 42 000 µg/day (1 700 000 IU/day), in vast excess of the minimal toxic level (95 µg, 3800 IU per day),[1] for 7 months. This isolated incident was caused either by the intentional or accidental mixing of crystalline vitamin D3 into the table sugar of this family. When last seen, in April, 2001, the son's serum 25(OH)D was 250 nmol/L; creatinine, 125 mmol/L. The father was last seen in June, 2001, his serum 25(OH)D was 181 nmol/L; creatinine, 179 µmol/L. Both had no symptoms, and continued to take prednisolone.



Absorption spectra characteristic of vitamin D3
(17 000 nmol/L), at 3 min (arrow); 25(OH)D3 (2400 nmol/L), at 8 min (arrowhead), eluted with hexane/isopropanol from a silica high performance liquid chromatography column.

These patients initially posed a diagnostic challenge which highlights the need to consider poisoning as part of the differential diagnosis in metabolic disorders, especially if more than one family member is affected. Fortunately, the poison and its source were identified. All known poisonings of adults with vitamin D3 reflect misuse on an industrial scale. Huge excesses of vitamin D3 have been added in error to milk,[2] or to a food supplement.[3] There are two reports of households where industrial concentrates of vitamin D3 were mistaken for cooking oil.[4,5] In contrast, all reports of iatrogenic vitamin D intoxication of adults have involved vitamin D2, a synthetic analogue of the physiological compound, vitamin D3.[5] Our cases offer a perspective into the risks, management and prognosis of the worst possible form of vitamin D3 toxicity.

Lancet 2002; **359:** 672

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References

1 Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D(3) intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr* 2001; 73: 288-94.
2 Blank S, Scanlon KS, Sinks TH, Lett S, Falk H. An outbreak of hypervitaminosis D associated with the overfortification of milk from a home-delivery dairy. *Am J Public Health* 1995; 85: 656-59.
3 Koutkia P, Chen TC, Holick MF. Vitamin D intoxication associated with an over-the-counter supplement. *NEJM* 2001; 345: 66-7.
4 Down PF, Polak A, Regan RJ. A family with massive acute vitamin D intoxication. *Postgrad Med J* 1979; 55: 897–902.
5 Pettifor JM, Bikle DD, Cavaleros M, Zachen D, Kamdar MC, Ross FP. Serum levels of free 1,25-dihydroxyvitamin D in vitamin D toxicity. *Ann Int Med* 1995; 122: 511–13.

RC#21 – AFZAL, N.A.; ALBERT, D; THOMAS, A.L.; THOMSON, M. A child with oesophageal strictures. **The Lancet**, v. 359, n. 9311, p. 1032, 2002.

CASE REPORT

Case report

A child with oesophageal strictures

Nadeem Ahmad Afzal, David Albert, Adrian Lloyd Thomas, Mike Thomson

An 18-month-old girl was brought to the hospital in August, 2000, after accidentally swallowing some caustic soda. She was in discomfort, and had burns around the mouth and tongue, but no haematemesis or dysphagia. She was observed for 6 h and then discharged as her discomfort had resolved, with no treatment. 1 month later she was regurgitating lumpy food, although she tolerated pureed food, yoghurt, and liquids. An upper gastrointestinal endoscopy and barium swallow showed a 1 mm stricture, 3–5 mm in length, 3 cm distal to the tracheo-oesophageal bifurcation (figure A). We dilated the stricture to 12 mm with a balloon dilator expanded with water to 35 psi, for 2 min twice, separated by 1 min deflation. We were then able to pass a neonatal endoscope (Olympus GIF N30, diameter 5·2 mm), and found a second stricture, 3 mm in diameter, and 1·5 cm in length, located 8 cm from the tracheo-oesophageal bifurcation (figure B). We dilated this stricture to 12 mm using the same technique, and gave the child fluticasone propionate 100 ug twice daily by metered dose inhaler. Her dysphagia for solid foods resolved temporarily, but she needed a second dilatation 5 days later. This time we injected dexamethasone (1 mg, four times) circumferentially into the stricture. Recurrent dysphagia for solids and drooling necessitated weekly dilatations on a further 14 occasions; the size of the balloon progressively increased to 18 mm with 35 psi for 2–7 min.

As the proximal stricture was so close to the tracheo-oesophageal bifurcation, we did not think that surgical stent placement was feasible. We discussed the possibility of using topical mitomycin C with the child's parents, as it had been shown to be useful in tracheal stenosis. They gave their consent. We gave the child general anaesthesia, dilated the stricture again, and applied mitomycin C topically by a cotton pledget soaked in solution (0·1 mg/mL). We held the pledget in a pair of forceps under endoscopic vision for 2 min at the stricture, and repeated the procedure 1 week later. She needed only one additional endoscopic dilatation. 3 months after applying mitomycin, it was possible to pass a paediatric endoscope (Fujinon EG 410PE, 8·4 mm diameter) without dilatation. We saw little residual stenosis, and oesophageal manometery and motility tests were normal. When last seen in March, 2002, she had no symptoms and was growing well.

Lancet 2002; **359:** 1032

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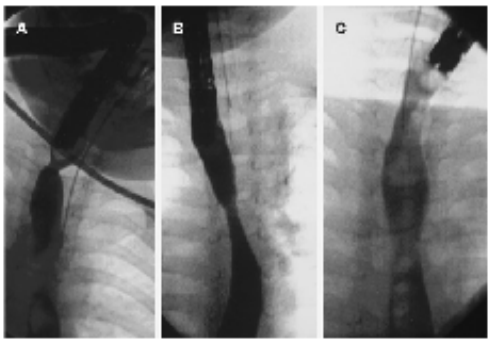

Fluoroscopy of proximal (A) and distal (B) oesophageal strictures before, and 3 months after (C) treatment with topical mitomycin C

Children under 5 years of age often accidentally swallow cleaning chemicals, which can cause deep circumferential burns of the oesophagus. Endoscopic dilatation of oesophageal scarring and stenosis may have to be repeated many times,[2] and has a success rate of 41–100% depending on the number and extent of stenoses.[4] Mitomycin C, an anthracycline derived from streptomyces, has been successfully used as an anti-fibrotic agent to prevent scar formation when treating childhood glaucoma, lachrymal duct and tracheal stenosis.[4] It interferes with the G2 stage of RNA synthesis, inhibiting fibroblast proliferation. Topical application at the concentration we used (0·1 mg/mL) has been used with no complications after 18 months' follow-up,[4,5] but adverse effects have been reported with high-dose long-term topical use. Mitomycin C may be a useful adjunct to endoscopic dilatation in the gastrointestinal tract, potentially preventing the need for future surgery.

References

1 Anderson KD, Rouse TM, Randolph JG. A controlled trial of corticosteroids in children with corrosive injury of the oesophagus. *NEJM* 1990; **323:** 637–40.
2 Broto J, Asensio M, Jorro CS, et al. Conservative treatment of caustic esophageal injuries in children: 20 years of experience. *Ped Surg Int* 1999; **15:** 323–35.
3 Panieri E, Rode H, Millar AJ, Cywes S. Oesophageal replacement in the management of corrosive strictures: when is surgery indicated? *Ped Surg Int* 1998; **13:** 336–40.
4 Ward RF, Apfil MM. Mitomycin C in the treatment of tracheal cicatrix after tracheal reconstruction. *Int J Pediatr Otorhinolaryngol* 1998; **44:** 221–26.
5 Rahbar R, Shapshay SM, Healy GB. Mitomycin: effects on laryngeal and tracheal stenosis; benefits and complications. *Ann Otol Rhinol Laryngol* 2201; **110:** 1–6.

RC#22 – SANDER, H.W.; MAGDA, P.; CHIN, R.L.C.; WU, A.; BRANNAGAN III, T.H.; GREEN, P.H.R.; LATOV, N. Cerebellar ataxia and coeliac disease. **The Lancet**, v. 362, n. 9395, p. 1548, 2003.

CASE REPORT

Case report

Cerebellar ataxia and coeliac disease

Howard W Sander, Paul Magda, Russell L Chin, Anita Wu, Thomas H Brannagan III, Peter H R Green, Norman Latov

A 37-year-old woman presented in July, 2002, with a 12-year history of progressive dysarthria and ataxia. Her symptoms became noticeably worse during pregnancy in 1999 and 2001. She had also been anaemic for the past 7 years, and coeliac disease had been diagnosed in 1997. At that time, she had high serum concentrations of IgG and IgA antibodies to gliadin, an endomysial titre of 1:32, and duodenal atrophy on endoscopy; a duodenal biopsy showed subtotal villous atrophy. Neurological tests were done at the same time; median somatosensory evoked potentials showed a delay between the lower brainstem and cortex. She underwent tests for spinocerebellar ataxia,[1–3] brainstem auditory and visual evoked potentials, and cerebral MRI, none of which showed any abnormalites. Cervical spine MRI showed mild degenerative changes. For 5 years, she had followed a strict gluten-free diet, but on examination in 2002 she had severe dysarthria, left finger-to-nose dysmetria, poor right rapid-alternating and fine-finger movements, diminished pedal pin-perception, ankle areflexia, and a severely ataxic, wide-based gait. A modified (without Archimedes Spiral) International Cooperative Ataxia Rating scale (ICARS) score was 31/96.[4] We did many serological tests for autoimmune disease including IgG and IgA antibodies to gliadin, purkinje cells, and voltage-gated calcium channels. The only abnormal results were increased IgA antibodies to transglutaminase, and glutamic acid decarboxylase (GAD). Cerebral MRI showed superior vermis atrophy, whereas lumbosacral MRI was normal. Sensory nerve conduction amplitudes were low. H reflexes were absent. Electromyography showed prolonged durations of motor unit potentials distally. We did not do a nerve biopsy, and we do not have the facilities to do indirect immunohistochemistry or immunofluoresence.

We treated her with intravenous immunoglobulin (IVIg) 2 g/kg initially, and 0.5 g/kg 2 weeks later. Within a month, she reported substantial improvements in her speech and gait. She was able to safely hold her children. Acquaintances noted that the audible slap of her walk disappeared. Squatting, walking, stair-climbing, tandem gait, and standing on one leg all became much easier, and she no longer spilt cups of liquid. On examinaton, we found that all the neurological signs had improved; she still had slight dysarthria and left finger-nose dysmetria, an unsteady gait with a widened base and very slight slapping, and impaired tandem walking, and we calcuated a modified ICARS score of 3/96. She developed a slight rash, so we stopped IVIg and gave her a single dose of methylprednisolone. However, 5 weeks later, she deteriorated, and 8 weeks after the last IVIg infusion, her modified ICARS score had worsened to 17/96. We changed to another brand of IVIg and again started with 2 g/kg after hydrocortisone pretreatment. 3 weeks later, she was much improved, with a modified ICARS score of 3/96. When last seen in September, 2003, she had been stable for 6 months, on maintenance doses of IVIg, 0·5 g/kg/month.

Coeliac disease occurs in approximately 9% of patients with idiopathic cerebellar ataxia. Patients can present with ataxia of limb, station, and gait, and/or dysarthria, oculomotor, sensory, or bladder dysfunction.[1] The ataxia occasionally improves after a prolonged gluten-free diet.[2] Ataxic patients also have a higher incidence of gluten-sensitivity, defined as the presence of antibodies to gliadin or transglutaminase in the absence of histological evidence of coeliac disease.[1] IVIg has had a beneficial effect in patients with sporadic cerebellar ataxia, in the context of GAD antibodies,[3] and gluten sensitivity,[5] but has not yet been shown to work for the combination of ataxia and coeliac disease. It would be interesting to test plasmapheresis or corticosteroids, as an alternative to costly IVIg, and to ascertain whether all ataxic patients with coeliac disease eventually respond to therapeutic long-term immunosuppression.

Lancet 2003; **362:** 1548

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References

1 Hadjivassiliou M, Grunewald R, Sharrack B, et al. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain* 2003; 126: 685–91.

2 Pellecchia MT, Scala R, Perretti A, et al. Cerebellar ataxia associated with subclinical celiac disease responding to gluten-free diet. *Neurology* 1999; 53: 1606–08.

3 Vianello M, Tavolato B, Armani M, Giometto B. Cerebellar ataxia associated with anti-glutamic acid decarboxylase autoantibodies. *Cerebellum* 2003; 2: 77–79.

4 Trouillas P, Takayanagi T, Hallett M, et al. International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. *J Neurol Sci* 1997; 145: 205–11.

5 Burk K, Melms A, Schulz JB, Dichgans J. Effectiveness of intravenous immunoglobin therapy in cerebellar ataxia associated with gluten sensitivity. *Ann Neurol* 2001; 50: 827–28.

RC#23 – CLAYTON, P.T.; SURTEES, R.A.H.; DEVILLE, C.; HYLAND, K.; HEALES, S.J.R. Neonatal epileptic encephalopathy. **The Lancet**, v. 361, n. 9369, p. 1614, 2003.

Case report

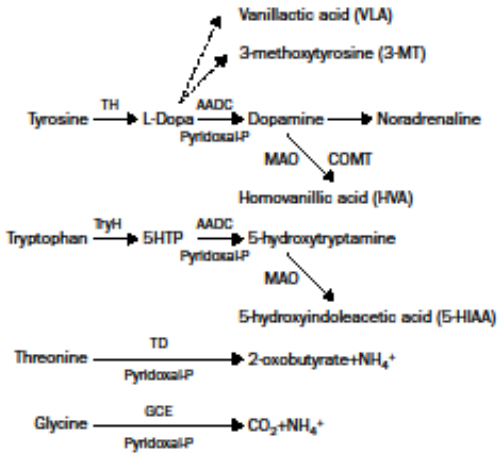
Neonatal epileptic encephalopathy

P T Clayton, R A H Surtees, C DeVille, K Hyland, S J R Heales

In July, 2002, a boy was born at 35 weeks' gestation by Caesarean section for fetal distress. His consanguineous parents were of East African Asian origin. A daughter born at 33 weeks (also by emergency section for fetal distress) had developed metabolic acidosis and intractable seizures on the first day of life; she died 6 weeks later. This infant developed transient respiratory distress and metabolic acidosis. Seizures commenced on day one and rapidly progressed to status epilepticus. An electroencephalogram showed severe generalised burst suppression. He showed no sustained response to anticonvulsants nor to oral pyridoxine (50 mg twice daily increasing to 100 mg twice daily for 5 days). Urine organic-acid analysis showed vanillactic acid (VLA). Analysis of cerebrospinal fluid showed: homovanillic acid (HVA) 151 nM (normal 324–1098); 5-hydroxyindoleacetic acid (5-HIAA) 122 nM (199–608); 3-methoxytyrosine (3-MT) 885 nM (<300); threonine 88 μM (10–45); and glycine 24 μM (4–14). Plasma glycine and threonine were raised when dietary protein intake was normal (eg, glycine 2884 M (100–330), threonine 311 μM (70–220).

The VLA, HVA, 5HIAA, and 3-MT results suggested reduced activity of aromatic L-aminoacid decarboxylase (AADC), a pyridoxal phosphate (pyridoxal-P)-dependent enzyme required for synthesis of dopamine and serotonin.[1,2] However, when AADC activity in plasma was measured at a saturating concentration of pyridoxal-P, it was normal. Moreover, the glycine and threonine results suggested reduced activity of other pyridoxal-P enzymes. At 3 weeks, the infant was given 50 mg of pyridoxal-P via a nasogastric tube. One hour later, seizures had stopped but he was extremely hypotonic, unresponsive, and apnoeic (like an infant with pyridoxine dependency when given pyridoxine). For 4 days (on 30 mg/kg/d of pyridoxal-P) he remained akinetic, unresponsive, and apnoeic, then woke up seizure free and rapidly started to behave normally. On treatment, VLA was not found in his urine, CSF 3-MT was normal, there had been a rise in CSF HVA (277 nM) and 5HIAA (173 nM), and a fall in CSF glycine and threonine. The plasma aminoacid profile (on a normal diet) showed no abnormality. On pyridoxal-P and vigabatrin the infant has had infrequent seizures. However, in March, 2003, at 8 months, examination showed microcephaly (0-4th centile), significant developmental delay, and increased tone in all four limbs.

Neonatal epileptic encephalopathy (NEE) often presents within hours of birth with intractable seizures. Progressive deterioration can lead to death within weeks. Bräutigam et al reported twins with fatal NEE and biochemistry suggestive of reduced activity of AADC (figure).[1,2] We are aware of two similar cases in the UK which were also fatal (M Champion, personal communication). In some patients with NNE, a response to pyridoxine treatment suggests a metabolic basis for NEE but the exact defect has not been confirmed (pyridoxine dependency, OMIM 266100). A report from Taiwan described an infant whose seizures were controlled by pyridoxal-P but not by pyridoxine, suggesting defective conversion of pyridoxine to pyridoxal-P.[3] This case report demonstrates that NEE with biochemical findings mimicking AADC deficiency is the same disorder as the syndrome of pyridoxine-resistant pyridoxal-P-sensitive seizures. Biochemical investigation of NEE can reveal a potentially fatal disorder that responds dramatically to pyridoxal-P. Defective conversion of pyridoxine to pyridoxal-P is probably due to deficiency of pyridox(am)ine phosphate oxygenase.[4] In a neonate who has had fetal distress and acidosis, there is a danger of attributing seizures to hypoxic-ischaemic encephalopathy, when there may be a rare but treatable metabolic disease.



TH=tyrosine hydroxylase
AADC=aromatic amino-acid decarboxylase
MAO=monoamine oxidase
COMT=catechol O-methyl transferase
TryH=tryptophan hydroxylase
TD=threonine dehydratase
GCE=glycine cleavage enzyme

Pyridoxal-P-dependent pathways

Research into the molecular genetics of pyridoxine-resistant pyridoxal-P-sensitive seizures is funded by the Birth Defects Foundation

References

1 Bräutigam C, Hyland K, Wevers R, et al. Clinical and laboratory findings in twins with neonatal epileptic encephalopathy mimicking aromatic L-amino acid decarboxylase deficiency. *Neuropediatrics* 2002; 33: 113–17.

2 Hyland K, Surtees RA, Rodeck C, Clayton PT. Aromatic L-amino acid decarboxylase deficiency: clinical features, diagnosis, and treatment of a new inborn error of neurotransmitter amine synthesis. *Neurology* 1992; 42: 1980–88.

3 Kuo MF, Wang HS. Pyridoxal phosphate-responsive epilepsy with resistance to pyridoxine. *Pediatr Neurol* 2002; 26: 146–47.

4 Ngo EO, LePage GR, Thanassi JW, Metsler LM. Absence of pyridoxine-5'-phosphate oxidase (PNPO) activity in neoplastic cells: isolation, characterization, and expression of PNPO cDNA. *Biochemistry* 1998; 37: 7741–48.

Lancet 2003; **361:** 1614

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RC#24 – SCHOTT, J.M.; HARKNESS, K.; BARNES, J.; ROCCHETTA, A.I.; VINCENT, A.; ROSSOR, M.N. Amnesia, cerebral atrophy, and autoimmunity. **The Lancet**, v. 361, n. 9365, p. 1266, 2003.

