

## Carotid artery stenosis

### Carotid artery stenting is not yet ready to replace endarterectomy



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Carotid endarterectomy is currently the most effective intervention to prevent stroke in patients with recent symptoms of carotid stenosis.<sup>1,2</sup> It also prevents future stroke in younger patients (under 75 years) who have not yet had symptoms, as long as the risk of stroke and death from surgery is not more than 3%.<sup>3,4</sup>

Patients naturally prefer carotid artery stenting to open surgery, but stenting has not been shown to be acceptably safe in clinical trials. Carotid endarterectomy has been in widespread use for more than 50 years, but carotid artery stenting is a more recent development. In the linked systematic review, Meier and colleagues assessed the short term safety and intermediate term efficacy of carotid endarterectomy versus carotid artery stenting. They found that the short term (30 day) hazards of stroke and death after stenting in recent trials of symptomatic patients have improved but are not yet as good as those seen after surgery.<sup>5</sup> In the intermediate term, the two treatments did not differ significantly for stroke or death (hazard ratio 0.90, 95% confidence interval 0.74 to 1.1).

In the most recent trial included in the systematic review, the International Carotid Stenting Study (ICSS), surgery was significantly less likely than stenting to cause stroke, myocardial infarction, or death (5.1% v 8.5%; odds ratio 0.57, 0.39 to 0.85). A subgroup analysis in five centres found more new ischaemic brain lesions after stenting (46% v 14%; odds ratio 5.2, 2.6 to 10.5), and about half of these new lesions were still present on follow-up scanning six weeks later.<sup>6</sup>

Results from the remaining trial in symptomatic people, CREST (Carotid Revascularisation Endarterectomy versus Stenting Trial) are expected in 2010. An interim systematic review recommends that patients should continue to be stented only within the context of a clinical trial.<sup>7</sup>

Longer term follow-up (two to 10 years) after successful carotid artery stenting and carotid endarterectomy indicates that the procedures are equally effective in preventing stroke. Arterial restenosis seems to be more likely after stenting, but it is rare to develop associated symptoms.

A learning curve exists for stenting, and a consensus of European stenting specialists reported that experience with at least 150 procedures was needed before the operator could be considered safe. Several earlier trials analysed in this article do not compare like with like—some stenters had very little experience, but surgeons generally had much more. As time has passed, results of stenting have improved and the gap in results has narrowed, but currently it is recommended that only people with experience should perform carotid artery

stenting and train others, and that they should do so within the confines of clinical trials.<sup>8</sup>

Although people who perform stenting are now more experienced and the devices have improved, practical difficulties still make stenting hazardous for symptomatic patients. Emboli from symptomatic plaques are common and “embolic protection devices”—expensive umbrella-like catheter systems—were developed to trap emboli released during stenting and balloon angioplasty. Considerable skill and judgment are needed to pass a catheter beyond the symptomatic plaque and position the device, because more emboli are released until the device is safely in place and open. Despite their name, there is no level 1 evidence that the widespread use of these devices is definitely beneficial. They were optional in the German SPACE trial, where results of carotid artery stenting and carotid endarterectomy were similar, and although they were eventually made compulsory in the French EVA3-S trial, they were not shown to offer any additional stroke protection. It would take a trial of many thousands of patients in whom EPDs could be used to determine whether they were of definite benefit.

As trial data accumulate carotid artery stenting still looks hazardous for symptomatic patients. The attraction of using stents rather than surgery in asymptomatic patients (no symptom, no incision) is obvious, but the balance between early risk and longer term benefit is unclear. For asymptomatic patients undergoing carotid endarterectomy, a procedural risk of stroke or death above 3% would be unacceptable because the longer term net benefit (6% absolute risk reduction for stroke over the next five years) would be lost.<sup>3</sup>