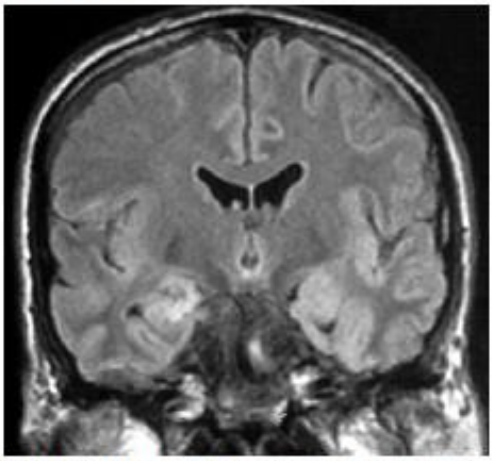
Case report

Amnesia, cerebral atrophy, and autoimmunity

J M Schott, K Harkness, J Barnes, A Incisa della Rocchetta, A Vincent, M N Rossor

A 57-year-old man was admitted to hospital in December, 2001, with a seven-day history of memory impairment and confusion after an influenza-like illness. In hospital, he had complex-partial and generalised seizures. Despite treatment with aciclovir, sodium valproate, phenytoin, risperidone, and haloperidol his condition declined, and he was transferred to the National Hospital for Neurology. On arrival, in April, 2002, he was often unresponsive. There was intermittent jerking of his left arm and right leg, and occasional violent outbursts. He had had hebephrenic schizophrenia and seizures during his teenage years but he had been well since. Laboratory studies showed a persistent syndrome of inappropriate secretion of antidiuretic hormone (lowest sodium 118 mmol/L). Two specimens of cerebrospinal fluid were examined; matched oligoclonal bands were present in the first, but absent in the second. Polymerase chain reactions for herpes simplex viruses 1–7 were negative in both. Tests for antineuronal antibodies for paraneoplastic syndromes, HIV, vasculitis, thyroid autoantibodies, tumour markers, electromyography, computed tomography of the chest, and whole body ^{18}F-fluorodeoxyglucose positron-emission tomography were normal or negative. Electroencephalography showed generalised slowing, with focal sharp and slow waves over the left frontal region. Magnetic resonance imaging (MRI) showed increased signal in the medial temporal lobes, compatible with limbic encephalitis (figure). Neuropsychological testing during his lucid intervals showed deficits in memory (Recognition Memory Test: 14/25 words, 10/25 faces), naming (Graded Naming Test 1/30) and frontal lobe function, with preservation of visuoperceptual function.

In view of a recent report of voltage-gated potassium channel (VGKC) antibody-associated limbic encephalitis,[1] these antibodies were measured and found to be raised at 4005 pM (normal range: <100). Five days of intravenous immunoglobulin were given in June, after which prednisolone was begun at 60 mg daily, subsequently reduced. At this time VGKC antibodies were 1244 pM. He was discharged but readmitted in September for reassessment. His mental state improved and he had fewer seizures. VGKC antibodies were 335 pM. He received five days of plasma exchange. Two weeks later his seizures stopped but he had profound amnesia for the previous months. His sodium concentration was now normal, and neuropsychological performance had improved. Repeat MRI in October, 2002, showed profound cerebral atrophy, particularly affecting the medial temporal lobes. Measurements from serial volumetric MRI scans showed 11·4% whole brain and 22·6% (left) and 39·6% (right) hippocampal volume loss over 6 months. In November, 2002, VGKC antibodies were 97 pM.



Initial coronal FLAIR magnetic resonance image shows medial temporal late signal change

The differential diagnosis of limbic encephalitis includes herpes simplex encephalitis and paraneoplastic syndromes.[2] Raised VGKC antibodies and sustained clinical response to immunosuppression, strongly favour an autoimmune aetiology in this case. VGKC antibodies are typically associated with neuromyotonia and Morvan's syndrome,[3] in which excess secretions (eg, sweating, lacrimation, and salivation) are common.[4] Two cases of reversible limbic encephalitis, associated with VGKC antibodies have been reported.[1] Unlike the two previously reported cases, this patient had no excessive secretions. Prompt immunosuppression in this condition may hasten recovery and prevent the longer-term morbidity caused by rapid cerebral (and particularly medial temporal lobe) atrophy.

Lancet 2003; **361:** 1266

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J M Schott, M N Rossor, and K Harkness cared for the patient and wrote the paper; J Barnes analysed the images; A Incisa della Rocchetta did neuropsychological testing; A Vincent supervised the antibody testing and contributed to the writing of the paper. There are no conflicts of interest. We thank Linda Clover for assaying VGKC antibodies and John Stevens for radiological advice. J Schott is supported by an Alzheimer's Society research fellowship.

References

1 Buckley C, Oger J, Clover L, et al. Potassium channel antibodies in two patients with reversible limbic encephalitis. *Ann Neurol* 2001; 50: 73–78.
2 Voltz R. Paraneoplastic neurological syndromes: an update on diagnosis, pathogenesis and therapy. *Lancet Neurology* 2002; 1: 294–305
3 Morvan A. De la chorée fibrillaire. *Gaz. Hebdomadaire Med Chir* 1890; 27: 173–2000
4 Liguori R, Vincent A, Clover L, et al. Morvan's syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels. *Brain* 2001; 124: 2417–26.

RC#25 – ROWSHANI, A.T.; SCHOT, L.J.; ten BERGE, J.M. c-ANCA as a serological pitfall. **The Lancet**, v. 363, n. 9411, p. 782, 2004.

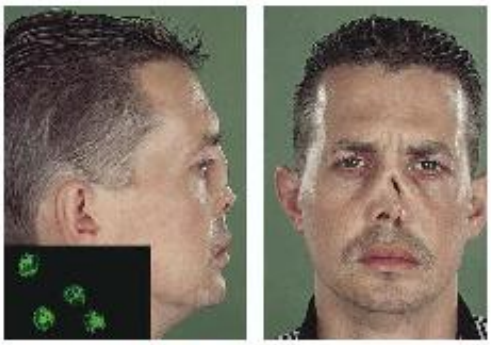
Case report

c-ANCA as a serological pitfall

Ajda T Rowshani, Linda J Schot, Ineke J M ten Berge

A 30-year-old man presented in February, 2000, for a third opinion on recalcitrant Wegener's granulomatosis. 10 years previously, he had first presented elsewhere with arthralgia, palpable purpura on his legs, and glomerulonephritis with a creatinine clearance of 81 mL/min/m², proteinuria of 1·2 g/24 h, and urinary red cell casts. His PR3-ANCA (proteinase-3 antineutrophilic cytoplasmic antibody) titre was reportedly 1:128 (figure, inset), and a kidney biopsy showed crescentic glomerulonephritis with vasculitis and fibrinoid necrosis. Immunohistochemical staining showed mesangial IgA deposition and no staining for other immunoglobulins or complement factors. A radiograph of the chest showed no abnormalites, and a biopsy of the nasal mucosa showed non-specific necrotising ulceration. He had recurrent episodes of purulent rhinitis, leading to necrosis of the septal cartilage, which was surgically reconstructed. The differential diagnosis at this point was Henoch-Schönlein purpura or Wegener's granulomatosis, and he was given methylprednisolone 1 g daily for 3 days, followed by oral cyclophosphamide 2 mg/kg and prednisone 20 mg daily. He continued to take various antibiotics for recurrent nasal infections with *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

In July, 1999, dissatisfied with his lack of response to treatment, persistent rhinitis and recurrent septal perforation, he requested a second opinion in another hospital. Tests were repeated; he had no signs of other organ involvement and no detectable serum ANCA. Doctors suspected that he had progressive Wegener's granulomatosis and prescribed a variety of immunosuppressive regimens including cyclophosphamide, azathioprine, mycophenolate mofetil, and methotrexate. In February, 2000, he came to see us, complaining of nasal obstruction. The cartilaginous pyramid was severely deformed, and he had almost complete destruction of the nasal septum. The lateral wall of the nasal cavity was visible as a mucosal layer and, combined with a defect in the velum palatine, caused a nasal-oral fistula (figure) resulting in considerable dysphagia and dysphonia. He had no other complaints. We found that he had an erythrocyte sedimentation rate of 80 mm/h and a PR3-ANCA titre of 1:256. We suspected cocaine use, which was confirmed by the presence of urinary metabolites. We explained the possible link between his drug use and his symptoms, and advised him to stop taking cocaine. When last seen in November, 2003, he was in good physical condition and his creatinine clearance was 122 mL/min/m² with no proteinuria or erythrocyturia.



Clinical and laboratory findings
Profile (left) and frontal (right) views showing deformation of the nasal septum, and a nasal-oral fistula. Immunofluorescence showing c-ANCA (inset).

This patient had destructive rhinitis due to cocaine use after an initial presentation with Henoch-Schönlein purpura. A relation has been shown between cocaine use and biopsy-proven cerebral vasculitis, ischaemic stroke, or Henoch-Schönlein purpura.[1–3] Cocaine use can mimic vasculitis and is frequently accompanied by positive ANCAs. Cocaine-induced midline destructive lesions are characterised by mucosal damage and ischaemic necrosis of the nasal septum. Histopathological similarity with leukocytoclastic vasculitis and the presence of PR3-ANCA can lead to confusion between Wegener's granulomatosis and cocaine-induced midline destructive lesions.[4,5] The ANCA response in cocaine-induced midline destructive lesions may be related to polyclonal B-cell stimulation by cocaine or non antigen-specific T-cell and B-cell stimulation by superantigens of *S aureus*. Nephrologists may feel that typical upper airway inflammation with positive c-ANCA in the presence of glomerulonephritis justifies the diagnosis of Wegener's granulomatosis without the need for renal biopsy. This patient reminds us that severe upper airway inflammation with positive c-ANCA, even with a history of transient glomerulonephritis, does not necessarily lead to the diagnosis of Wegener's granulomatosis.

Lancet 2004; **363:** 782

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References

1 Chevalier X, Rostoker G, Larget-Piet B, Gherardi R. Schoenlein-Henoch purpura with necrotizing vasculitis after cocaine snorting. *Clin Nephrol* 1995; 43: 348–49.
2 Krendel DA, Ditter SM, Frankel MR, Ross WK. Biopsy-proven cerebral vasculitis associated with cocaine abuse. *Neurology* 1990; 40: 1092–94.
3 Gertner E, Hamlar D. Necrotizing granulomatous vasculitis associated with cocaine use. *J Rheumatol* 2002; 29: 1795–97.
4 Armstrong M Jr, Shikani AH. Nasal septal necrosis mimicking Wegener's granulomatosis in a cocaine abuser. *Ear Nose Throat J* 1996; 75: 623–26.
5 Trimarchi M, Gregorini G, Facchetti F, et al. Cocaine-induced midline destructive lesions: clinical, radiographic, histopathologic, and serologic features and their differentiation from Wegener granulomatosis. *Medicine (Baltimore)* 2001; 80: 391–404.

RC#26 – ROMI, N.S.; KRÄNKE, B.; ABERER, W. A silver man. **The Lancet**, v. 363, n. 9408, p. 532, 2004.

Case report

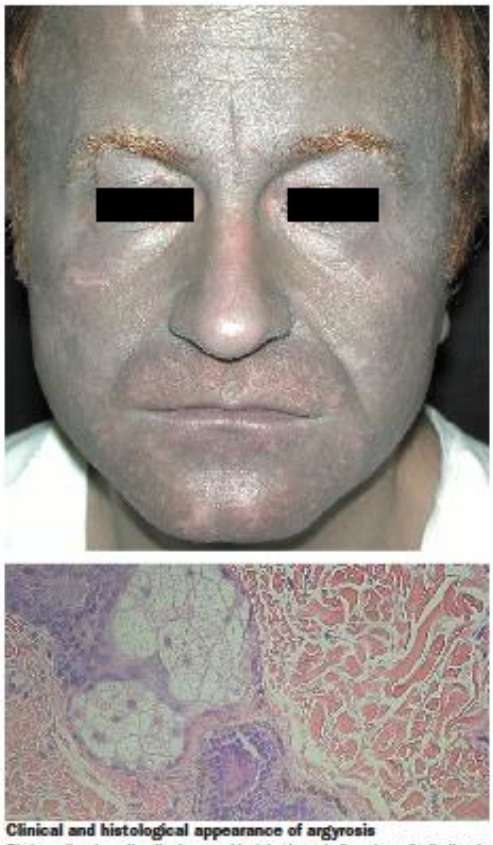
A silver man

Nordwig Sebastian Tomi, Birger Kränke, Werner Aberer

A 42-year-old non-smoking white man presented in May, 2002, complaining of skin discolouration. He had initially noticed a slightly blue-grey tinge to his skin some months previously, which had increased over time. On examination we found a peculiar slate, blue-grey discolouring of the entire tegument, sclera, mucosal surfaces, and nails. The changes were more obvious in sun-exposed areas (figure, top). He had no previous medical complaints, with the exception of allergic rhinitis, and he denied any exposure to heavy metals, amiodarone, chlorpromazine, or antimalarials. To ameliorate the symptoms of allergic rhinitis, he had been applying one to two 10 mL bottles of a topical vasoconstrictor, Coldargan (Sigmapharm, Vienna) weekly over the past 4 years, causing drug-induced rhinopathy.

One drop of Coldargan contains 0·85 mg silver protein, 0·68 mg ephedrine levulinate, 0·24 mg sodium levulinate, and 0·075 mg calcium levulinate. We made a clinical diagnosis of generalised argyrosis and took a punch biopsy from the left neck. Microscopy showed brownish-black perivascular pigment deposits in muscle, nerve, sweat glands, and the dermis (figure, bottom). We did a small chemical peel on the left cheek, and advised the patient to use sun protection, and to stop using his nose drops. When last seen in December, 2002, although shaving scars and the area of chemical peel showed slight improvement, his grey tinge was still quite evident.

Metallic discolouration of the skin can be caused by haematogenous spread or topical application of silver, bismuth, arsenic, iron, titanium, mercury, or gold. The slate-grey discolouration in argyria is caused by dermal deposits of insoluble silver albuminate. Iatrogenic causes include silver-containing sutures used in ophthalmological surgery, and silver nitrate[1–4] used as an antimicrobial, particularly in large doses to treat the first stage of syphilis. Occupational exposure to silver in the mining industry is also a known cause. Since most cases reported in the past 50 years have been of the localised type, generalised argyrosis has become an anachronistic diagnosis. It is also an unfortunate one, because the discolouration is irreversible. Although the silver deposits are neither toxic nor allergenic, the cosmetic change is so severe that patients suffer considerable embarrassment and social withdrawal. Drugs that contain silver protein should be used with caution, especially when they are available over the counter or over the internet.[5] Such medications can cause serious side-effects with chonic use. A clear warning label should be mandatory on all silver-containing drugs to prevent argyrosis due to therapy or misuse.



Clinical and histological appearance of argyrosis
Obvious discolouration (top) caused by intradermal silver deposits (bottom).

Lancet 2004; **363:** 532

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References

1 Frommann C. Ein Fall von Argyria mit Silberanlagerungen in Darm, Leber, Nieren und Milz. *Arch Path Anat* 1859; **17:** 135–147.
2 Olson G. Argyria locally due to organic silver preparations. *JAMA* 1917; **69:** 87–90.
3 Blumberg H, Carey TN. Argyremia. *JAMA* 1934; **103:** 1521–24.
4 Becher E, Hawranek Th, Muß W, Hintner H. Generalized argyria caused by a preparation containing trace elements. *Z Hautkr* 1994; **69:** 388–90.
5 White JML, Powell AM, Brady K, Russel-Jones R. Severe generalized argyria secondary to ingestion of colloidal silver protein. *Clin Exp Dermatol* 2003; **28:** 254–56.

RC#27 – WHITE, J.M.L.; BARKER, R.D.; SALISBURY, J.R.; FIFE, A.J.; LUCAS, S.B.; WARCHURST, D.C.; HIGGINS, E.M. Granulomatous amoebic encephalitis. **The Lancet**, v. 364, n. 9429, p. 220, 2004.

Case Report

Granulomatous amoebic encephalitis

Lancet 2004; 364: 220

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A 32-year-old man presented in March, 2003, with a purple nodule on his right elbow (figure). He had had a motorcycle accident in Bolivia the previous year, sustaining minor abrasions to the elbow. A purple mass developed at the same site months later, followed by similar nodules on the trunk. He was otherwise asymptomatic and had no history of drug use. We found no palpable lymphadenopathy or hepatosplenomegaly. We considered the diagnoses of cutaneous lymphoma, lupus vulgaris or deep fungal infection. His full blood count, urea and electrolytes, erythrocyte sedimentation rate, immunoglobulins, syphilis, yeast and HIV 1 and 2 serology, mycobacterial and fungal culture, and chest radiograph were all unremarkable. His CD4 count was 621 (range: 775–1385) with a normal CD8 count. We took skin biopsies which showed dense non-caseating granulomata in the lower dermis with no clonal proliferation. We started itraconazole while awaiting cultures, but the patient stopped treatment after 14 days. 8 weeks later, he was admitted in an acute confusional state. Cerebral CT showed multiple space-occupying lesions in the right cerebral hemisphere with oedema, hydrocephalus and a midline shift. This was consistent with cerebral lymphoma, although infection could not be excluded. We did another skin biopsy which showed amoebic trophozoites within granulomata. *Balamuthia* serology was strongly positive at a titre of 1:10 000 confirming disseminated *Balamuthia mandrillaris* infection.

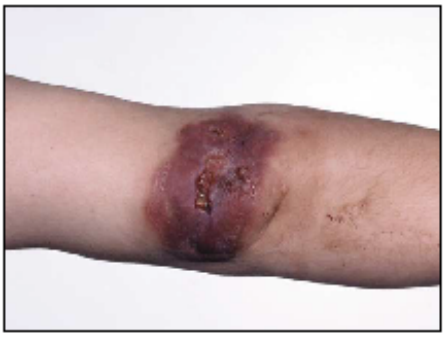

Figure: Purple nodule at the site of an abrasion sustained in Bolivia

We started co-trimoxazole, rifampicin, ketoconazole and azithromycin (500 mg daily) as well as dexamethasone (4 mg qds) for cerebral oedema. The patient deteriorated rapidly with swinging pyrexia of 41°C and died 2 weeks later, in September, 2003. Post-mortem examination showed herniation induced by raised intra-cranial pressure. Smear of brain tissue showed *B mandrillaris*, which was isolated in culture at Birkbeck College, using human brain microvascular endothelial cells.

Balamuthia mandrillaris is an amoeba originally isolated from the brain of a baboon. It has only recently been isolated from the environment. It is not easily cultured but may be grown on agar seeded with viable *Acanthamoeba*.[1] Balamuthia encephalitis is very rare and follows a prolonged cutaneous phase.[2] The route of infection may be via the nasal mucosa or skin trauma,[3] as in our patient with presumed inoculation from skin abrasions. Haematogenous spread to the lungs or brain[4] may cause vasculitis of cerebral vessels, leading to haemorrhagic necrosis. This makes brain biopsy hazardous. Diagnosis is made on culture, serology or immunofluorescence, and often only after death. Serology is relatively non-invasive, therefore a useful screening test. Many of the reported cases are children and only two cases have survived.[5] They were treated with flucytosine, pentamidine, fluconazole, sulfadiazine and either azithromycin or clarithromycin. In a cell-free in vitro system, pentamidine appears to be most active agent against *B mandrillaris*. Optimal treatment has not yet been defined. Given the extreme rarity of infection, patients with *Balamuthia* may display deficient humoral immune-responses or poor cell-mediated immunity. Precise mechanisms have not yet been identified. Balamuthia encephalitis has been reported with HIV infection, although many patients are ostensibly immunocompetent. Our patient's low CD4 count may have been a factor in susceptibility. *B mandrillaris* should be considered in the context of a granulomatous skin condition. Identifying an immune defect in these patients may help identify those at risk of this fatal disease.

References

1 Schuster FL, Dunnebacke TH, Booton GC, et al. Environmental isolation of *Balamuthia mandrillaris* associated with a case of amebic encephalitis. *J Clin Microbiol* 2003; 1: 3175–80.

2 Deol I, Robledo L, Meza A, Visvesvara GS, Andrews RJ. Encephalitis due to a free-living amoeba (*Balamuthia mandrillaris*): case report with literature review. *Surg Neurol* 2000; 53: 611–16.

3 Galarza M, Cuccia V, Sosa FP, Monges JA. Pediatric granulomatous cerebral amebiasis: a delayed diagnosis. *Pediatr Neurol* 2002; 26: 153–56.

4 Healy JF. Balamuthia amebic encephalitis: radiographic and pathologic findings. *Am J Neuroradiol* 2002; 23: 486–89.

5 Deetz TR, Sawyer MH, Billman G, Schuster FL and Visvesvara GS. Successful treatment of Balamuthia amoebic encephalitis: presentation of 2 cases. *Clin Infect Dis* 2003; 37: 1304–12.