Worldwide, many more carotid artery stenting and carotid endarterectomy procedures are performed in patients who have not yet had symptoms than on those with symptoms and results from large registries have recently been published suggesting similar short term hazards of procedure related stroke and death (2.9%, 2.4% to 3.4%) in patients under 80 years of age.<sup>9</sup> Stenting an asymptomatic plaque might be more appropriate than open surgery, but evidence is needed. The current Asymptomatic Carotid Surgery trial, ACST-2, is comparing stenting and surgery in a randomised trial of at least 5000 patients.<sup>10</sup>

The natural course of carotid arterial disease is changing, and data from surgical trials of 10-20 years ago may be less relevant today<sup>1,2</sup> because aspirin and other anti-thrombotic drugs are routinely prescribed (especially in symptomatic patients), blood pressure control is better, and lipid lowering treatments are effective. The SPARCL

trial and the Cholesterol Treatment Trialists' Collaboration found that high doses of statins reduced vascular events including ischaemic stroke by around 30%.<sup>11 12</sup> Good medical management leads to longer survival, and—although heart attack and stroke are still common causes of death—the remaining risk of stroke may be further reduced by appropriate carotid intervention.

The case for stenting symptomatic carotid stenosis has not been proved, and when intervention by experienced operators is planned and both procedures are feasible, then randomisation between carotid endarterectomy and carotid artery stenting is still ethical. The asymptomatic carotid stenotic plaque may prove more appropriate for stenting, but only time and a large randomised controlled trial will tell.

- 1 North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade carotid stenosis. *N Engl J Med* 1991;325:445-53.
- 2 European Carotid Surgery Trialists' Collaborative Group. Randomised trial of Endarterectomy for recently symptomatic carotid stenosis: final results of the European Carotid Surgery Trial (ECST). *Lancet* 1998;351:1379-87.
- 3 Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid stenosis. *JAMA* 1995;273:1421-8.
- 4 MRC Asymptomatic Carotid Surgery Trial Collaborative Group. Prevention of fatal and disabling strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;363:1491-502.

- 5 Meier P, Knapp G, Tamhane U, Chaturvedi S, Gurm HS. Short term and intermediate term comparison of endarterectomy versus stenting for carotid artery stenosis: systematic review and meta-analysis of randomised controlled clinical trials. *BMJ* 2010;440:c467.
- 6 European Stroke Conference. Safety results of the International Carotid Stenting Study (ICSS): early outcome of patients randomised between carotid stenting and endarterectomy for symptomatic carotid stenosis. Sweden, 2009. [www.ion.ucl.ac.uk/cavatas\\_icss/downloads/FirstResultsofICSS.pdf](http://www.ion.ucl.ac.uk/cavatas_icss/downloads/FirstResultsofICSS.pdf).
- 7 Coward LJ, Featherstone RL, Brown MB. Safety and efficacy of endovascular treatment of carotid artery stenosis compared with carotid endarterectomy: a Cochrane systematic review of the randomised evidence. *Stroke* 2005;36:905-11.
- 8 Cremonesi A, Setacci C, Bignamini A. Carotid artery stenting. First consensus document of the ICSS-SPREAD Joint Committee. *Stroke* 2006;37:2400-9.
- 9 Gray WA, Chaturvedi S, Verta S; on behalf of the Investigators and the Executive Committees. Thirty-day outcomes for carotid artery stenting in 6320 patients from 2 prospective, multicenter high-surgical-risk registries. *Circ Cardiovasc Intervent* 2009;2:159-66.
- 10 Rudarakanchana N, Dialynas M, Halliday A. Asymptomatic Carotid Surgery Trial-2: rationale for a randomised clinical trial comparing carotid endarterectomy with carotid artery stenting in patients with asymptomatic carotid artery stenosis. *Eur J Vasc Endovasc Surg* 2009;38:239-42.
- 11 Sillesen H, Amarenco P, Hennerici MG, Callahan A, Goldstein LB, Zivin J, et al. Atorvastatin reduces the risk of cardiac events in patients with carotid atherosclerosis. A secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial. *Stroke* 2008;39:3297-302.
- 12 Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino L, et al; Cholesterol Treatment Trialists' Collaborators. Efficacy and safety of cholesterol-lowering treatment; prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-78.

## Improving the selection of medical students

Non-academic personal qualities should be taken into account

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In a study reported in this issue, James and colleagues assess whether a new test, the UK Clinical Aptitude Test (UKCAT), improves the selection process for school leaver applicants to medical (and dental) schools.<sup>1</sup>

Doctors, of whatever specialty calling, need specialist medical knowledge and a complementary palette of skills and personality traits if they are to be professionally competent. Regardless of the specialty—surgeon or psychiatrist, general practitioner or pathologist—most would agree on what basic skills and traits doctors should have; conversely on what traits, attitudes, and behaviours that they should not possess. Any competency list for a generic medical practitioner should comprise excellent academic ability, good cognitive skills, and the ability to use academic knowledge appropriately in quantitative, verbal, and spatial domains. Practitioners should also have well developed decision making skills, professional integrity, highly developed moral standards, and excellent interpersonal skills, in addition to being accomplished and confident communicators who can empathise with patients. They must be able to function professionally when under stress, have a good measure of self control, and not be prone to taking inappropriate risks in a practice setting. Their mental resilience and emotional stability must be high. We are not talking about a superhero, we are talking about the doctor we would all like to see when we are sick.

Medical school training—that five or six year period between school or university and entry to professional practice—can give the future doctor the basic knowledge required, and foster their skills for updating that knowledge to ensure continued academic competence. It can also teach or nurture the development of some of the other skills and attitudes in the competency list. But it is unreasonable and unrealistic to expect that medical education can do it all, particularly if the student doesn't have the right attitude or psychological constitution, or—worse—if they have any of a range of negative traits.

Acceptance of this line of thought must lead us to acknowledge that we should take particular care in selecting medical students—future medical practitioners—basing our choice on a range of criteria that reflect the picture of the generic good doctor. Generally, we haven't done this very well—for the past several decades in the United Kingdom the main selection criterion has been previous academic achievement tempered only mildly by assessment of some personal qualities by interview and reading between the lines of a candidate's personal statement and his or her referee's report. This is not to say that the result has been all bad: most of those who enter medical school graduate as doctors and develop into practitioners who are a credit to the profession and are well regarded by, and of immense benefit to, their patients. But on the negative side, there has always been a small proportion of individuals who



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should not have been accepted into medical school. There are those who during their studies cause their teachers and mentors continual concern for a range of reasons other than academic progress,<sup>2</sup> and those whose psychological stamina is insufficient to meet the demands of medical school training or clinical responsibility.<sup>3,4</sup> After graduation, inadequate and unprofessional doctors are regularly identified by patients,<sup>5</sup> and the published “restriction to practise” statistics of the General Medical Council show that many complaints are justified.<sup>6</sup>

Another problem with a selection method based principally on academic achievement is the pronounced difference between the medical school population and the population at large, which is important in the context of doctors being representative of the community they serve. As described in the study by James and colleagues, which mirrors earlier findings,<sup>7</sup> medical students selected predominantly on their A level grades are mostly white, from the highest socioeconomic group, and have been educated at independent schools or grammar schools. It is no surprise that those who go to better schools get better A level results and thus have a better chance of entering medical school.

James and his colleagues' study focuses on whether a new selection instrument, the UKCAT, adds value to the selection process for medical students, in particular whether it reduces socioeconomic biases. The answer is “yes” and “no.” On the no side, the data indicate that the same biases remain if selection decisions are based on UKCAT scores rather than A level grades. On the yes side, the UKCAT measures cognitive abilities—intellectual skills independent of academic knowledge—which are indeed important in the context of the generic good doctor.