RC#28 – RADCLIFFE, M.; SCADDING, G.; BROWN, H.M. Lupin flour anaphylaxis. **The Lancet**, v. 365, n. 9467, p. 1360, 2005.

Case Report

Lupin flour anaphylaxis

Lancet 2005; 365: 1360

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In August, 2004, a 25-year-old woman was transferred to hospital following a restaurant meal of chicken, French-fried potatoes, and onion rings. During the meal, her mouth itched and her lips and tongue started to swell. Fifteen minutes later she was having difficulty breathing, her throat had narrowed, and she felt very weak. An ambulance was called, anaphylaxis diagnosed, and she was given intramuscular adrenaline. In spite of this treatment she continued to deteriorate and during the journey to hospital required continuous oxygen and two further doses of adrenaline. On arrival, intravenous fluids, hydrocortisone, and chlorphenitramine were given, and she recovered without further complications. She had a history of mild asthma and at the age of 15 had had severe anaphylaxis after eating a peanut. Occasional minor allergic reactions had occurred since then due to inadvertent peanut ingestion. Peanut contamination of the meal was therefore considered the most likely cause of her anaphylaxis. The restaurant chef assured her that this was unlikely and referred her to the onion ring distributor.

They informed her that lupin flour, an ingredient of the batter, might have caused her attack. An allergy consultant (HMB) contacted the company and the Anaphylaxis Campaign (info@anaphylaxis.org.uk) who suggested allergy clinic referral. Skin prick tests were done to common inhalant allergens but only birch pollen was positive. The skin prick test to peanut (1:10 dilution of the standardised extract) was strongly positive, and the patient had positive reactions to garden pea and soya. Skin prick tests to Brazil nuts and hazelnuts were negative. A crude 1:100 w/v volume eluate of lupin was prepared by mixing lupin flour with sterile isotonic saline. A skin prick test was strongly positive (weal diameter 14 mm). Specific IgE to lupin (12·5 kUA/L; reference range, <0·35 kUA/L) was identified by the UniCAP test (Pharmacia Diagnostics, Uppsala, Sweden). The patient was unwilling to undergo an oral challenge.

IgE-mediated food allergy is an important cause of dangerous anaphylaxis. Peanuts, tree nuts such as Brazil nuts, cashew nuts, or hazelnuts, and seafood, are the commonest causes in adults. The first report of lupin allergy was in 1994 and involved a 5-year-old girl with a known peanut allergy who developed urticaria and angioedema after eating spaghetti fortified with lupin flour.[1] Lupin flour allergy has been mainly reported in European patients known to be allergic to other legumes, particularly peanut, soya or pea.[2–5] The first report of lupin anaphylaxis was in 1999.[2] The prevalence of lupin allergy has increased markedly in some countries, especially in France, where the addition of lupin flour to wheat flour was first permitted in 1997.[2] In 2002, lupin was the fourth most frequent cause of severe food-associated anaphylaxis reported to the French Allergy Vigilance Network. Three cases of anaphylaxis due to lupin have been reported from Australia, where over 800 000 tonnes is grown annually. Although mainly in use as an animal feed, since 2001 it has been increasingly supplied to food manufacturers as a substitute for the more expensive traditional cereal grains. The Australian Department of Agriculture is proposing lupin as the next major competitor to soya beans. The use of lupin for human food has been permitted in the UK since 1996. A new directive on food labelling came into force in Europe in November 2004 (2003/89/EC) requiring food manufacturers to specifically list 12 potentially allergic ingredients (gluten, fish, crustaceans, eggs, peanuts, soy, milk and dairy products, nuts, celery, mustard, sesame seed, and sulphites), and their allergenic derivatives. Lupin flour is not included in this listing in spite of a recommendation from the UK-based Institute of Food Science & Technology.

The Food Standards Agency has advised us that it is difficult to assess the scope of its current use, but until recently, lupin flour was limited to certain baked goods imported from Europe. However, two of us (MJR and GKS) have since identified a further case of life-threatening anaphylaxis caused by lupin flour in an Italian apple tart and are investigating two other possible cases. Without knowledge of lupin flour allergy all of these episodes would have been misdiagnosed as idiopathic anaphylaxis. Further work will be required to establish the prevalence and significance of lupin food allergy. Meanwhile, those with peanut allergy (around 1% of the UK population, including 250 000 pre-school children) appear to be at particular risk as up to half may be pre-sensitised. These people should be advised to avoid all products containing lupin until they can be specifically tested.

Figure: Lupin flour was present in the onion ring batter

References:

1 Hefle SL, Lemanske RF, Bush RK. Adverse reaction to lupin fortified pasta. *J Allergy Clin Immunol* 1994; 33: 256–67.

2 Moneret-Vautrin DA, Guerin D, Danny G, Flabbee J, Morisset M. Cross-allergenicity of peanut and lupin: the risk of lupin allergy in patients allergic to peanuts. *J Allergy Clin Immunol* 1999; 104: 883–88.

3 Mathieu V, De Barrio M, Sierra Z, Gracia-Vara MT, Tornero P, Ibarra ML. Lupin-induced anaphylaxis. *Ann Allergy Asthma Immunol* 1999; 83: 406–8.

4 Kanny G, Guerin L, Moneret-Vautrin DA. Risk of serious asthma due to lupin flour associated with peanut allergy. *Rev Mal Inaers* 2000; 21: 191–94.

5 Gutierrez D, Conde A, Duran S, et al. Contact urticaria from lupin. *Contact Dermatitis* 1997; 36: 311.

RC#29 – PALMIERI, C.; FISHER, R.A.; SEBIRE, N.J.; LINDSAY, I.; SMITH, J.R.; McCLUGGAGE, W.G.; SAVAGE, P.; SECKL, M.J. Placental site trophoblastic tumour arising from a partial hydatidiform mole. **The Lancet**, v. 366, n. 9486, p. 688, 2005.

Case Report

Placental site trophoblastic tumour arising from a partial hydatidiform mole

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Lancet 2005; 366: 688

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In June, 2003, a 29-year-old woman had a routine abdominal ultrasound at 12 weeks' gestation, which showed a possible molar pregnancy. Dilation and curettage (D&C) showed a partial hydatidiform mole (figure, A). Flow cytometry showed that the tissue was triploid. We monitored the patient's β-human chorionic gonadotropin (βhCG), which returned to normal (<5 IU/L) in November, 2003. In April, 2004, her βhCG was increased, and an abdominal ultrasound showed a gestational sac. 1 month later, she developed vaginal bleeding; miscarriage was suspected and D&C showed decidua but no fetal tissue. The bleeding continued, her βhCG remained raised, and in June, 2004, a further D&C showed gestational trophoblastic disease. We reviewed the histological specimen, and diagnosed placental site trophoblastic tumour (PSTT) (figure, B). Her βhCG was 1924 IU/L, and a uterine doppler ultrasound showed a 105 mL uterus with a 4 cm vascularised mass extending into the left adnexa and ovary. Full-body CT showed bilateral pulmonary metastases. MRI of the brain showed no abnormalities. We started her on systemic chemotherapy in conjunction with intrathecal methotrexate as prophylaxis for occult central nervous system disease involvement. βhCG returned to normal after 11 weeks of treatment, and the left adnexal and thoracic lesions disappeared. She then had a hysterectomy and left sided salpingo-oophorectomy to debulk any residual tumour. Histopathology showed that the only viable tumour persisted as isolated cells in the left ovary (figure, C).

We genotyped the patient, her partner, and the histological specimens. There were four fully informative microsatellite polymorphisms, and the partial mole showed both maternally and paternally derived alleles. For two of these markers the molar tissue was trisomic with one maternal and two paternal alleles, and for the other two markers the ratio of paternal to maternal DNA was also consistent with trisomy from one maternal and two paternal contributions. Genotyping therefore confirmed a partial mole of dispermic origin. Analysis of the DNA from the subsequent PSTT also showed paternal alleles. Both maternal alleles were present for all markers in the DNA prepared from the trophoblastic tissue due to contamination of the tumour sample with infiltrating maternal cells. The proportion of maternal and paternal DNA showed that the PSTT originated in the previous partial hydatidiform mole. We gave the patient chemotherapy for a further 8 weeks; when last seen in May, 2005, she was healthy and had a normal serum concentration of βhCG.

Gestational trophoblastic neoplasia is a group of pregnancy-related disorders ranging from the pre-malignant complete hydatidiform mole and partial mole to the malignant invasive mole, choriocarcinoma, and PSTT. Complete moles occur in about 1 per 1000 pregnancies and partial moles in 3 per 1000 pregnancies.[1,2] Although both secrete βhCG, complete moles are diploid and nearly always androgenetic in origin. By contrast, partial moles are triploid, consisting of one maternal and two paternal sets of chromosomes.[3] After uterine evacuation, 16% of complete and 0·5% of partial moles undergo malignant change.[4] For complete moles this malignant change includes invasive mole, choriocarcinoma, and PSTT. Partial moles can also change into choriocarcinoma but have never been shown to progress to PSTT. PSTT is usually curable if diagnosed within 4 years of the associated pregnancy.[5] Delay in recognising malignant change after molar pregnancy can result in haemorrhage, uterine perforation, metastasis, and death. Since partial moles can become choriocarcinomas and PSTTs, and this malignant change can be effectively detected by simply monitoring serum concentrations of βhCG, patients should be followed up after partial molar pregnancy.

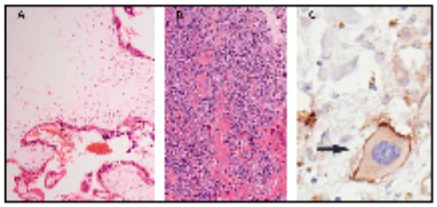

Figure: Photomicrographs of (A) the initial products of conception showing hydropic chorionic villi with irregular outlines and abnormal trophoblast proliferation with a focally vacuolated phenotype (H&E ×40), (B) D&C specimen showing myometrial infiltration by sheets of monomorphic cells with focal vacuolation (H&E ×40), and (C) left ovarian section showing single infiltrating cells staining strongly (Mel-CAM ×200).

Acknowledgements

This work was funded by the UK Department of Health, Cancer Treatment and Research Trust, and National Translational Cancer Research Network.

References

1 Jacobs PA, Hunt PA, Matsuura JS, Wilson CC. Complete and partial hydatidiform mole in Hawaii: cytogenetics, morphology and epidemiology. *Br J Obstet Gynaecol* 1982; 89: 258–66.
2 Sutgrad SJ. Epidemiology of gestational trophoblastic diseases. *Best Pract Res Clin Obstet Gynaecol* 2003; 17: 837–47.
3 Lawler SD, Fisher RA, Pickthall VJ, Povey S, Wyn Evans M. Genetic studies on hydatidiform moles. I. The origin of partial moles. *Cancer Genet Cytogenet* 1982; 5: 309–20.
4 Seckl MJ, Fisher RA, Salerno GA, et al. Choriocarcinoma and partial hydatidiform moles. *Lancet* 2000; 356: 36–39.
5 Papadopoulos AJ, Foskett M, Seckl MJ, et al. Twenty-five years' clinical experience of placental site trophoblastic tumors. *J Reprod Med* 2002; 47: 460–64.

RC#30 – PAVLU, J.; HARRINGTON, D.J.; VOONG, K.; SAVIDGE, G.F.; JAN-MOHAMED, R.; KACZMARSKI, R. Superwarfarin poisoning. **The Lancet**, v. 365, n. 9459, p. 628, 2005.

Case Report

Superwarfarin poisoning

Lancet 2005; 365: 628
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A 26-year-old Indian woman attended Hillingdon Hospital with nausea, vomiting, abdominal pain, haematuria, and bleeding gums in June, 2004. Her medical history and physical examination were unremarkable except for diffuse gum bleeding; she had no bruises. Blood tests showed a prolonged prothrombin time of >150 s (normal 9–12·6) and activated partial thromboplastin time (APTT) of 92 s (22–32), which was fully corrected when mixed with normal plasma (50:50). Other investigations (fibrinogen, urea, electrolytes, and liver function tests) were normal. The coagulopathy was thought to be the result of vitamin K deficiency and she was given 10 mg of vitamin K intravenously. Further studies confirmed deficiency of vitamin K-dependent clotting factors: factor X=1·3 U/dL (50–200) and factor VII=3·5 U/dL (50–150). Concentrations of factor V were normal at 118 U/dL (50–150). She was admitted and the gum bleeding stopped 6 h after she was given vitamin K. 12 h later her clotting remained abnormal (prothrombin time 53 s, APTT 59 s, and APTT and INR 5·0). Further doses of intravenous vitamin K (10 mg) daily for 3 days failed to return her coagulation tests to normal. The next day she was not given any vitamin K and her prothrombin time (>150 s) and APTT (56 s) became dangerously prolonged. She was given vitamin K 100 mg orally each day until her clotting became normal on day 7. The dose was then reduced to 30 mg a day.

Serum was sent to St Thomas' Hospital where screening for vitamin K antagonists showed the rodenticide (superwarfarin) brodifacoum (0·86 mg/L) and commensurate elevations in descarboxyprothrombin (70·79 AU/mL [<0·2 AU/mL]) and vitamin K_1O 2,3-epoxide (41·36 μg/L [<0·05 μg/L]), indicative of vitamin K antagonism. She denied intentional ingestion of superwarfarin and thought it was unlikely that anybody would deliberately wish to cause her harm. She was unmarried and lived with four friends. They prepared meals and ate together. None of her friends had been ill. We asked them to attend for blood tests. None of them had abnormalities in INR, or circulatory concentrations of descarboxyprothrombin or vitamin K_1O 2,3-epoxide. Neither the patient's general practitioner nor Hillingdon Hospital's Accident and Emergency department knew of other cases of unexplained bleeding. She firmly refused to allow us to report her poisoning to the police or public-health authorities, and would not accept a psychiatric consultation. After extensive discussion, we decided that we were obliged to respect her wishes. We tested her blood regularly for 77 days after her discharge from hospital. During this time, circulatory concentrations of brodifacoum fell to 0·16 mg/L with a terminal half-life of 31 days, while raised concentrations of descarboxyprothrombin and vitamin K_1O 2,3-epoxide persisted (0·24 AU/mL and 205·34 μg/L, respectively). The patient's clotting remained normal after stopping vitamin K. She decided to return to India and left the UK in September, 2004.

Superwarfarin poisoning should be suspected when there is a severe deficiency of vitamin K-dependent clotting factors of unknown aetiology with a transient or no response to standard doses of vitamin K. Management of such patients typically involves prolonged administration of high doses of vitamin K. The anticoagulant effect (indicated by elevated descarboxyprothrombin and vitamin K_1O 2,3-epoxide concentrations) may persist in the absence of detectable brodifacoum. Although it has been over 20 years since the first descriptions of superwarfarin rodenticide poisoning in humans,[1] awareness of the problem among physicians remains minimal. Superwarfarins are potent, highly lipophilic 4-hydroxycoumarin derivatives and like warfarin they exert their anticoagulant effect by inhibiting the vitamin K epoxide reductase enzyme complex that recycles vitamin K 2,3-epoxide to vitamin K hydroquinone, the cofactor required by γ-glutamyl carboxylase for the post-translational modification of coagulation factors II, VII, IX, X, and other polypeptides.[2] These compounds are available without restrictions and are used with increasing frequency to control infestation of warfarin-resistant rats. In the UK there is no statutory obligation that requires reporting of poisoning by brodifacoum (or other superwarfarin type rodenticides) to the public health authorities or to the police. Self-administration by adults with Munchausen syndrome or those attempting suicide, or accidental ingestion by children, account for the majority of reported episodes of poisoning with vitamin K antagonists.[3] Incidences of malicious poisoning are also known.[4] Reporting without patients' consent would represent a breach of confidentiality. Legal judgments have established that patients' right to privacy may be breached but only when there is an overriding public interest.[5] We question whether the unrestricted availability of superwarfarin-type compounds should continue.

References

1 Barlow AM, Gay AL, Park BK. Difenacoum (Neosorex) poisoning. *BMJ* 1982; 285: 541.

2 Suttie JW. The biochemical basis of warfarin therapy. *Adv Exp Med Biol* 1987; 214: 3–16.

3 Chua JD, Friedenberg WR. Superwarfarin poisoning. *Arch Intern Med* 1998; 158: 1929–32.

4 Babcock J, Hamman K, Pedersen A, Murphy M, Alving B. Rodenticide-induced coagulopathy in a young child. A case of Munchausen syndrome by proxy. *Am J Pediatr Hematol Oncol* 1993; 15: 126–30.

5 Confidentiality. In: British Medical Association Ethics Department. Medical ethics today—the BMA's handbook of ethics and law. 2nd edn, London: BMJ Publishing Group; 2004: 165–97.

RC#31 – KOREN, G.; CAIRNS, J.; CHIAYAT, D.; GAEDIGK, A.; LEEDER, S.J. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. **The Lancet**, v. 368, n. 9536, p. 704, 2006.

Case Report

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

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Lancet 2006; 368: 704

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In April, 2005, a full-term healthy male infant, delivered vaginally, showed intermittent periods of difficulty in breastfeeding and lethargy starting on day 7. During a well-baby paediatric visit on day 11, the paediatrician noted that the baby had regained his birthweight. On day 12, however, he had grey skin and his milk intake had fallen. He was found dead on day 13. Postmortem analysis showed no anatomical anomalies. Blood concentration of morphine (the active metabolite of codeine) was 70 ng/mL by gas chromatography-mass spectrometry (GC-MS)—neonates breastfed by mothers receiving codeine typically have morphine serum concentrations of 0–2·2 ng/mL.[1] The mother had been prescribed a combination preparation of codeine 30 mg and paracetamol 500 mg after birth for episiotomy pain (initially two tablets every 12 h, reduced to half that dose from day 2 because of somnolence and constipation). She continued the tablets for 2 weeks. Because of poor neonatal feeding, she stored milk on day 10, which was later assayed for morphine by GC-MS. A morphine concentration of 87 ng/mL was found—the typical range of milk concentrations after repeated maternal codeine is 1·9–20·5 ng/mL at doses of 60 mg every 6 h.

Genotype analysis was done for cytochrome P450 2D6 (*CYP2D6*), the enzyme catalysing the O-demethylation of codeine to morphine.[2] The mother was heterozygous for a *CYP2D6*2A* allele with *CYP2D6*2x2* gene duplication, classified as an ultra-rapid metaboliser. This genotype leads to increased formation of morphine from codeine, consistent with the somnolence and constipation she experienced.[3] The maternal grandfather, the father, and the infant had two functional CYP2D6 alleles (*CYP2D6*1/*2* genotypes), classified as extensive metabolisers. The maternal grandmother was an ultra-rapid metaboliser.

The clinical and laboratory picture is consistent with opioid toxicity leading to neonatal death. Most of the analgesic and central-nervous-system depressant effects of codeine are secondary to its metabolism to morphine by CYP2D6.[2] Neonates invariably have impaired capacity to metabolise and eliminate morphine. Codeine is a commonly used analgesic after labour for pain associated with episiotomy and caesarean section. The American Academy of Pediatrics lists codeine as compatible with breastfeeding, despite lack of sufficient published data to support this recommendation.[4] This case shows that polymorphism of *CYP2D6* can be life threatening for some breastfed babies. Given that the frequency of *CYP2D6* ultra-rapid metaboliser genotypes ranges from 1% in Finland and Denmark to 10% in Greece and Portugal, and 29% in Ethiopia, this polymorphism is clinically important.[5] Several strategies can be considered to prevent life-threatening neonatal toxicity (table). Careful follow-up of breastfeeding mothers using codeine, and their infants, may be a useful approach. Testing of mother–child pairs when the mother or neonate is experiencing symptoms consistent with opioid toxicity may be necessary—eg somnolence, or poor milk intake. The facilities to measure morphine concentrations are not routine in most hospitals; in any suspicious case, naloxone can reverse, and, therefore, corroborate opioid toxicity. Above all, avoidance of codeine use during breastfeeding, with its use being retained as second or third line for uncontrolled pain, could also avert this situation. Whatever clinical approach is taken, codeine cannot be considered as a safe drug for all infants during breastfeeding.

References

1 Merry RG, Naumburg EG, Algor LS, Brill-Miller H, Brown S. Codeine and the breastfed neonate. *J Hum Lact* 1993; 9: 237–40.
2 Meyer UA. Pharmacogenetics of adverse drug reactions. *Lancet* 2000; 356: 1667–71.
3 Gasche Y, Daali Y, Fathi M, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med* 2004; 351: 2827–31.
4 Committee on Drugs. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89.
5 Ciszarbi I. Pharmacogenetics of cytochrome P4502D6: genetic background and clinical implication. *Eur J Clin Invest* 2003; 33 (suppl 2): 17–22.

Action	Advantages	Disadvantages
Avoid codeine when breastfeeding, use paracetamol or non-steroidal anti-inflammatory drugs	Avoids potential neonatal toxicity	Potential uncontrolled maternal pain
Avoid high-dose codeine (240 mg daily) for more than a few days	Minimises potential neonatal toxicity	Suboptimal maternal pain control Dose may still be too high a dose for ultra-rapid metabolisers
Avoid breastfeeding when taking codeine	Avoids potential neonatal toxicity	Loss of the benefits of breastfeeding
Inform and monitor mother and baby for signs of opioid toxicity	Ability to intervene early and prevent serious toxicity	Parental anxiety and false positive identification of toxicity
Genotype mother for CYP2D6	Predicts mothers at risk of producing excess of morphine	Expensive Not presently routine

Table: Clinical strategies to manage breastfeeding while on codeine

RC#32 – BODENMANN, P.; GENTON, B. Chikungunya: an epidemic in real time. **The Lancet**, v. 368, n. 9531, p. 258, 2006.

Case Report

Chikungunya: an epidemic in real time

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Lancet 2006; 368: 258
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On Feb 15, 2006, a 28-year-old woman attended our clinic because of fever, headache, and photophobia that had lasted for 3 days and rash of 1 day's duration. 2 days earlier she had returned from a 2-week trip to Mauritius. She reported many mosquito bites during her trip. On examination, there was painful inguinal lymphadenopathy and a maculopapular rash on her trunk (figure), and her thighs; knees, wrists, and hands were painful. The differential diagnosis included Chikungunya fever because of the continuing and large epidemic in Mauritius,[1] the compatible chronology, and the typical clinical presentation. Less likely diagnoses were primary HIV infection, rickettsiosis, malaria, and dengue, typhoid, or relapsing fever (see www.fevertravel.ch for details on differential diagnosis).[2] Rapid diagnostic test and microscopy were negative for malaria. Full blood count showed a low white-cell count ($2·8\times10^9$/L; normal range $4–10\times10^9$/L) and monocytosis (15%; 2–8%). No other laboratory tests were done other than serology for Chikungunya.

Because of the high probability of Chikungunya, she was given symptomatic treatment, discharged the same day, and followed up as an outpatient. Chikungunya fever was later confirmed by serology results (IgM positive 0·42 [positive if >0·15] and IgG negative [positive if >0·10] on Feb 15; IgM 3·51 and IgG 0·72 on Feb 28). When the patient was last seen on Feb 22, 2006, fever had subsided but diffuse arthralgia on both hands persisted.

Chikungunya is transmitted by *Aedes aegypti* or *A albopictus*. In his original report of this arbovirosis, Robinson[3] mentioned fever (100% of the cases diagnosed on La Réunion), arthralgia (100%), myalgia (97%), headache (84%), and diffuse maculopapular rash (33%).[4] Symptoms appear 4–7 days after the infecting bite and can be associated with lymphadenopathy, gastrointestinal symptoms, and mild haemorrhagic signs. In Swahili, Chikungunya means the illness of the bended walker; indeed, arthralgia is often severe and can persist for a long time—12% of patients have chronic arthralgia 3 years after onset of illness.[5] During the recent epidemic in the Indian Ocean islands, 12 cases of meningoencephalitis have been confirmed, which could suggest that the present strain is more virulent than those causing previous epidemics; six cases were diagnosed in neonates whose mothers had contracted the virus 48 h before giving birth and six in elderly people. 77 death certificates issued in the region between Jan 1, 2006, and March 2, 2006, state Chikungunya as the cause of death, but, for most of them, there was underlying comorbidity (median age 78 years).[4] Thanks to the rapid development of internet surveillance networks, more developed countries can be informed in real time about the dynamic of an epidemic that potentially threatens travellers' health. Chikungunya on La Réunion is a good example: once the epidemic worsened in January, 2006, reports rapidly accumulated with detailed description of clinical cases, rate, and type of complications. However, the local population had to wait for the first cases in tourists to see the deployment of effective control measures. As travel-medicine physicians, we were pressurised by the media and our patients to give informed advice on whether to go or to cancel a planned journey. After thorough assessment of the documents available on the internet, we developed recommendations based on the evidence from several disease-surveillance systems.[1,4] We strongly discouraged pregnant women, families with young children, people older than 70 years, and those with significant comorbidity from travelling to the Indian Ocean islands. We informed other patients about the magnitude of the risk of contracting the disease and let them decide according to their own judgment. We reinforced the message on protective measures against mosquito bites. This case emphasises the importance of disease-surveillance communication networks, which allow the constant modification of preventive and therapeutic measures.

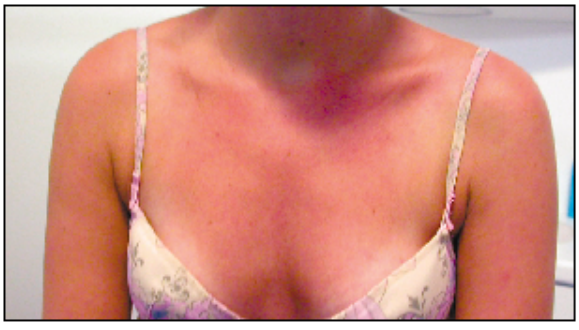

Figure: Maculopapular rash at presentation

Acknowledgments

We thank M Bucher and P Vaucher from the Medical Outpatient Clinic for clinical care and literature search, respectively.

References

1 Edisan. Médecine des voyages. http://www.edisan.fr (accessed March 13, 2006).
2 D'Acremont V, Burnand B, Ambrosin AE, Genton B. Practice guidelines for the evaluation of fever in returning travelers and migrants. *J Travel Med* 2003; 10 (suppl 2): 525–50.
3 Robinson MC. An epidemic of virus disease in southern province, Tanganyika Territory, in 1952–53: I clinical features. *Trans R Soc Trop Med Hyg* 1955; 49: 28–32.
4 Eurosurveillance. http://www.eurosurveillance.org (accessed March 2, 2006).
5 Brighton SW, Prozesky OW, De La Harpe AL. Chikungunya virus infection: a retrospective study of 107 cases. *S Afr Med J* 1982; 63: 313–15.

RC#33 – YU, H.; SHU, Y.; Hu, S.; ZHANG, H.; GAO, Z.; CHEN, H.; DONG, J.; XU, C.; ZHANG, Y.; XIANG, N.; WANG, M.; GUO, Y.; COX, N.; LIM, W.; LI, D.; WANG, Y.; YANG, W. The first confirmed human case of avian influenza A (H5N1) in Mainland China. **The Lancet**, v. 367, n. 9504, p. 84, 2006.

Case Report

The first confirmed human case of avian influenza A (H5N1) in Mainland China

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Lancet 2006; 367: 84
Published online December 20, 2005
DOI:10.1016/S0140-6736(05)67894-4

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On Oct 8, 2005, a previously healthy 12-year-old girl in rural Hunan, China, developed fever, sore throat, and cough. She consulted a village outpatient clinic 4 days later, and was admitted to the local hospital on Oct 13. On admission she had a fever (40·4°C), and chest radiography showed shadowing in the left middle and lower lobes. Blood tests showed white cell count $3·28\times10^9$/L, lymphocytes $0·64\times10^9$/L, platelets 94×10^9/L, alanine aminotransferase 80 IU/L, and creatinine 99 mmol/L. On Oct 16, she was taken to the Hunan Provincial Children's Hospital because of increasing dyspnoea and cyanosis. Chest radiography showed diffuse bilateral consolidation with air bronchogram. Her condition continued to deteriorate despite oxygen therapy, broad spectrum antibiotics (azithromycin, cefotaxime), and corticosteroid treatment, and she was intubated and ventilated on the same day. She died of acute respiratory distress syndrome, disseminated intravascular coagulation, and multiorgan distress syndrome on Oct 17.

In the meantime, her 9-year-old brother developed fever and cough on Oct 10. He was admitted to hospital on Oct 17 where he responded to treatment including amantadine, ribavirin, corticosteroids, and broad spectrum antibiotics; he was discharged on Nov 12. At his final follow-up on Dec 9, 2005, he remained asymptomatic.

Under the nationwide surveillance system established in July, 2004, patients admitted with pneumonia of unexplained origin are reported to the Chinese Center for Disease Control and Prevention. This family cluster was recognised on Oct 18. Like other families in the rural area, backyard poultry-raising is commonly practised; before the outbreak, the family had 22 chickens and five ducks kept in cages in a confined area adjacent to the bathroom and toilets within the house. Because of the National Day holidays (from Oct 1 to Oct 7), children were in the house for a longer period of time. It was noted in retrospect that a few chickens and ducks had begun to die in the village from Sept 16. Between Oct 6 and Oct 12, up to six birds in the affected household died per day; by Oct 19, only one chicken and one duck remained alive. The mother cooked the dead and dying birds for consumption by the family. The patients' close contacts—totalling 191 persons—were all healthy following medical observation for 10 days after their last exposure to the two cases. Only one serum specimen taken 8 days after onset of symptoms could be obtained from the girl, which was negative for H5-specific antibodies in both microneutralisation and haemagglutination-inhibition assays against the A/Hunan-Xiangnan-he/12/2005 virus, which was isolated from the only live chicken remaining in the household. The boy's samples, collected on days 8, 17, and 22 after the onset of the illness, showed a 4-fold or greater rise in antibody titre. Throat swabs for RT-PCR were, however, negative. The HA gene of the virus is closely related to that of H5N1 viruses isolated from poultry in Fujian Province in 2005, belonging to clade 2. The aminoacid residues involved in the receptor-binding site of haemagglutinin are similar to those of other H5 viruses, with α2-3 sialic acid receptor binding specificity, and the haemagglutinin has a polybasic aminoacid cleavage site (RERRRRR).[1]

The 12-year-old girl in the cluster is the first clinically diagnosed case of human H5N1 infection reported in mainland China, 8 years after the first documented outbreak in Hong Kong.[2] Although another family cluster in Hong Kong in 2003 gave a previous history of travel to Fujian Province, the specific source of the infections was not ascertained.[3] Clinically, the respiratory distress in the infected children was similar to that reported elsewhere, and human-to-human transmission appeared to be inefficient.[4] It is plausible that our cases had acquired the virus from diseased poultry rather than from one another. Our investigation highlights the major public health challenges in the unique setting of backyard farming where infection control measures remain to be improved, and where access to diagnosis and treatment is often limited. Hopefully, lessons from this and other cases will be translated into effective strategies to minimise the adverse impact of pathogenic H5N1 infections.

Conflict of interest statement
None declared.

Role of the funding source
The entire investigation was supported by Chinese Center for Disease Control and Prevention, Hunan Provincial Center for Disease Control and Prevention, and by 973 programmes 2005CB523005.

Acknowledgments
We thank Hunan Provincial Health Bureau, Xiangtan City CDC, Xiangtan County CDC, Maternity and Children Hospital in Xiangtan City and Hunan Provincial Children's Hospital for assisting in coordinating investigations and providing logistics support. We thank Shui Shan LEE (Center for Emerging Infectious Diseases, The Chinese University of Hong Kong) for assistance in preparing the manuscript.

1 Subbarao K, Klimov A, Katz J, et al. Characterization of an avian influenza A (H5N1) virus isolated from a child with a fatal respiratory illness. *Science* 1998; 279: 393–96.
2 Yuen KY, Chan PKS, Peiris M, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *Lancet* 1998; 351: 467–71.
3 Peiris JSM, Yu WC, Leung CW, et al. Re-emergence of fatal human influenza A subtype H5N1 disease. *Lancet* 2004; 363: 617–19.
4 Beigel JH, Farrar J, Han AM, et al. Avian influenza A (H5N1) infection in humans. *N Engl J Med* 2005; 353: 1374–85.

RC#34 – WOOD, D.M.; DARGAN, P.I.; BUTTON, J.; HOLT, D.W.; OVASKA, H.; RAMSEY, J.; JONES, A.L. Collapse, reported seizure—and an unexpected pill. **The Lancet**, v. 369, n. 9571, p. 1490, 2007.

Case Report

Collapse, reported seizure—and an unexpected pill

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Lancet 2007; 369: 1490
See Comment page 1411

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In May, 2006, on a Bank Holiday weekend, an 18-year-old woman presented to an inner-city London emergency department. She had been at a nightclub with friends and purchased tablets, which she understood to be Ecstasy or amfetamines, from a dealer. After ingesting five tablets, she collapsed in the nightclub and appeared to have a seizure lasting 10 min. On arrival in the emergency department, she was agitated and had dilated pupils (8 mm), sinus tachycardia (156 bpm), and a blood pressure of 150/51 mm Hg. Her score on the Glasgow coma scale was 15 and she was apyrexial (35·9°C). She had no significant past medical history and was on no regular medication.

She was one of seven patients to attend the department that night with a similar presentation. We therefore considered it possible that she had taken a contaminated drug, or a substance not previously sold in the area; and we took a serum sample for analysis, in addition to treating the patient symptomatically with intravenous benzodiazepines (4 mg lorazepam followed by 15 mg diazepam). After 12 h, she was asymptomatic and discharged with advice to avoid recreational drugs. The serum sample was analysed by gas chromatography with mass-spectrometric detection (GCMS); 1-benzylpiperazine was detected at a concentration of 2·5 mg/L. Toxicological screening of the same serum sample did not detect the presence of other piperazines, other drugs, or ethanol. A tablet purchased by the patient (figure) was also analysed, and found to contain 1-benzylpiperazine.

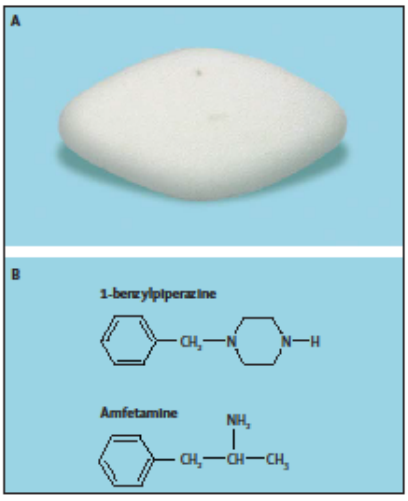

Figure: 1-benzylpiperazine
(A) One of the tablets purchased by the patient. (B) 1-benzylpiperazine and amfetamine.

1-benzylpiperazine is one of the piperazine family of drugs, initially developed as veterinary anthelmintic agents in the 1950s. Its chemical structure is similar to that of amfetamine.[1] Piperazines are marketed in the UK, where they are legally available in shops and over the internet, as having similar effects to controlled recreational drugs; pills containing piperazines are known as "pep pills".[2] No reliable data are available on the consumption of piperazines in the UK, although one manufacturer claims that "over 20 million pills have been consumed in New Zealand with no deaths, or significant lasting injuries".[2] However, in initial clinical trials of 1-benzylpiperazine, adverse effects similar to those of amfetamines were noted.[3] A prospective study in New Zealand identified adverse effects including nausea, vomiting, tachycardia, hypertension, anxiety, and agitation among 80 patients presenting to emergency departments after 1-benzylpiperazine ingestion.[4] Seizures were reported in 15 (19%), at up to 8 h after ingestion. Three patients had potentially life-threatening recurrent seizures; ingestion of 1-benzylpiperazine by these patients was confirmed by toxicological screening of their urine. Other potentially serious adverse effects included QTc prolongation (QTc duration 430–490 ms in 32 patients) and hyponatraemia (serum sodium concentration 118 mmol/L and serum osmolality 242 mmol/kg) in one patient. Clinicians should be aware of the potential presenting features of piperazine toxicity, particularly because commercially available urine toxicological screening kits for drugs of abuse may not detect piperazines. All patients with strongly suspected or reported ingestion of 1-benzylpiperazine should have an initial baseline ECG, to seek features of cardiotoxicity. They should be observed for up to 8 h after ingestion, because the onset of seizures can be delayed. Initial treatment should be based on the clinical presentation. Further management can require the advice of a clinical toxicologist.

References
1 Wikström M, Holmgren P, Ahlner J. A 2 (N-benzylpiperazine) a new drug of abuse in Sweden. *J Anal Toxicol* 2004; 28: 67–70.
2 Spiritualhigh.co.uk—Staying safe on PEP pills. http://www.spiritualhigh.co.uk/information/drug-harm-minimisation-and-legal-highs/staying-safe-on-pep-pills/3-7-7-19 (accessed April 2, 2007).
3 Bye C, Munro-Faure A D, Peck AW, Young PA. A comparison of the effects of 1-benzylpiperazine and dexamphetamine on human performance tests. *Eur J Clin Pharmacol* 1973; 6: 163–69.
4 Gee P, Richardson S, Wolhersdorf W, Moore G. Toxic effects of BZP-based herbal party pills in humans: a prospective study in Christchurch, New Zealand. *N Z Med J* 2005; 118: U1784.

RC#35 – LEUNG, W.K.; BJARNASON, I.; WONG, V.W.S.; SUNG, J.J.Y.; CHAN, F.K.L. Small bowel enteropathy associated with chronic low-dose aspirin therapy. **The Lancet**, v. 369, n. 9561, p. 614, 2007.

Case Report

Small bowel enteropathy associated with chronic low-dose aspirin therapy

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Lancet 2007; 369: 614

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In April, 2005, a 79-year-old Chinese man presented with severe iron deficiency anaemia (haemoglobin 67 g/L). He had no history of peptic ulcer disease and there were no signs or symptoms of gastrointestinal bleeding or disease. He had had a myocardial infarction in 1999, and had been taking aspirin 80 mg daily since then; he was not using any non-steroidal anti-inflammatory drugs (NSAIDs) or herbal preparations. Upper and lower gastrointestinal endoscopy failed to identify any bleeding lesions. He was supportively transfused, and misoprostol 400 µg daily was empirically added.

In the subsequent 7 months, he had a progressive drop in haemoglobin from 106 g/L (post-transfusion) to 54 g/L. He developed bilateral ankle oedema, with serum albumin concentration dropping from 39 g/L to 23 g/L. There was no proteinuria and the cause of hypoalbuminaemia was suspected to be loss from the gastrointestinal tract. A technetium-99m-labelled human serum albumin scan, which is purported to be a sensitive test for a protein losing enteropathy, was normal. Small bowel capsule endoscopy (Olympus, Tokyo, Japan), however, showed multiple small bowel ulcers, particularly in the ileal region (figure A and B). In view of the possible link between aspirin therapy and small bowel enteropathy, aspirin was withheld. A repeat capsule endoscopy 3 months later showed a few small healing erosions only (figure C and D). When last seen in July, 2006, our patient remained asymptomatic with no oedema or anaemia (haemoglobin 122 g/dL), and his serum albumin was 41 g/L.