Measuring cognitive ability is a step in the right direction, but it doesn't tackle “widening participation”—the admission of people from lower socioeconomic groups or those whose education has been compromised by attending poorer schools. And neither does UKCAT yet provide selectors with information on the non-cognitive characteristics and personal qualities that are fundamentally



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essential (and those that are undesirable) in the generic good doctor. This challenge remains for the future. Two recently published articles—one in an academic journal,<sup>8</sup> the other a commentary in the *New York Times*,<sup>9</sup> may stimulate moves to reach this particular “future” sooner rather than later. These articles advocate, and provide, some compelling evidence for adopting the selection criteria for medical students implied above.

- 1 James D, Yates J, Nicholson S. Comparison of A level and UKCAT performance in students applying to UK medical and dental schools in 2006: cohort study. *BMJ* 2010;340:c478.
- 2 Yates J, James D. Predicting the “strugglers”: a case-control study of students at Nottingham University Medical School. *BMJ* 2006;332:1009-13.
- 3 Dahlin ME, Runeson B. Burnout and psychiatric morbidity among medical students entering clinical training: a three year prospective questionnaire and interview-based study. *BMC Med Educ* 2007;7:6.
- 4 Willcock SM, Daly MG, Tennant CC, Allard BJ. Burnout and psychiatric morbidity in new medical graduates. *Med J Aust* 2004;181:357-60.
- 5 Southgate L, Cox J, David T, Hatch D, Howes A, Johnson N, et al. The assessment of poorly performing doctors: the development of the assessment programs for the General Medical Council's performance procedures. *Med Educ* 2001;35(suppl 1):2-8.
- 6 General Medical Council. Regulating doctors, ensuring good medical practice. [www.gmc-uk.org/concerns/hearings\\_and\\_decisions/fitness\\_to\\_practise\\_decisions.asp](http://www.gmc-uk.org/concerns/hearings_and_decisions/fitness_to_practise_decisions.asp).
- 7 Powis D, Hamilton J, McManus IC. Widening access by changing the criteria for selecting medical students. *Teaching Teacher Educ* 2007;23:1235-45.
- 8 Bore M, Munro D, Powis D. A comprehensive model for the selection of medical students. *Med Teacher* 2009;31:1066-72.
- 9 Chen PW. Do you have the “right stuff” to be a doctor? *New York Times* 2010 Jan 14. [www.nytimes.com/2010/01/15/health/14chen.html](http://www.nytimes.com/2010/01/15/health/14chen.html).

## Chemical castration for sex offenders

Doctors should avoid becoming agents of social control



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In November 2009, in response to several high profile sex offences committed against children, Polish President Lech Kaczynski signed a law allowing for the compulsory treatment of some sex offenders with antiandrogenic drugs, commonly referred to as chemical castration. Following a sexual killing carried out by a repeat sex offender in France, the French National Assembly is considering legislation that would make chemical castration mandatory for some sex offenders. Laws in several American states allow compulsory medical treatment of offenders who have committed serious sex offences. Chemical, as well as physical, castration of sex offenders takes place in psychiatric hospitals in the Czech Republic under the legal framework of “protective treatment.” Meanwhile, in

England the Department of Health is supporting an initiative to facilitate the prescription of drugs on a voluntary basis for sex offenders in the criminal justice system.<sup>1</sup>

Demand for the prescription of antiandrogens or physical castration for sex offenders is a common reaction by lawmakers and politicians when a high profile sexual crime is committed. Although castration is ostensibly for public protection, it also carries with it a sense of symbolic retribution. Whether medical or surgical, the procedure requires the participation of doctors, and this gives rise to questions regarding the basis of medical involvement. Some people argue that not only does medical input in these cases straddle the border between treatment and punishment,<sup>2</sup> but that it also shifts the

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doctor's focus from the best interests of the patient to one of public safety.