Small bowel injury is increasingly recognised to be an important complication of NSAID therapy. NSAIDs cause varying degrees of small bowel injury from increased intestinal permeability, intestinal inflammation, protein loss, blood loss, and ulcerations, to perforation and diaphragm-like strictures.[1] In our study, comparing the gastrointestinal tolerability of celecoxib with diclofenac and a proton pump inhibitor, we found that 30% of the serious gastrointestinal events were distal to the duodenum with one death due to small bowel perforation.[2] Post-hoc analysis of a large-scale clinical outcome trial showed that lower gastrointestinal events accounted for 40% of all serious gastrointestinal events in patients on NSAIDs.[3] The difficulty in assessing the severity of NSAID-enteropathy was previously hampered by the lack of reliable tests for examining the small bowel. With the advent of capsule endoscopy and double balloon enteroscopy, small bowel injury can now be directly visualised. Capsule endoscopy corroborates the high prevalence of NSAID-enteropathy demonstrating that about 70% of regular NSAID users have small bowel erosions and ulcers.[4] Here we illustrate a case of severe enteropathy induced by low-dose aspirin that has many striking similarities with NSAID-enteropathy. Although aspirin at anti-inflammatory drug doses can cause stomach and duodenal ulcers, it is generally believed that aspirin does not cause any small bowel damage based on intestinal permeability and faecal inflammatory marker studies.[3] Our observation not only challenges the safety of aspirin on small bowel mucosa but also raises questions about the efficacy of misoprostol as a prophylactic treatment against enteropathy.[5] Low-dose aspirin, used for cardiovascular prophylaxis, is one of the most commonly prescribed medications worldwide. The demonstration of a severe form of enteropathy with this drug suggests the need to define the extent of this potential problem. Increasing clinical awareness and appropriate early investigation are needed to establish the proper diagnosis.

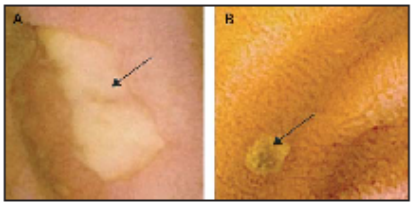

Figure: Small bowel ulcers
Large small bowel ulcers noted on first capsule endoscopy while the patient was taking aspirin (A). Follow-up examination 3 months after termination of aspirin showing a small and healing small bowel ulcer (B).

Acknowledgments

I Bjarnason has received research grants or lecture fee honoraria from Otsuka Pharmaceuticals, Pfizer, Novartis, and AstraZeneca. J J Y Sung is a consultant to AstraZeneca and Altana. F K L Chan has received a research grant from Pfizer NY and lecture fee honorarium from TAP Pharmaceuticals; he is also a consultant to Takeda Japan. There was no source of funding for this case report.

References

1 Bjarnason I, Hayllar J, MacPherson AJ, Russell AS. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. *Gastroenterology* 1993; 104: 1832–47.
2 Chan FKL, Hung LC, Suen BY, et al. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. *N Engl J Med* 2002; 347: 2104–10.
3 Laine L, Connors LG, Reicin A et al. Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. *Gastroenterology* 2003; 124: 288–92.
4 Graham DY, Opekun AR, Willingham FF, Qureshi WA. Visible small-intestinal mucosal injury in chronic NSAID users. *Clin Gastroenterol Hepatol* 2005; 3: 55–59.
5 Morris AJ, Murray L, Sturrock RD, Madhok R, Capell HA, Mackenzie JF. Short report: the effect of misoprostol on the anaemia of NSAID enteropathy. *Aliment Pharmacol Ther* 1994; 8: 343–46.

RC#36 – SCHRAUDER, A.; HENKE-GENDO, C.; SEIDEMANN, K.; SASSE, M.; CARIO, G.; MOERICKE, A.; SCHRAPPE, M.; HEIM, A.; WESSEL, A. Varicella vaccination in a child with acute lymphoblastic leukaemia. **The Lancet**, v. 369, n. 9568, p. 1232, 2007.

Case Report

Varicella vaccination in a child with acute lymphoblastic leukaemia

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Lancet 2007; 369: 1232

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In July, 2003, during reinduction treatment 5 months after diagnosis of acute lymphoblastic leukaemia (ALL), a 4-year-old girl presented with generalised tonic-clonic seizures. She had been treated according to protocol ALL-BFM 2000. Cranial CT and analysis of cerebrospinal fluid showed no signs of cerebral haemorrhage. Ultrasonography showed an enlarged liver and no signs of ascites or veno-occlusive disease. Her skin appeared normal, with no vesicular rashes. Blood tests showed only raised concentrations of aminotransferases. During the next few hours, she developed respiratory insufficiency, petechiae, haematomas, and vesicular lesions of the oral and vaginal mucosal. On the assumption of an underlying infectious cause, intravenous treatment with piperacillin, sulbactam, tobramycin, IgG, and aciclovir was initiated. 48 h after the first seizure, her laboratory test results deteriorated, with aspartate and alanine aminotransferase concentrations increasing to 20 864 U/L and 16 029 U/L, respectively, and the full blood cell count indicated pancytopenia. Within 12 h, she developed multi-organ failure (liver, renal, and circulatory failure, and acute respiratory distress syndrome [ARDS]), necessitating artificial ventilation. Serostatus for varicella-zoster virus (VZV) was negative, but PCR for VZV was positive in peripheral blood samples (7×10^6 genome copies per mL). VZV was also isolated from a nasopharyngeal swab but not from cerebrospinal fluid. PCR analysis of peripheral blood was negative for hepatitis B and C viruses, herpes simplex virus 1 and 2, Epstein-Barr virus, cytomegalovirus, adenovirus, enterovirus, human herpes virus 6, and parvovirus B19. High doses of VZV-IgG were added to the treatment. Despite haemodialysis and ventilation, the child died of progressive ARDS and multi-organ failure 10 days after admission.

On receiving the positive VZV-PCR results, the mother recalled that her daughter had received live attenuated VZV vaccine (Varilrix) at another hospital 32 days before the onset of symptoms. Partial sequencing of VZV genes 38 and 54[2] isolated from the patient excluded a wild-type VZV infection and showed that viraemia was caused by the VZV vaccine strain OKA (figure). Vaccination was done 5 months after complete remission had been achieved; at that time lymphocyte count was more than $1\cdot5\times10^9$/L, and chemotherapy was interrupted for 1 week before and after vaccination.

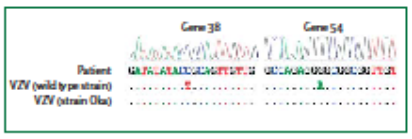

Figure: Comparison of VZV sequences isolated from the patient with several fully sequenced VZV database entries including two VZV OKA vaccine strains
Two genes (or[]38 and or[]54) were sequenced and aligned to VZV sequences (accession numbers: DQ008354 and X04370) by use of the ClustalW-algorithm. Dots indicate homology to the patient's sequence.

Deaths after vaccinations with numerous attenuated viruses are well established. Fatal wild-type VZV infections have been reported in ALL patients during chemotherapy[1] and after bone-marrow cell transplantation.[2] Therefore, VZV vaccination is a useful, and generally accepted, therapeutic measure for patients with ALL in remission. Studies of VZV vaccination 3–4 months after autologous stem-cell transplantation,[4] and in early ALL maintenance therapy,[5] did not show fatal side-effects. However, any interruption of maintenance therapy in ALL can adversely affect outcome for the patient. In our patient, liver failure developed 5 weeks after VZV vaccination, which indicates longstanding replication of OKA strain in the liver. This suggestion accords with observations of late onset of complications (fever, vesicles, and severe hepatitis) in immunocompromised patients after VZV vaccination.[3] Therefore, although we cannot fully exclude that intensification of chemotherapy could have aggravated her symptoms, we suggest that VZV vaccination in seronegative children with leukaemia, who are in complete remission for at least 12 months, should not be undertaken until at least 9 months after the end of immunosuppressive treatment (including maintenance therapy) and not before a lymphocyte count of at least $1\cdot5\times10^9$/L has been ascertained. In addition, high-risk patients should remain under close surveillance in the critical phase (6 weeks after vaccination) so that immediate antiviral treatment with aciclovir can be initiated in symptomatic children.

Acknowledgments
André Schrauder and Cornelia Henke-Gendo contributed equally to the report.

References

1 Sauerbrei A, Wutzler P. Laboratory diagnosis of central nervous system infections caused by herpes viruses. *J Clin Virol* 2002; 25 (suppl 1): S45–51.
2 Muller I, Aspinus C, Beck R, Baltmann B, Niethammer D, Klingebiel T. Noncutaneous Varicella-zoster virus (VZV) infection with fatal liver failure in a child with acute lymphoblastic leukemia (ALL). *Med Pediatr Oncol* 2001; 37: 145–47.
3 David DS, Tegtmeier BR, O'Donnell MR, Paz IB, McCarty TM. Visceral varicella-zoster after bone marrow transplantation: report of a case series and review of the literature. *Am J Gastroenterol* 1998; 93: 810–13.
4 Ljungman P, Wang FZ, Nilsson C, Solheim V, Linde A. Vaccination of autologous stem cell transplant recipients with live varicella vaccine: a pilot study. *Support Care Cancer* 2003; 11: 739–41.
5 Leung TF, Li CK, Hung EC, et al. Immunogenicity of a two-dose regime of varicella vaccine in children with cancers. *Eur J Haematol* 2004; 72: 353–57.

RC#37 – RUSSELL, K.; BROADBRIDGE, C.; MURRAY, S.; WAGHORN, D.; MAHONEY, A. Gardening can seriously damage your health. **The Lancet**, v. 371, n. 9629, p. 2056, 2008.

Case Report

Gardening can seriously damage your health

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Lancet 2008; 371: 2056

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In May, 2007, a 47-year-old man was admitted with a 1-week history of productive cough, pleuritic chest pain, increasing shortness of breath, fever, and myalgia. He smoked ten cigarettes per day, and worked as a welder; he had no other medical history of note, and had previously been in good health. On presentation, his respiration rate was 30 breaths per min, and he had a fever (38°C). There were coarse crackles throughout both lungs. The patient had neutrophilia ($17·3\times10^9$/L; white cell count $18·6\times10^9$/L), but was also lymphopenic ($0·4\times10^9$/L). Chest radiography showed many irregular nodules throughout both lungs. Intravenous co-amoxiclav and clarithromycin were started for a presumed community-acquired pneumonia. However, the fever and dyspnoea did not abate. 2 days after admission, a C-reactive-protein concentration of 442 mg/L (417 mg/L on admission) suggested that inflammation was increasing; chest radiography showed extensive consolidation and nodular shadowing throughout both lungs (figure). After further blood tests and sputum cultures were taken, flucloxacillin was added. However, 24 h later, the patient became so short of breath despite supplementary oxygen, that he was transferred to the intensive-care unit (ICU). His arterial blood had a pH of 7·17, PaO_2 of 6·2 kPa, $PaCO_2$ of 6·6 kPa, and base deficit of 9·5. Serial blood gas measurements showed that endotracheal intubation and ventilation were not providing adequate gas exchange. With signs of overwhelming sepsis, including tachycardia, hypotension, pyrexia, and worsening renal function, we prescribed an inotrope (norepinephrine) and activated protein C and referred the patient to a regional specialist unit, for probable extracorporeal membrane oxygenation (ECMO). An HIV test was negative, but *Aspergillus fumigatus* had grown from two sputum samples. On closer questioning, the patient's partner revealed that his symptoms had started less than 24 h after he had dispersed rotting tree and plant mulch in the garden, when clouds of dust had engulfed him. Before transfer, we started treatment with intravenous liposomal amphotericin B.

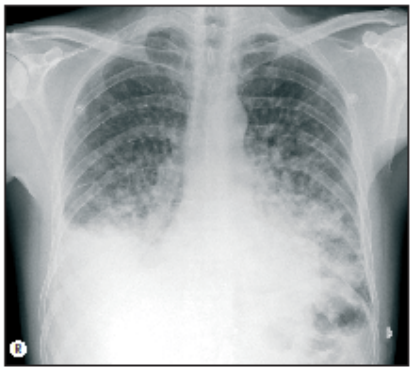

Figure: Acute invasive aspergillosis
Radiograph showing extensive consolidation and small round opacities (consistent with discrete infiltrates) throughout both lungs.

On arrival at the regional centre, less than 12 h after admission to our ICU, the patient was given venovenous ECMO via his femoral veins. Despite being given increasing amounts of inotropes, he remained hypotensive and developed acute renal failure. Continuous haemodiafiltration was begun, but his acidosis worsened and further treatment escalation was considered inappropriate. ECMO was withdrawn after 72 h; the patient died shortly thereafter. The diagnosis of aspergillosis was confirmed when the Mycology Reference Centre, Leeds, UK, analysed two serum samples, collected before the patient's transfer. The first sample contained a high aspergillus galactomannan antigen titre (index value >5·46, positive >0·5); the second sample showed significant aspergillus antibodies (40 mgA/L).

Aspergillus spores are often found on decaying plant matter. Inhalation of spores can cause allergic bronchopulmonary aspergillosis, pulmonary aspergilloma, or pulmonary aspergillosis—which can be acute and invasive, as in our patient, or chronic and necrotising. Unlike most patients with acute, invasive aspergillosis, our patient did not seem to be immunosuppressed;[1] however, smoking and welding could have damaged his lungs, increasing his vulnerability.[2] Since he died so quickly, we cannot exclude the possibility that he had an undetected immunodeficiency.[1] Acute aspergillosis after contact with decayed plant matter is rare, but may be considered an occupational hazard for gardeners.[3,4] Prompt treatment with an appropriate intravenous antifungal agent is essential. Although liposomal amphotericin B has been used in such cases, and was recommended treatment of choice within our hospital trust at the time of this case, more recent guidelines suggest voriconazole may currently be the optimum empirical therapy.[5]

References

1 Siddiqui S, Anderson VL, Hilligos DM, et al. Fulminant mulch pneumonitis: an emergency presentation of chronic granulomatous disease. *Clin Infect Dis* 2007; 45: 673–81.

2 Balkissoon R. A 26-year-old welder with severe non-reversible obstructive lung disease. *COPD* 2006; 3: 63–67.

3 Arendrup MC, O'Driscoll BR, Petersen E, Denning DW. Acute pulmonary aspergillosis in immunocompetent subjects after exposure to bark chippings. *Scand J Infect Dis* 2006; 38: 945–49.

4 Batard E, Ramadan K, Morin O, et al. Fatal acute granulomatous pulmonary aspergillosis in a healthy subject after inhalation of vegetal dust. *Eur J Clin Microbiol Infect Dis* 2003; 22: 357–59.

5 Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008; 46: 327–60.

RC#38 – ANDERSSON, M.I.; HUGHES, J.; GRDON, F.H.; IJAZ, S.; DONATI, M. Of pigs and pregnancy. **The Lancet**, v. 372, n. 9644, p. 1192, 2008.

Case Report

Of pigs and pregnancy

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Lancet 2008; 372: 1192

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In March, 2007, a 31-year-old woman was advised by her midwife to attend the antenatal department at St Michael's Hospital, because she had been itching all over her body for a week. She was 24 weeks pregnant. She had been pregnant twice before. Her first pregnancy had ended in miscarriage, at 11 weeks, and her second in intrauterine death, at 30 weeks. The cause of intrauterine death had not been identified; a thrombophilia screen and liver function tests had given normal results. The medical history was otherwise unremarkable.

The patient had no rash. Blood pressure, and findings on basic neurological examination, were normal. Although she was not jaundiced, and had no signs of chronic liver disease, liver function was very abnormal (figure); blood test results were otherwise normal. Ultrasonography of the fetus, and doppler ultrasonography of the umbilical artery (UA), showed nothing abnormal. An autoantibody screen was negative; tests showed no evidence of recent or active infection with hepatitis A, B, or C viruses, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, adenovirus, parvovirus B19, toxoplasma, chlamydia, *Mycoplasma pneumoniae*, or Q fever. HIV-antibody testing gave a negative result. Histopathology of a liver biopsy sample showed no fibrosis or cirrhosis; however, we saw a patchy lymphocytic infiltrate, and interface hepatitis (ie, piecemeal necrosis). These findings were consistent with autoimmune active chronic hepatitis. We therefore gave the patient a steriod. The patient had no apparent risk factors for hepatitis E: she had not recently been abroad, had not eaten any unusual foods, and did not live in an area of increased risk.[1] Nonetheless, as part of our routine screen, we sent a blood sample to a reference laboratory, to test for hepatitis E. During the remainder of the pregnancy, we assessed the patient weekly, estimating fetal weight, measuring the amniotic fluid volume index (AFI), and doing doppler ultrasonography of the UA.

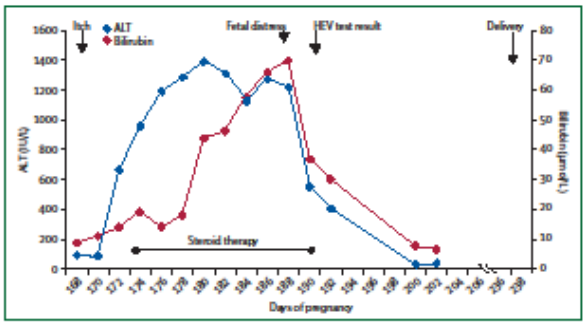

Figure: Hepatitis E in pregnancy

Results were normal, except for a transiently reduced AFI, and increased pulsatility of the UA, at 27 weeks. We gradually reduced the dose of the steriod, so it was discontinued at just over 27 weeks. Just before discontinuation, liver function test results started to improve; at around the same time, we received the hepatitis E test results. Hepatitis E IgM and genotype 3 RNA were detected, indicating recent, autochthonous infection.[1] We subsequently documented the presence of IgG, indicating seroconversion. At 34 weeks, the patient's membranes ruptured, so labour was induced by administration of prostaglandin. A healthy baby, weighing 1·85 kg, was delivered.

Hepatitis E is caused by a small, non-enveloped virus with an RNA genome. Transmission is faecal-oral; waterborne epidemics have been described in some resource-poor countries, such as Sudan (Darfur) and India. The virus is found in pigs. Contact with pigs, or with certain foods (shellfish, pig liver, venison, boar), seems to be linked to sporadic infections in developed countries.[1,2] Since 2004, the number of reported cases of hepatitis E in the UK has substantially increased. White men more than 55 years of age, living in coastal or estuarine areas, have been especially vulnerable.[1,2] People whose infection seems unrelated to travel have a virus with genotype 3, closely related to that found in British pigs.[3] Hepatitis E virus can cause no symptoms, self-limiting hepatitis, or acute liver failure; immunocompromised patients are at risk of chronic infection.[4] In late pregnancy, infection can be especially severe, and cause fetal infection; infection causing jaundice is associated with intrauterine death, stillbirth, and premature delivery.[4] We do not think that infection with hepatitis E caused our patient's previous stillbirth, since, at the time of assessment, her infection was acute. However, hepatitis infection may have caused the transient probable fetal distress at 27 weeks; we were unable to measure fetal antibodies, to test this hypothesis. In common with others,[1,2,5] we believe that testing for hepatitis E should be routine in the UK, in cases of suspected viral hepatitis.

References

1 Ijaz S, Arnold E, Banks M, et al. Non-travel-associated hepatitis E in England and Wales: demographic, clinical, and molecular epidemiological characteristics. *J Infect Dis* 2005; 192: 1166–72.

2 Dalton HR, Thurairajah PH, Fellows HJ, et al. Autochthonous hepatitis E in southwest England. *J Viral Hepat* 2007; 14: 304–09.

3 Kamar N, Selves J, Mansuy JM, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. *N Engl J Med* 2008; 358: 811–17.

4 Patra S, Kumar A, Trivedi SS, Puri M, Sarin SK. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. *Ann Intern Med* 2007; 147: 28–33.

5 Herremans M, Vennema H, Bakker J, et al. Swine-like hepatitis E viruses are a cause of unexplained hepatitis in the Netherlands. *J Viral Hepat* 2007; 14: 140–46.

RC#39 – FLEMING, J.D.; McSORLEY, A.; BATES, K.M. Blood, semen, and an innocent man. **The Lancet**, v. 371, n. 9616, p. 958, 2008.

Case Report

Blood, semen, and an innocent man

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Lancet 2008; 371: 958

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In August, 2007, a 30-year-old doctoral student, from Nigeria but living in London, noticed bright red blood in his ejaculate. The problem persisted for 2 months, so he went to see his general practitioner. There was no history of injury to the genitals or the prostate; the patient had used barrier contraception with his current and previous two girlfriends. The patient was not physically examined, but was advised to attend a walk-in genitourinary clinic. When he did so, 3 days later, his blood pressure was 244/170 mm Hg. He was given 5 mg amlodipine, and sent to hospital. There, repeated measurements, with a manual sphygmomanometer, gave a blood pressure of around 239/141 mm Hg, in both arms.

The patient's blood pressure had last been measured 10 years before, when he had been told it was "a little high". He had never taken antihypertensive drugs. He had been feeling entirely well, although, on close questioning, he described having had a nosebleed and headache 2 months before noticing the blood in his ejaculate. He had no other relevant medical history, and was a lifelong non-smoker. Inspection showed no signs of Cushing's syndrome, acromegaly, or systemic sclerosis. Physical examination, including neurological, genital, and rectal examination, showed nothing abnormal—notably, radiofemoral delay and renal bruits were absent, and the patient scored 10/10 on the abbreviated mental test score. Dipstick testing of urine showed much protein, but not blood. Urine microscopy showed no casts. Blood tests showed nothing abnormal: notably, concentrations of calcium, creatinine, C-reactive protein, autoantibodies, and prostate-specific antigen were normal. Serological and immunological testing showed no evidence of HIV or tuberculosis, respectively. Microscopy and culture of urethral swabs showed no evidence of syphilis, chlamydia, or gonorrhoea. An electrocardiogram showed severe left-ventricular hypertrophy; radiography of the chest showed no evidence of aortic coarctation. Fundoscopy showed bilateral papilloedema, but no haemorrhages. Ultrasonography showed kidneys of normal size, without cysts. CT of the abdomen showed nothing abnormal—and specifically, no adrenal masses. The patient's blood pressure was lowered gradually, over several days, with amlodipine, ramipril, and intravenous glyceryl trinitrate; meanwhile, we took three 24-h urine collections: after the collections were done, we started treatment with atenolol, having stopped the glyceryl trinitrate. Urinary concentrations of catecholamines were normal, confirming that the patient did not have a phaeochromocytoma. Retinal photography showed resolution of the papilloedema, but many cotton-wool spots and nerve-fibre-layer ("flame") haemorrhages (figure)—consistent with grade 3 hypertensive retinopathy. The plasma renin:aldosterone ratio is awaited. The diagnosis is essential hypertension or hyperaldosteronism. The patient was discharged 10 days after admission. When last seen by us, in late November, 2007, his blood pressure was around 150/96 mm Hg; he continued to feel well, and had no blood in his semen.

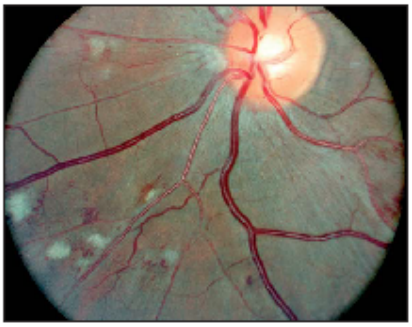

Figure: Retinal photography of a man with malignant hypertension

Haematospermia is most commonly caused by infection or injury—including iatrogenic injury from taking biopsy samples of the prostate.[1] Other causes include stones, cysts, vascular abnormalities—and severe hypertension,[1] which causes an estimated 5% of cases.[2] Malignant hypertension is defined as blood pressure over 180/100 mm Hg, with papilloedema or retinal haemorrhage.[3] Although malignant hypertension can occur in essential hypertension, causes of secondary hypertension should always be sought. Apart from haematospermia, our patient was asymptomatic—as are around 10% of people with malignant hypertension.[4] Nonetheless, left-ventricular hypertrophy, proteinuria, and retinopathy indicated pronounced end-organ damage, consistent with severe, longstanding hypertension.

Acknowledgments

We thank Paul Kinnear and John Arnold, for ophthalmological review and technical support.

References

1 Ahmad I, Krishna NS. Hemospermia. *J Urol* 2007; 177: 1613–18.
2 Jinza S, Noguchi K, Hosaka M. Retrospective study of 107 patients with hematospermia. *Hinyokika Kiyo* 1996; 43: 103–07.
3 Williams B, Poulter NR, Brown MJ, et al. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004; 18: 139–85.
4 Lip GY, Beevers M, Beevers G. The failure of malignant hypertension to decline: a survey of 24 years' experience in a multiracial population in England. *J Hypertens* 1994; 12: 1297–305.

RC#40 – PETER, J.V.; PRABHAKAR, A.T.; PICHAMUTU, K. In-laws, insecticide—and a mimic of brain death. **The Lancet**, v. 371, n. 9612, p. 622, 2008.

Case Report

In-laws, insecticide—and a mimic of brain death

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Lancet 2008; 371: 622
See Comment page 538
See Articles page 579
See Review page 597

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In December, 2006, a 28-year-old woman from Andhra Pradesh, India, impulsively swallowed 50 mL of phorate (a diethyl organophosphorus insecticide) after quarrelling with her husband's family, with whom she lived. Her in-laws saw her vomit and briefly lose consciousness—and, suspecting what she had done, took her by moped to a local hospital. The patient was given gastric lavage, before being transferred by ambulance to the emergency department at our hospital, 400 km away. The patient arrived 9 h 30 min after her suicide attempt. Her giddiness and vomiting had persisted, and she now also had abdominal pain; but she was stable.

5 h after arrival, the patient became increasingly breathless; her arterial oxygen saturation decreased to 77%, necessitating intubation and ventilation. She was transferred to our intensive-care unit. We prescribed atropine, at 4 mg/h, to counteract the effects of organophosphate. Although the chest radiograph was clear, we suspected that the breathlessness was caused by aspiration, and prescribed penicillin and levofloxacin. We also prescribed morphine and lorazepam, to keep the patient comfortable but easily arousable. We titrated the dose of atropine to the patient's heart rate, but aimed also for quiet bowel sounds, pupils that were neither contracted nor dilated, a clear-sounding chest, and a systolic blood pressure higher than 90 mm Hg. The patient recovered steadily until her 4th day in hospital, when her score on the Glasgow coma scale (GCS) decreased to 8T (figure), prompting us to discontinue sedation. Over the next 12 h, the patient's limbs trembled and jerked, although she did not have seizures; we noted that the muscular tone of the limbs had increased. The GCS score then decreased to 2T over the next 12–24 h. We could not find any cause for the coma, other than organophosphate poisoning, despite doing blood tests (including arterial blood gases), CT of the head, a lumbar puncture, and monitoring the patient's arterial oxygen saturations. The serum concentration of pseudocholinesterase was 254 IU/mL (normal range 3000–6000 IU/mL). During the coma, findings on examination were largely consistent with brain death: oculocephalic, pupillary, corneal, and deep-tendon reflexes were absent; the patient did not react to painful stimuli or caloric stimulation; she did not breathe spontaneously. Unlike in brain death, however, the pupils remained constricted. An electroencephalogram showed global suppression of cortical activity. We continued to prescribe atropine. After 5 days of deep coma, the patient started to recover, and was fully conscious by day 15. She later developed pneumonia, but was discharged from the hospital, in good health, after a 39-day stay. When last seen, in March, 2007, she was well.

Organophosphates inhibit acetylcholinesterase, causing overstimulation of nicotinic, muscarinic, and central acetylcholine receptors. Neurological manifestations of organophosphate poisoning range from anxiety, restlessness, and tremors to seizures, central respiratory depression, and coma.[1] Although neurological manifestations are usually observed shortly after poisoning occurs, they can be delayed.[2,3] Recognition of delayed symptoms and signs can avert unfortunate misdiagnoses, such as brain death. Phorate is lipid-soluble: we conclude that much of the swallowed insecticide was absorbed by the patient's body fat, and released several days into her hospital stay.[2] Patients who have swallowed lipid-soluble organophosphates may benefit from treatment with oximes, which separate organophosphate from acetylcholinesterase, for longer than patients who have swallowed other organophosphates. By contrast, gastric lavage may not be helpful,[4] although patients' relatives may demand it, as a sign that all possible efforts are being made. Most hospitals in rural India are able to provide gastric lavage and atropine—however, few are able to intubate and ventilate the patient, and many prefer to avoid the legal and administrative complications of suicide attempts. Banning the most toxic pesticides in China and India could save more than 150 000 lives a year.[5]

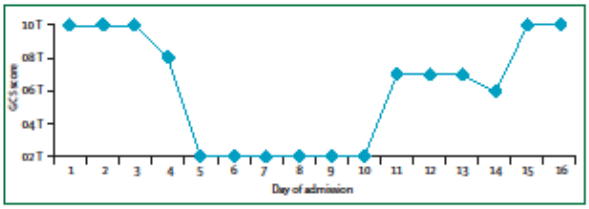

Figure: Delayed-onset coma in organophosphate poisoning
Since the verbal component of the GCS cannot be accurately assessed in patients who are intubated, the GCS is given on a scale of 2T–10T, where 2T is equivalent to 3, and 10T is equivalent to 15.

References

1 Peter JV, Cherian AM. Organic insecticides. *Anaesth Intensive Care* 2000; 28: 11–21.

2 Davies JE, Barquet A, Freed VH, et al. Human pesticide poisonings by a fat-soluble organophosphate insecticide. *Arch Environ Health* 1975; 30: 608–13.

3 Yardan T, Baydin A, Aygun D, Karatas AD, Deniz T, Doganay Z. Late-onset intermediate syndrome due to organophosphate poisoning. *Clin Toxicol (Phila)* 2007; 45: 733–34.

4 Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. *Lancet* 2008; 371: 597–607.

5 Gunnell D, Fernando R, Hewagama M, Priyangika WDD, Konradsen F, Eddleston M. The impact of pesticide regulations on suicide in Sri Lanka. *Int J Epidemiol* 2007; 36: 1235–42.

RC#41 – KIDD, I.M.; DOWN, J.; NASTOULI, E.; SCHULMAN, R.; GRANT, P.R.; HOWELL, D.C.J.; SINGER, M. H1N1 pneumonitis treated with intravenous zanamivir. **The Lancet**, v. 374, n. 9694, p. 1036, 2009.

Case Report

H1N1 pneumonitis treated with intravenous zanamivir

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Lancet 2009; 374: 1036
Published Online September 4, 2009
DOI:10.1016/S0140-6736(09)61528-2

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For additional laboratory test results and further reading see Online for webappendix

On July 8, 2009, a 22-year-old woman, neutropenic after chemotherapy for Hodgkin's disease, was referred to ICU with 3 days' (d) increasing dyspnoea, bilateral chest infiltrates, and laboratory-confirmed pandemic H1N1 2009 influenza virus infection not responding to oseltamivir 75 mg twice daily and broad-spectrum antimicrobials (meropenem, teicoplanin, and caspofungin). No other organisms were detected from blood or respiratory tract. Deterioration necessitated invasive ventilation from ICU d 3 (figure). She remained in single organ failure requiring high inspired oxygen, protective lung ventilation (tidal volumes ≤6–8 mL/kg), and neutral fluid balance. Hydrocortisone was given (d 3–6), then gradually reduced and discontinued (d 13). Neutropenia recovered by d 6, although lymphopenia remained (webappendix). High level H1N1 RNA was detected in bronchoalveolar lavage (BAL) on d 10, despite 6 d oseltamivir given nasogastrically; in view of high volume gastric aspirates, this was replaced by nebulised zanamivir (d 6–13). Treatment escalation on d 13–16 delivered neither clinical nor virological response (figure).

On d 16, intravenous zanamivir 600 mg twice daily (provided by GlaxoSmithKline, Brentford, Middlesex) was started as unlicensed antiviral monotherapy; agreement for use was granted by the Hospital Formulary Committee and next of kin. Methylprednisolone was also started. Our patient's condition improved within 48 h, with a decrease in BAL viral load on d 21. She was extubated on d 21 and discharged to the ward on d 24. Antiviral and steroid treatment were stopped on d 26 and d 28, respectively. Since ICU discharge she remains stable. Of four nasopharyngeal swabs taken post-ICU, the third, taken on d 10 post-ICU, showed H1N1 RNA C_t of 24, although a repeat sample taken the next day was negative. In view of her immunosuppressed state and ongoing lymphopenia, inhaled zanamivir was started as a precaution, although her clinical status remained unchanged.

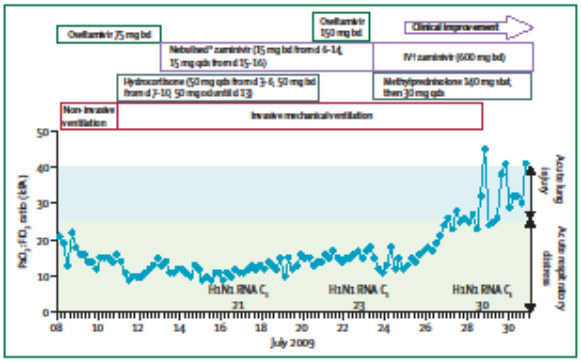

Figure: Temporal course
*Unlicensed route. †Unlicensed preparation.

Deaths due to pandemic H1N1 are primarily related to severe respiratory failure.[1] Our patient did not respond to extensive antiviral treatment and 2 weeks' mechanical ventilation. RT-PCR detects viral RNA rather than infectious virus, but is used to semi-quantitatively assess replication. The small difference in C_t between d 10 and 16 implied continued high-level replication. Effective treatment depends on adequate enteral absorption (oseltamivir) and an uninhibited access to the infected respiratory tissue (zanamivir). In view of high volume gastric aspirates, we used nebulised zanamivir. Since her inflamed, atelectatic lungs were probably impeding adequate drug absorption, and clinical improvement was not forthcoming, we used intravenous (unlicensed) zanamivir. High dosing achieves effective respiratory epithelial concentrations and is well-tolerated.[2,3] Our patient recovered with no side-effects. Despite inherent sampling inconsistencies, the change in BAL C_t from 23 to 30 after 5 d treatment indicates an approximate 128-fold fall in viral load. Persisting high-level H1N1 replication may drive ongoing lung inflammation and fibrosis (implied by our patient's poor lung compliance). We reasoned that synergism could exist between intravenous zanamivir and high-dose corticosteroids, although this approach may be considered controversial and is not recommended in treatment guidelines.[1] However, controlled trials are lacking and a rationale does exist for the use of corticosteroids in ARDS.[4] Although this is a single case report and direct cause and effect cannot be confirmed, the improvement in clinical status following intravenous zanamivir encourages prompt further investigation, both alone and in combination with high-dose methylprednisolone.

Contributors

All authors contributed to patient care and writing the report.

Acknowledgments

Support provided by the UK DoH NIHR CBRC funding scheme.

References

1 CDC. Interim guidance on antiviral recommendations for patients with novel influenza A (H1N1) virus infection and their close contacts (May, 6 2009). http://www.cdc.gov/h1n1flu/recommendations.htm (accessed August 21, 2009).
2 GSK. Guidance document: zanamivir aqueous solution for compassionate use in serious influenza illness. July 29, 2009, GSK: Greenford, UK.
3 Calfee DP, Peng AW, Cass LM, Lobo M, Hayden FG. Safety and efficacy of intravenous zanamivir in preventing experimental human influenza A virus infection. *Antimicrob Agents Chemother* 1999; 43: 1616–20.
4 Tang BM, Craig JC, Eslick GD, Seppelt I, McLean AS. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care Med* 2009; 37: 1594–603.

RC#42 – KASKI, D.; MEAD, S.; HYARE, H.; COPER, S.; JAMPANA, R.; OVERELL, J.; KNIGHT, R.; COLLINGE, J.; RUDGE, P. Variant CJD in an individual heterozygous for PRNP codon 129. **The Lancet**, v. 374, n. 9707, p. 2128, 2009.

Case Report

Variant CJD in an individual heterozygous for *PRNP* codon 129

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Lancet 2009; 374: 2128

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A 30-year-old man was admitted to hospital in June, 2008, with a 13-month history of personality change, progressive unsteadiness, and intellectual decline. He complained of severe leg pain and poor memory. 2 months later he developed visual hallucinations and falsely believed he had an abdominal tumour. Symptoms worsened over the next 3 months. In October, 2008, his score on the mini mental state examination was 26/30. Pursuit eye movements were saccadic. He had a pout reflex. There was mild ataxia in the arms. His legs were severely ataxic with brisk tendon reflexes and a left extensor plantar response. He needed two crutches to walk. Medical history included tonsillectomy and removal of a cervical lymph node 15 years previously but he had never had a blood transfusion or received implantation of other human tissues.

EEG showed slow wave activity. CSF protein, glucose, and cell count were normal but the 14-3-3 protein was positive. MRI of the brain was consistent with the pulvinar sign (figure A). Although not all neuroradiologists consulted considered the pulvinar sign positive, quantitative assessment showed symmetrical higher signal in the pulvinar nuclei than the caudate nuclei (figure B). Extensive screens for genetic, metabolic, and autoimmune diseases, including those induced by neoplasia, were negative. *PRNP* analysis did not show any known disease-associated mutations; codon 129 was heterozygous. A clinical diagnosis of variant Creutzfeldt-Jakob disease (vCJD) was made on the basis of a characteristic clinical onset and progression, exclusion of other diagnoses, and MRI findings. Sporadic CJD was judged unlikely given the combination of young age, clinical features, MRI findings, and absence of pseudoperiodic complexes on EEG. His carers did not want further investigation. His condition deteriorated and he died in January, 2009. Autopsy was not done.

Human prion diseases have acquired, sporadic, and inherited aetiologies, show wide phenotypic heterogeneity, and are associated with propagation of infectious prions of many distinct strain types.[1] Since 1994, about 200 cases of vCJD, causally related to exposure to bovine spongiform encephalopathy (BSE) prions, have been identified worldwide. vCJD is generally seen in young adults, has characteristic neuropathological features and tissue distribution of infectivity, and a distinctive type 4 (London classification) molecular strain type.[2] A polymorphism at codon 129 (encoding methionine or valine) of the human prion protein gene (*PRNP*), constitutes a powerful susceptibility factor in all types of prion disease. In vCJD, every case genotyped to date has been methionine homozygous. In the other acquired prion diseases, cases have occurred in all genotypes but with different mean incubation periods,[1] which can span decades;[2] *PRNP* codon 129 heterozygotes generally have the longest incubation periods. There is a report of a recipient of a blood transfusion from a donor incubating vCJD who died of unrelated causes but showed signs of prion infection at autopsy and was *PRNP* codon 129 heterozygous.[3] Animal studies have suggested that different clinicopathological phenotypes could occur in people with various *PRNP* codon 129 genotypes.[4,5] The majority of the UK population have potentially been exposed to BSE prions but the extent of clinically silent infection remains unclear. About a third of the UK population are *PRNP* codon 129 methionine homozygous. If individuals with other genotypes are similarly susceptible to developing prion disease after BSE prion exposure, but with longer incubation periods, further cases, which may or may not meet diagnostic criteria for vCJD, would be expected in these *PRNP* codon 129 genotypes. However, prion disease susceptibility and incubation periods are also affected by other genetic loci, and the possibility remains that cases of vCJD to date may have unusual combinations of genotypes at these loci, yet to be fully characterised.

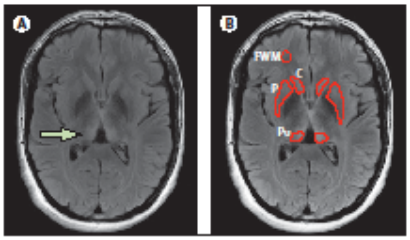

Figure: MRI
(A) Increased signal intensity in the pulvinar nucleus bilaterally (arrow). (B) MR signal intensity in the pulvinar (Pu) is higher than in the head of the caudate nuclei (C), putamen (P), and right frontal white matter (FWM).

Contributors
All authors were involved in discussion about diagnosis, care of the patient, and preparation of the report. Written consent to publish was obtained.

Conflicts of interest
JC is a director and shareholder of D-Gen Ltd, an academic spin-out company in the field of prion disease diagnosis, decontamination, and therapy. The other authors declare that they have no conflicts of interest.

References

1 Collinge J. Prion diseases of humans and animals: their causes and molecular basis. *Annu Rev Neurosci* 2001; 24: 519–50.
2 Collinge J, Whitfield J, McKintosh E, et al. Kuru in the 21st century—an acquired human prion disease with very long incubation periods. *Lancet* 2006; 367: 2068–74.
3 Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. *Lancet* 2004; 364: 527–29.
4 Asante E, Linehan J, Gowland I, et al. Dissociation of pathological and molecular phenotype of variant Creutzfeldt-Jakob disease in transgenic human prion protein 129 heterozygous mice. *Proc Natl Acad Sci USA* 2006; 103: 10759–64.
5 Wadsworth JD, Asante E, Desbruslais M, et al. Human prion protein with valine 129 prevents expression of variant CJD phenotype. *Science* 2004; 306: 1793–96.

RC#43 – KHOSROSHAHI, A.; STONE, J.R.; PRATT, D.S.; DESHPANDE, V.; STONE, J.H. Painless jaundice with serial multi-organ dysfunction. **The Lancet**, v. 373, n. 9673, p. 1494, 2004.

Case Report

Painless jaundice with serial multi-organ dysfunction

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Lancet 2009; 373: 1494

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In April, 2008, a 68-year-old man presented to us with pruritus and painless jaundice. 2 years earlier, he had developed aortic stenosis and undergone replacement of a bicuspid aortic valve and his dilated ascending aorta. Preoperative assessment showed extensive mediastinal and hilar lymphadenopathy. A lymph node obtained at the time of his surgery showed follicular hyperplasia. Pathology of the aorta was recorded as chronic sclerosing aortitis. 1 year later, he developed nodular, painless swellings in both submandibular regions. A diagnosis of sialadenitis was made. The submandibular gland swelling waxed and waned but remained largely asymptomatic. When he presented to us, total bilirubin was 88·92 µmol/L (normal <20·52 µmol/L), direct bilirubin was 53·01 µmol/L (<11·97 µmol/L), and alkaline phosphatase was 400 U/L (<120 U/L). CT of his abdomen showed a hypodense lesion in the liver and intrahepatic ductal dilatation, suggestive of malignant disease. There was also a mantle of soft tissue anterior to the aorta (figure A). Endoscopic retrograde cholangiopancreatography showed an ulcerated, stenotic papilla, with no evidence of malignant disease. His symptoms and hyperbilirubinaemia improved following a papillotomy.

His jaundice returned 2 months later. A repeat CT showed enlargement of the pancreatic head and a cystic lesion within the pancreas. His ESR was 128 mm/h (normal <20 mm/h). We remained concerned about undetected malignant disease. However, biopsy of the pancreas was negative for carcinoma. Liver biopsy showed a lymphoplasmacytic infiltrate, with positive staining for IgG4 (figure B). His serum IgG was 41·6 g/L (normal: 6·14 to 12·95 g/L), 86% of which was IgG4 (total IgG4 35·80 g/L; normal <1·35 g/L). Review of his aortic surgery specimen from 2 years earlier also demonstrated intense staining of plasma cells within the adventitia for IgG4 (figure C). Prednisone 40 mg/day led to a return to normal markers of liver function and serum IgG4 concentrations initially; azathioprine was added when our patient did not respond to the glucocorticoid taper. When last seen in March, 2009, he was asymptomatic on 12·5 mg of prednisone.

Our patient had IgG4-related systemic disease. His disease involved the aorta, liver, pancreas, and submandibular glands. The concept of IgG4-related systemic disease has emerged in the past several years from a clinical entity known as autoimmune pancreatitis. Autoimmune pancreatitis frequently mimics adenocarcinoma of the pancreas by causing painless jaundice, and has been diagnosed in 27% of patients undergoing the Whipple procedure.[1] IgG4-related systemic disease can affect various organs and anatomical sites, including the pancreas, biliary tract, salivary glands, retroperitoneum, aorta, kidney, lung, and prostate.[2,3] Most patients have marked increase of serum IgG4 concentrations. Extensive deposition of IgG4-positive plasma cells and T-lymphocyte infiltration are characterisitic of the disease. IgG4-related systemic diseases share certain pathological features irrespective of the affected organ. Tumorous swelling, diffuse lymphoplasmacytic infiltration, and obliterative phlebitis are common and have been reported in the setting of inflammatory abdominal aortic aneurysm.[4] The disease occurs predominantly in older men, is frequently associated with lymphadenopathy, and responds well to glucocorticoid therapy. The serum concentration of IgG4 can serve as a biomarker for treatment response. The triad of IgG4 concentration >1·35 g/L, infiltration of >50% IgG4+ plasma cells into tissue, and fibrosis or sclerosis has been proposed as preliminary diagnostic criteria.[4,5] However, the precise pathophysiology of this disease remains unclear. IgG4 may be a counter-regulatory mechanism to an elusive primary inflammatory process. IgG4-related systemic disease is a potential cause of multi-organ system dysfunction and a mimicker of malignancy. The disease is responsive to immunosuppressive therapy, and should therefore be borne in mind when a suspected carcinoma remains elusive to detection.

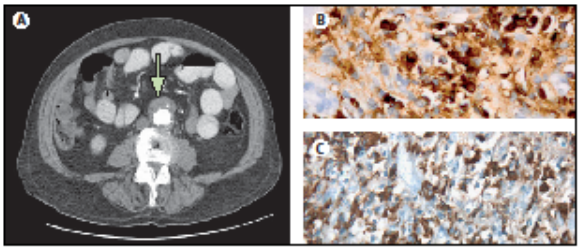

Figure: CT abdomen and immunohistochemistry for IgG4
(A) Soft tissue mantle anterior to abdominal aorta (arrow) suggestive of retroperitoneal fibrosis. (B) Hepatic tissue stains strongly for IgG4-positive plasma cells (magnification×400). (C) Re-examination of the aorta shows that more than 50% of the plasma cells within the inflammatory infiltrate stain strongly for IgG4 (×400).

Contributors
All authors contributed to patient management and in writing the report.

References

1 Chandan VS, Iacobuzio-Donahue C, Abraham SC. Patchy distribution of pathologic abnormalities in autoimmune pancreatitis: implications for preoperative diagnosis. *Am J Surg Pathol* 2008; 32: 1762–69.
2 Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003; 38: 982–84.
3 Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol* 2006; 41: 613–25.
4 Kasashima S, Zen Y, I. Kawashima A, et al. Inflammatory abdominal aortic aneurysm: close relationship to IgG4-related periaortitis. *Am J Surg Pathol* 2008; 32: 197–204.
5 Masaki Y, Dong L, Kurose N, et al. Proposal for a new clinical entity, IgG4-positive multi-organ lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis* 2008; published online August 13. DOI:10.1136/ard.2008.089169.

RC#44 – GLOCKER, E-O.; FREDE, N.; PERRO, M.; SEBIRE, N.; ELAWAD, M.; SHAH, N.; GRIMBACHER, B. Infant colitis—it's in the genes. **The Lancet**, v. 376, n. 9748, p. 1272, 2010.

Case Report

Infant colitis—it's in the genes

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Lancet 2010; 376: 1272

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For Polyphen see http://genetics.bwh.harvard.edu/pph/

For molecular modelling with Swiss PDBviewer see http://spdbv.vital-it.ch/

See Online for webappendix

In September, 2007, an 11-month-old girl presented to us with intractable inflammatory bowel disease; she had Crohn's-like colitis with formation of perianal and rectovaginal fistulae. Colonoscopy and histology of biopsy samples showed extensive ulceration of the ileum and focal active colitis with areas of patchy cryptitis and polymorphs entering surface epithelium (figure). Her colitis was resistant to treatment with immunosuppressants, and she was treated surgically. In February, 2010, an 8-month-old boy also presented to us with diarrhoea and rectal bleeding; his symptoms had started when he was 3 months old. The appearance of his bowel wall at colonoscopy, and histological features were similar to those of our first patient; treatment with immunosuppressants was also unsuccessful. Extensive immunological tests in both patients showed no striking abnormalities. The children were both from consanguineous marriages of South Asian parents.

We have recently found mutations in the interleukin-10 receptor that cause severe colitis in patients younger than 12 months.[1] Such patients have abrogated interleukin-10 signalling and present with excessive inflammation and a phenotype resembling inflammatory bowel disease.[2] Our two patients did not have mutations in the interleukin-10 receptor genes, therefore we sequenced the interleukin-10 gene itself. We assumed that mutations there could mimic the phenotype observed in patients with interleukin-10 receptor mutations and might lead to a similar phenotype to interleukin-10-deficient mice.[2] Both patients had a homozygous missense mutation at codon 113 that resulted in the replacement of a glycine residue with arginine; the parents were heterozygous for this mutation (see webappendix figure 1). We tested 100 healthy controls for this mutation; they all showed wild-type sequences. The mutation was also absent from genome databases including HGMD, Ensembl, and 1000 Genomes. The online tool Polymorphism Phenotyping (Polyphen) predicted that the mutation might be damaging, and molecular modelling with Swiss PDB viewer indicated changes in the formation of hydrogen bonds that might affect the tertiary structure of interleukin-10 and its dimerisation (see webappendix figure 2). To investigate whether the mutation is deleterious, we synthesised wild-type and mutated interleukin-10 in vitro. As expected, commercial (R&D, UK) and in-vitro-synthesised wild-type interleukin-10, but not the mutated interleukin-10, suppressed lipopolysaccharide-mediated release of tumour necrosis factor α (measured by ELISA; Peprotech, UK) in peripheral blood mononuclear cells (see webappendix figure 3). Both patients were given a final diagnosis of early-onset inflammatory bowel disease due to a mutation in interleukin-10. Owing to the resistance to treatment, bone-marrow transplantation has been offered to both children. The girl has started conditioning for her bone marrow transplant. The boy had his transplant in August 2010 and has greatly improved.

Despite the importance of interleukin-10 for intestinal immunity, in patients with Crohn's disease recombinant human interleukin-10 did not induce significant remission.[3] The use of genetically modified bacteria (eg, *Lactococcus* spp) that secrete the human protein could be an attractive therapy option, but its efficacy in patients with interleukin-10 mutations remains unproven.[4] Our clinical cases underline the importance of molecular diagnostics in modern clinical medicine. Exome sequencing, which enables analysis of all coding regions of the genome, might allow identification of further mutations causing chronic inflammation of the gut.[5]

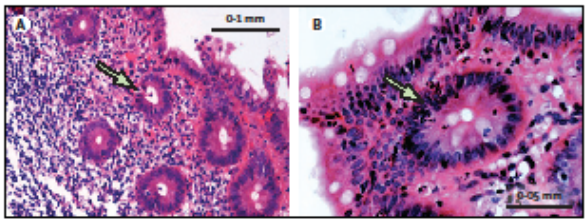

Figure: Haematoxylin and eosin stain of colonic mucosa from the first patient. ×200 magnification (A) and ×400 magnification (B)
Focal active colitis, with normal architecture but areas of patchy cryptitis (arrows) and clusters of polymorphs entering surface epithelium. There are no granulomata or other specific features.

Contributors

BG and EG designed the study and wrote the report; NSh and ME cared for the patients; NSe did the histopathology; EG, MP, and NF did the experiments. Written consent to publish was obtained.

Acknowledgments

This work was funded by the European Community under grant agreements MEXT-CT-2006-042316 (MC-PIAIDJ); FP7/201549 (EURO-PADnet) and FP7/223293 (EURO-GENE-SCAN).

References

1 Glocker EO, Kotlarz D, Boztug K, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N Engl J Med* 2009; 361: 2033–45.
2 Kühn, R, Löhler J, Rennick D, et al. Interleukin-10-deficient mice develop chronic enterocolitis. *Cell* 1993; 75: 263–74.
3 Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007; 369: 1641–57.
4 Braat H, Rottiers P, Hommes DW, et al. A phase I trial with transgenic bacteria expressing interleukin-10 in Crohn's disease. *Clin Gastroenterol Hepatol* 2006; 4: 754–59.
5 Ng SB, Turner EH, Robertson PD, et al. Targeted capture and massively parallel sequencing of 12 human exomes. *Nature* 2009; 461: 272–6

RC#45 – MURAKAMI, H.; TAMASAWA, N.; YAMASHITA, M.; TAKAYASU, S.; NIGAWARA, T.; MATSUI, J.; SUDA, T. Altered pain perception in schizophrenia. **The Lancet**, v. 375, n. 9717, p. 864, 2010.

Case Report

Altered pain perception in schizophrenia

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Lancet 2010; 375: 864

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In June, 2009, a 51-year-old woman presented with a 4-day history of abdominal swelling and fever, and a 2-week history of loss of appetite. There was no history of abdominal pain or nausea. She was febrile (38·4°C) and her abdomen was swollen but soft without spontaneous pain or tenderness. She had a history of schizophrenia since the age of 40 years which was well controlled with perospirone 12 mg/day and quetiapine 150 mg/day. At the age of 45 years, she was diagnosed with diabetes mellitus and had achieved good glycaemic control (HbA_{1c} 6·5%) with biphasic insulin aspart 30 (6 U/day). There was no sign of obvious peripheral neuropathy. Laboratory test results showed normocytic anaemia (haemoglobin 95 g/L), leucocytosis (13·3×10⁹/L) with neutrophilia (91·5%), high concentration of C-reactive protein (129 mg/L), and normal liver and kidney function. Urinalysis showed negative protein and no leucocytosis. Chest radiography showed normal lungs with no cardiac enlargement. Abdominal CT showed a large volume of partly encapsulated ascites (figure). The peritoneum in her pelvic cavity was thickened, and ascites in the right inferior abdominal cavity contained calcification and air (figure). The aspirated ascitic fluid had an unpleasant smell and was suppurated. Culture of the fluid was positive for pyogenic agents, including *Peptostreptococcus spp* and *Bacillus subtilis*. Blood culture was negative. We diagnosed severe bacterial pan-peritonitis.

Surprisingly, her general condition was stable and she did not complain of any abdominal pain. Abdominal drainage was done and antibiotics started (imipenem/cilastatin 1·5 g/day), but her symptoms did not improve. Therefore, laparotomy was done on the seventh day of admission. On laparotomy, a large amount of yellowish, turbid, gel-like material filled the abdominal cavity with retention of pus in the pouch of Douglas. The appendix was necrotic and contained faecolith. The bacterial peritonitis was suspected to be caused by perforation associated with acute appendicitis. Postoperative course was uneventful, and the patient recovered. When last seen in October, 2009, the patient was well.

Even though our patient had a purulent pan-peritonitis caused by a perforated appendix, she did not present with abdominal pain, tenderness, or guarding. Diminished pain sensitivity or loss of pain sensation in people with schizophrenia has previously been reported in cases of acute myocardial infarction and perforated gastrointestinal tract.[1] Clinically, diminished pain sensitivity in schizophrenia has been linked to key features of the disorder, such as positive symptoms, affective flattening, or attention deficits. Disturbances in dopamine, serotonin, glutamate, and opioids have been proposed to account for hypoalgesia in schizophrenia.[2] Hypoalgesia in schizophrenia has been reported throughout the acute phase of illnesses and in medicated stable or drug-free patients; neuroleptic drugs have been suggested to have minor analgesic effects.[2] Diabetes occurs in people with schizophrenia two to four times more often than in the general population.[4] Compared with people without diabetes, appendicitis in people with diabetes is more likely to result in perforation or other complications.[5] Decreased pain sensation may result in aggravation of the condition and in a delay of diagnosis and treatment. Our case is an important reminder that people with schizophrenia do not always present with typical clinical features of acute abdominal disease pathology.

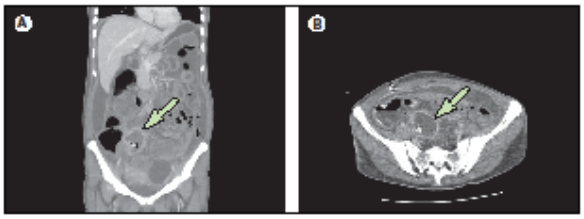

Figure: Abdominal CT before (A) and after (B) drainage of the abdominal cavity
Partly encapsulated ascites with thickened peritoneum in the pelvic cavity. Calcification and air (arrows) are visible in the right inferior aspect.

Contributors

All authors contributed to patient management and writing the report. Written consent to publish was obtained.

References

1 Marchand WE, Sarota B, Marble HC, Leary TM, Burbank CB, Bellinger MJ. Occurrence of painless acute surgical disorders in psychotic patients. *N Engl J Med* 1959; 260: 580–85.
2 Potvin S, Stip E, Tempier A, et al. Pain perception in schizophrenia: no changes in diffuse noxious inhibitory controls (DNIC) but a lack of pain sensitization. *J Psychiatr Res* 2008; 42: 1010–16.
3 Virit O, Savas HA, Altindag A. Lack of pain in schizophrenia: a patient whose arm was burned and amputated. *Gen Hosp Psychiatry* 2008; 30: 384–85.
4 Rouillon F, Sorbara F. Schizophrenia and diabetes: epidemiological data. *Eur Psychiatry* 2005; 20 (Suppl 4): S345–48.
5 Tsai SH, Hsu CW, Chen SC, Lin YY, Chu SJ. Complicated acute appendicitis in diabetic patients. *Am J Surg* 2008; 196: 34–39.

RC#46 – SAMMLER, E.M.; FOLEY, P.L.; LAUDER, G.D.; WILSON, S.J.; GOUDIE, A.R.; O`RIORDAN, J.I. A harmless high?. **The Lancet**, v. 376, n. 9742, p. 742, 2010.

Case Report

A harmless high?

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Lancet 2010; 376: 742

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In March, 2010, a 15-year-old girl presented to our accident and emergency department with altered mental status, nausea, and vomiting. During the previous evening she had been out with friends, and had consumed a white powdery substance together with alcohol. On the day of admission she had become increasingly unwell, with symptoms that could not be attributed to a hangover and presented to us in the afternoon. Upon arrival, our patient was somnolent with a Glasgow Coma Score of 11 she opened her eyes in response to speech, uttered inappropriate words, and localised to pain. Blood pressure was 108/58 mm Hg; pulse rate was 54 beats per min; respiratory rate was 15 breaths per min; and ear-temperature was 36°C. Arterial blood gas analysis and 12-lead electrocardiogram were normal. There was no evidence of external injury, neck stiffness, or localising neurological signs. Her pupils were dilated but reactive to light; there was no papilloedema. The remainder of the physical examination was normal.

Brain CT scan was unremarkable; however, the cerebrospinal fluid (CSF) opening pressure during lumbar puncture in the lateral decubitus position was raised at 350 mm of water. The CSF was otherwise normal with no signs of infection. Blood tests showed profound hyponatraemia at 118 mmol/L. Other relevant blood tests included: potassium, 4·5 mmol/L; bicarbonate, 23 mmol/L; urea, 3·3 mmol/L; creatinine, 46 umol/L; and blood glucose, 5·3 mmol/L. Serum osmolality was low at 256 mmol/kg, whereas urine osmolality was high at 742 mmol/kg. We suspected drug intoxication and did gas chromatography-mass spectroscopy of the patient's urine; this was unequivocally positive for mephedrone metabolites, but was negative for opioids, methadone, barbiturates, cocaine, cannabinoids, alcohol, benzodiazepines, and amphetamines including ecstasy. Analysis of the white powder was consistent with mephedrone. A presumptive diagnosis of mephedrone-induced euvolaemic hypo-osmotic hyponatraemia with encephalopathy and raised intracranial pressure was made. The patient was managed with fluid restriction and close surveillance. Her electrolyte imbalance resolved over 24 h and she became alert and oriented, with no focal neurological abnormalities other than mild dysphasia and anterograde amnesia. Three days after admission, cerebral MRI showed multifocal subcortical signal abnormalities (figure). Over the next few days her symptoms gradually improved and at follow-up in May, 2010, she had made a full recovery.

Mephedrone is a synthetic derivate of cathinone, a monoamine alkaloid found in the shrub *Catha edulis*; it has amphetamine-like psychostimulant effects.[1] This drug's easy availability and previous status as a legal high may have contributed to its increasing popularity among recreational drug users. However, mephedrone has recently been implicated in teenage morbidity and mortality, resulting in a heated media and public debate which has expedited a change in legislation.[1,2] As of April 16, 2010, possessing or supplying mephedrone is illegal in the UK.[3] Little is known about mephedrone's mechanism of action, spectrum of clinical signs and symptoms, and in particular, potential neurotoxic effects.[2] Given its chemical structure, mephedrone is thought to stimulate release and inhibit reuptake of monoamine neurotransmitters.[2] There is ample evidence that other amphetamines such as ecstasy are associated with clinically significant hyponatraemia.[4,5] Excessive sweating with electrolyte loss and increased fluid intake may be confounding factors, but there is also evidence from human and animal studies of ecstasy-induced secretion of antidiuretic hormone (ADH) mediated via serotonin.[4,5] We think that mephedrone, like ecstasy, promotes serotonin-mediated ADH release, and that a mephedrone-induced syndrome of inappropriate ADH secretion resulted in our patient's hyponatraemia and altered mental status. In the clinical setting, it is important to be aware of the possibility of mephedrone intoxication and possible neurological complications.

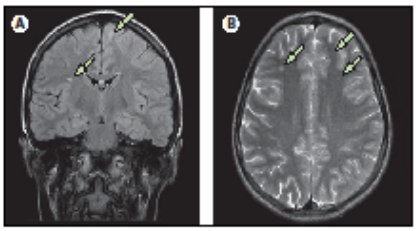

Figure: Cerebral MRI 3 days after admission
Coronal FLAIR (a) and axial T2 (b) weighted sequences showing subcortical white matter signal changes (arrowed) in the frontal and parietal lobes with sparing of the pons.

Contributors
All authors were involved with managing the patient and writing the report. Written consent to publish was obtained.

References:
1 Wood DM, Davies S, Puchnarewicz M, et al. Recreational use of mephedrone (4-methylmethcathinone, 4-MMC) with associated sympathomimetic toxicity. *J Med Toxicol* (in press) DOI: 10.1007/s13181-010-0018-5
2 Winstock AR, Marsden J, Mitcheson L. What should be done about mephedrone? *BMJ*; 340: c1605.
3 2010 No. 1207 DANGEROUS DRUGS. The Misuse of Drugs Act 1971 (Amendment) Order 2010 http://www.opsi.gov.uk/si/si2010/pdf/uksi_20101207_en.pdf (accessed Aug 3, 2010).
4 Rosenson J, Smollin C, Spore KA, Blanc P, Olson KR. Patterns of ecstasy-associated hyponatremia in California. *Ann Emerg Med* 2007; 49: 164–71, 71 e1.
5 Henry JA, Fallon JK, Kicman AT, Hutt AJ, Cowan DA, Forsling M. Low-dose MDMA ("ecstasy") induces vasopressin secretion. *Lancet* 1998; 351: 1784.

RC#47 – SCHEMBRI, G.; SCHOBER, P. Killing two birds with one stone. **The Lancet**, v. 377, n. 9759, p. 96, 2011.

Case Report

Killing two birds with one stone

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Lancet 2010; 377: 96

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For the **Patent** see http://www.freepatentsonline.com/y2009/0281911.html

In September, 2008, a 56-year-old man presented to our department with fever, myalgia, pharyngitis, and a maculopapular skin eruption. He reported having unprotected sex with a man 2 months prior to the onset of his symptoms. He was diagnosed with HIV seroconversion illness in view of a high HIV viral load (>14 280 000 copies per ml) and a third generation HIV antibody test that was weakly positive. During routine HIV follow-up in March 2009, his previously normal alkaline phosphatase had risen to 486 IU/L and his alanine aminotransferase was 185 IU/L. His total bilirubin was 15 µmol/L. He had no symptoms except for mild occasional right upper quadrant abdominal discomfort. An abdominal ultrasound scan showed multiple large stones in the gallbladder but was otherwise normal. His antimitochondrial antibody was strongly positive (1:4000 IgG, M2 and M4 positive), consistent with a diagnosis of primary biliary cirrhosis. A liver biopsy showed damaged interlobular bile ducts, with granulomas, and increased amounts of eosinophilic cytoplasm and intraepithelial inflammatory cells, also typical of primary biliary cirrhosis.

In April, 2009, his CD4 count was 360 cells per µL, and he was started on tenofovir 245 mg, emtricitabine 200 mg, and efavirenz 600 mg once daily. In June, 2009, owing to central nervous system side-effects, efavirenz was changed to lopinavir 400 mg and ritonavir 100 mg tablets twice daily. Ursodeoxycholic acid was introduced at a dose of 15 mg/kg per day in November, 2009. His liver function tests improved considerably once antiretroviral therapy was introduced (figure). In May, 2010, after 13 months of treatment with anti-retroviral therapy, and 6 months of ursodeoxycholic acid, his liver function tests were normal. His antimitochondrial antibodies decreased to 1:250. Using a branched chain hybridisation assay (Quanti-Gene™ Affymetrix, California, USA) we found that serum from our patient was strongly positive for human betaretrovirus RNA. He was last seen in June, 2010, and was asymptomatic, with no clinical or biochemical evidence of cirrhosis. His HIV virus was completely suppressed and his CD4 count increased to 580 cells per µL.

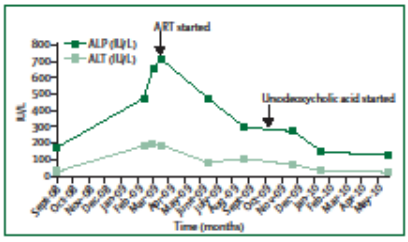

Figure: Alkaline phophatase (ALP) and alanine aminotransferase (ALT) levels showing improvement after anti-retroviral treatment started

In 2003, a human betaretrovirus closely related to mouse mammary tumour virus was cloned from the biliary epithelium from patients with primary biliary cirrhosis.[1] Viral infection of cholangiocytes with human betaretrovirus results in the aberrant expression of the mitochondrial E2 component of the pyruvate dehydrogenase complex. This protein, normally located on the inner mitochondrial membrane, appears on the cell surface in patients with primary biliary cirrhosis, and is thought to trigger the appearance of antimitochondrial antibodies.[2]The relation between betaretrovirus infection and primary biliary cirrhosis is controversial. It has been suggested that randomised controlled trials with antiviral therapy may provide supportive evidence for a causal role of viral infection.[3] Randomised controlled trials using combination lamivudine 150 mg and zidovudine 300 mg twice a day, have shown biochemical improvements in patients with primary biliary cirrhosis, but failed to achieve significant endpoints, possibly because of the development of viral resistance to therapy.[3] Other antiretrovirals that have proven effective against betaretrovirus in vitro, include: adefovir, tenofovir, and lopinavir.[4] Here, we report that the combination of tenofovir, emtricitabine, lopinavir, and ritonavir used to manage HIV infection, coincided with marked reduction of cholestatic liver function tests, before the institution of ursodeoxycholic acid. If an association between primary biliary cirrhosis and human betaretrovirus infection can be established, the efficacy of this highly active antiviral regimen can be tested in future controlled trials in patients with primary biliary cirrhosis unresponsive to ursodeoxycholic acid.

Acknowledgments

We thank Dr Andrew Mason, and team, University of Alberta, Canada, for performing the test for human betaretrovirus.

Contributors

GS and PS looked after the patient and wrote the report. Written consent to publish was obtained.

References

1 Xu L, Shen Z, Linsheng G, et al. Does a betaretrovirus infection trigger primary biliary cirrhosis? *PNAS* 2003; 100: 845–59.

2 Poupon R. Retrovirus infection as a trigger for primary biliary cirrhosis? *Lancet* 2004; 363: 260–61.

3 Mason AL, Wasilenko ST. Other potential medical therapies: the use of antiviral agents to investigate and treat primary ciliary cirrhosis. *Clin Liver Dis* 2008; 12: 445–60.

4 Montano-Loza AJ, Wasilenko S, Bintner J, Mason AL. Cyclosporine A inhibits in vitro replication of betaretrovirus associated with primary biliary cirrhosis. *Liver Int* 2010; 30: 871–77.

RC#48 – ABERER, E.; FINGERLE, V.; WUTTE, N.; FINK-PUCHES, R.; CERRONI, L. Within European margins. **The Lancet**, v. 377, n. 9760, p. 178, 2011.

Case Report

Within European margins

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Lancet 2011; 377: 178

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In June, 2008, an 88-year-old woman presented to us with a 4-month history of dark red, partly ulcerated cutaneous nodules and plaques on both feet (figure A). We suspected large B-cell lymphoma of the leg, cutaneous follicle centre lymphoma, or merkel-cell carcinoma. Full blood count was normal. Serum protein electrophoresis suggested a monoclonal IgG λ band. No antibodies to lymphotropic viruses, *Toxoplasma gondii*, or *Helicobacter pylori* were detected, but IgG antibodies to *Borrelia burgdorferi* were found. Sonography, chest radiography, and whole-body CT were normal. Biopsy samples from the plaques showed dense infiltrates with CD20-positive lymphocytes mixed with lymphoplasmacytoid plasma cells and small reactive lymphocytes (figure B). Dutcher bodies (PAS-positive, diastase-resistant nuclear pseudoinclusions found in malignant plasma cells) were observed, and also a monoclonal κ light-chain restriction of plasma cells. The presence of *B burgdorferi* DNA was shown by PCR targeting of the *OspA* gene. Sequence analysis of the amplified DNA showed that the strain belonged to the *Borrelia afzelii* genospecies.[1] Our patient did not recall a tick bite, and she had no history of erythema migrans, borrelia lymphocytoma, acrodermatitis chronica atrophicans, or other symptoms of Lyme borreliosis. Primary cutaneous marginal-zone lymphoma with plasmacytic differentiation induced by *B afzelii* was diagnosed. Ceftriaxone 2 g intravenously for 3 weeks was started.

2 months after the start of treatment, the plaques had substantially regressed. After 18 months, red, scaling, hyperpigmented eczematous lesions persisted only on the left foot. On histological examination, Dutcher bodies were greatly reduced. *B burgdorferi* antibody titres had decreased. On serum electrophoresis, there was a switch from λ to κ light chain, which was in line with the histological findings of monoclonal κ light chain proliferation. Our patient's lesions regressed gradually, but erythema was still present after 24 months. This phenomenon of slow regression is also seen in late Lyme borreliosis and suggests that the effectiveness of antibiotics might be misinterpreted.

Antibiotic therapy should be considered as a first-line treatment option in patients with cutaneous marginal-zone lymphoma, in the presence of *B burgdorferi* infection, or local radiotherapy in doses of 10–50 Gy.[2] We did not give radiotherapy because of our patient's age and stable disease state. *B burgdorferi* sensu lato has been shown by PCR in cutaneous B-cell lymphomas in European, but not in American, or Asian patients. Response to antibiotic treatment has been reported.[2,3] The phylogenetic link to the *B afzelii* genospecies has not been made for skin lymphomas. In our patient, *B afzelii* specific DNA was reported for the first time in skin lymphoma. The predominant species isolated from acrodermatitis chronica atrophicans and borrelia lymphocytoma in Europe is *B afzelii*.[4] Since *B afzelii* is not present in the USA, cutaneous B-cell lymphoma induced by this genospecies is probably a European phenomenon. *B burgdorferi* serology can be borderline or negative, even in patients with lymphoma with *B burgdorferi* positive PCR.[3] Acrodermatitis chronica atrophicans is a polyclonal lymphocytic proliferation, but clonal B-cell proliferation has been observed in erythema migrans.[5] Further studies are needed to show whether malignant lymphoproliferation is a unique phenomenon of *B afzelii* or is also induced by other *B burgdorferi* genotypes.

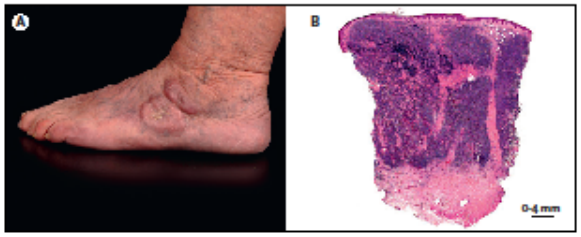

Figure: B afzelii induced cutaneous marginal zone lymphoma of the left foot
(A) Before treatment: two large red nodules on the left foot. (B) Dense, diffuse, lymphoid infiltrates in the dermis, without involvement of epidermis.

Contributors
RF-P looked after the patient. EA and NW wrote the report. LC and VF did the laboratory work.

References

1 Michel H, Wilske B, Hettche G, et al. An OspA-polymerase chain reaction/restriction fragment length polymorphism-based method for sensitive detection and reliable differentiation of all European *Borrelia burgdorferi* sensu lato species and OspA types. *Med Microbiol Immunol* 2005; 193: 219–26.

2 Senff NJ, Noordijk EM, Kim YH, et al. Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. *Blood* 2008; 112: 1600–09.

3 Kütting B, Bonsmann G, Metze D, et al. *Borrelia burgdorferi*-associated primary cutaneous B cell lymphoma: complete clearing of skin lesions after antibiotic pulse therapy or intralesional injection of interferon alfa-2a. *J Am Acad Dermatol* 1997; 36: 311–14.

4 Lenormand C, Jaulhac B, De Martino S, et al. Species of *Borrelia burgdorferi* complex that cause borrelial lymphocytoma in France. *Br J Dermatol* 2009; 161: 174–76.

5 Böer A, Breisch M, Dayrit J, et al. Erythema migrans: a reassessment of diagnostic criteria for early cutaneous manifestations of borreliosis with particular emphasis on clonality investigations. *Br J Dermatol* 2007; 156: 1263–71.

RC#49 – PRASAD, N.; GHIYA, B.C.; BUMB, R.A.; KAUSHAL, H.; SABOSKAR, A.A.; LEZAMA-DAVILA, C.M.; SALOTRA, P.; SATOSKAR, A.R. Heat, Oriental sore, and HIV. **The Lancet**, v. 377, n. 9765, p. 610, 2011.

Case Report

Heat, Oriental sore, and HIV

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Lancet 2011; 377: 610

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For the ELISA HIV TRI-DOT and HIV COMB test see http://jmitra.co.in/jmiwebsdiagnopid.aspx

For ThermoMed see www.thermosurgery.com

In January, 2009, a 34-year-old man presented to our hospital with a 6-month history of four, well-defined, non-tender, erythematous plaques of area 1–3 cm² on his right hand (figure A). Parasitological examination of a skin smear and biopsy sample confirmed a diagnosis of cutaneous leishmaniasis. Restriction-fragment length polymerisation PCR identified[1] the causative species as *Leishmania tropica*. Our patient also had oral candidosis. He had no history of overseas travel, but his work as a truck driver took him all over India and he had had multiple sexual contacts with sex workers from many regions. HIV infection was confirmed by ELISA HIV TRI-DOT and HIV COMB (Delhi, India). His viral load was 145 600 copies per mL and CD4-cell count was 180 per µL.

Our patient's HIV infection was treated with zidovudine, lamivudine, and nevirapine. The cutaneous leishmaniasis was treated with twice-weekly intralesional injections of sodium stibogluconate 0·5 mL/cm² (100 g/L) for 6 weeks. Despite an increase in CD4-cell count to 240 per µL after 24 weeks, he did not improve clinically or parasitologically. The lesions were then treated by a single application of radiofrequency-induced heat therapy for 60 s under local anaesthesia (2% lidocaine) by use of a localised current field radiofrequency generator (ThermoMed 1.8; Thermosurgery Technologies Inc; Arizona, USA). He was given oral nimesulide and topical fusidic acid cream for 5 days. Our patient responded well to the heat therapy, with complete healing of the lesions within 12 weeks. At follow-up a year later, the fine scarring and hyperpigmentation of the lesions had decreased (figure B).

Leishmania spp can cause cutaneous, mucocutaneous, and visceral disease. Systemic pentavalent antimonials are the recommended treatment for cutaneous leishmaniasis, but they are toxic, and adherence with treatment is poor because daily injections for 3 weeks or longer are needed. In HIV-infected individuals antimonial treatment is associated with relapses because a healthy immune system and CD4-expressing T cells are needed for optimal anti-parasitic activity.[2] However, cutaneous leishmaniasis in HIV-infected patients taking antiretroviral therapy can respond to antimonials probably owing to improved immune function.[3] Our patient did not respond to intralesional sodium stibogluconate despite an increase in CD4 cells after HAART, perhaps because the causative agent was *L tropica*. Cutaneous leishmaniasis caused by this species is difficult to treat, takes longer to heal, and can visceralise.[4] Successful management in HIV-infected individuals is crucial, because HIV-induced immune suppression can lead to rapid widespread dissemination of parasites and development of diffuse disease. Radiofrequency-induced heat therapy is effective and even better than antimonials in treatment of lesions caused by *L tropica* in immunocompetent individuals,[5] but its effectiveness in immunocompromised patients is unclear. The treatment is effective, causes little or no damage to underlying healthy tissue, and is easy to administer, and adherence by patients is better. As well as in this patient, heat therapy was highly effective in cutaneous leishmaniasis in a 28-year-old HIV-infected man who did not respond to sodium stibogluconate and subsequent rifampicin for 3 months. Both patients have remained disease free for a year after treatment. Therefore, radiofrequency heat therapy should be considered as first-line treatment for cutaneous leishmaniasis in HIV-infected patients.

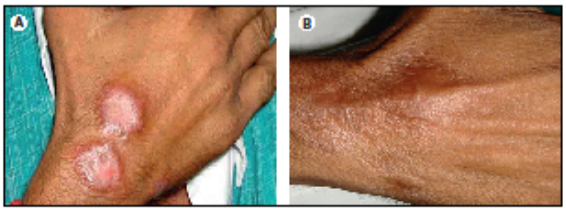

Figure: Successful treatment of antimonial-refractory cutaneous leishmaniasis in HIV-infected patient by local radiofrequency heat therapy
Lesions before start of the treatment (A), and same lesions showing complete healing with minimal scarring 1 year after treatment (B).

Conflicts of interest
The patient was treated with a ThermoMed 1.8 heat therapy machine donated by Thermosurgery Inc to S P Medical College, Bikaner.

Contributors
NP, BCG, RAB, and ARS looked after the patient; HK and PS did the PCR analysis; AAS reviewed the pathology; RAB, ARS, and CML wrote the paper. Written consent to publish was obtained.

References

1 Schonian G, Nasereddin A, Dinse N, et al. PCR diagnosis and characterisation in local and imported clinical samples. *Diagn Microbiol Infect Dis* 2003; 47: 349–58.
2 Niamba P, Traore A, Coumbri-Lompo O, et al. Cutaneous leishmaniasis in HIV patients in Ouagadougou: clinical and therapeutic aspects. *Ann Dermatol Venereol* 2006; 133: 537–42.
3 Chio CM, Lerner EA. Leishmaniasis: recognition and management with a focus on the immuno-compromised patient. *Am J Clin Dermatol* 2002; 3: 91–105.
4 Magill AJ, Grogl M, Gasser RA, et al. Visceral infection caused by *Leishmania tropica* in veterans of Operation Desert Storm. *N Engl J Med* 1993; 328: 1383–87.
5 Reithinger R, Mohsen, M, Wahid M, et al. Efficacy of thermotherapy to treat cutaneous leishmaniasis caused by *Leishmania tropica* in Kabul, Afghanistan: a randomized, controlled trial. *Clin Infect Dis* 2005; 40: 1148–55.