Antiandrogenic drugs and physical castration undoubtedly reduce sexual interest (libido) and sexual performance,<sup>3</sup> and they reduce sexual reoffending. Physical castration of sex offenders was carried out in several European countries in the first part of the 20th century, and although morally dubious and not always targeted at high risk cases (many of those castrated were homosexual, mentally ill, or learning disabled), recidivism rates of less than 5% over long follow-up periods are invariably reported, compared with expected rates of 50% or more.<sup>4</sup>

Studies of the use of antiandrogenic drugs report similar efficacy,<sup>5-7</sup> and a large meta-analysis of treatment in sex offenders found that "organic" interventions (surgical castration and hormones) reduce recidivism much more than any other treatment approach (although the authors found that nowadays drugs are usually used alongside psychological treatment).<sup>8</sup> Double blind placebo controlled studies of antiandrogens are virtually absent because of the practical difficulties of carrying them out (among other things, it is not easy to convince an ethics committee of the wisdom of giving placebo to dangerous offenders), but the evidence supports the efficacy of these treatments.

It is not surprising that antiandrogens have such a big effect on the risk of sexual offences. Regardless of the strong psychological factors that contribute to sexual offending, at its root lies the pressure exerted by sexual drive and sexual arousal, mediated by biological mechanisms dependent on testosterone. The main drugs used are cyproterone acetate (in the United Kingdom, Europe, and Canada); medroxyprogesterone (in the United States); and increasingly the more expensive but possibly more potent gonadotrophin releasing hormone agonists such as leuprolide, goserelin, and tryptorelin.<sup>9-10</sup> Although these drugs act in different ways, they all reduce serum testosterone concentrations in men to prepubertal values. Castration, however—whether chemical or physical—is associated with serious side effects, including osteoporosis, cardiovascular disease, metabolic abnormalities, and gynaecomastia. Physical castration is mutilating and irreversible, and it carries the potential for serious psychological disturbance, although some offenders request it nonetheless.<sup>11</sup>

Given the risk to the individual's health, is there a clear medical rather than social reason for prescribing powerful drugs, let alone carrying out such a drastic surgical procedure? Part of the problem lies in the poor diagnostic conceptualisation of the sexual deviations, with DSM-IV-TR (*Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision) and ICD-10 (*International Classification of Diseases*, 10th revision) definitions dominated by notions of the unconventional nature of the drive, rather than its psychological or physical characteristics. When the intensity or ability to control sexual arousal is the presenting feature—whether it manifests as frequent rumination and fantasy or strong and recurrent urges—then treatment directed towards the biological drive makes sense. Treatment protocols can then be based on the medical indication (remembering that drugs other than the antiandrogens, such as selective serotonin reuptake inhibitors, can also

be effective, particularly when sexual rumination is the presenting problem<sup>12</sup>) rather than on risk.

When drugs work the clinical effect is often dramatic, with offenders reporting great benefit from no longer being preoccupied by sexual thoughts or dominated by sexual drive. These drugs can also allow offenders to participate in psychological treatment programmes where previously they may have been too distracted to take part. Given the transparency of benefits and risks, there is no obvious reason why an offender should not be able to make an informed choice about drugs. Some argue that freedom of choice is lost in instances where long term detention is the only alternative to drugs,<sup>2</sup> but it is not clear why this should not be part of the person's calculation. Indeed, preventing this choice may condemn men to years of further imprisonment.

Overall, it probably makes most sense for medical treatment to be viewed as part of a wider package of care and supervision, dependent on the individual's consent but with no decisions wholly dependent on compliance. In this context, the doctor does not assume responsibility for public safety but contributes to it by helping the offender to tackle those factors that make him more likely to reoffend.<sup>6</sup> Physical castration as part of a rehabilitative strategy may even have a place, although the observations of the Council of Europe's committee for the prevention of torture ([www.cpt.coe.int/documents/cze/2009-08-inf-eng.pdf](http://www.cpt.coe.int/documents/cze/2009-08-inf-eng.pdf)) should not be overlooked given the significant risk of human rights abuses, with individuals acquiescing rather than consenting in the belief that it is the only way to avoid indefinite confinement.

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- 1 National Probation Service. Probation circular 35: medical treatment for sex offenders. 2007. [www.probation.homeoffice.gov.uk/files/pdf/PC35%202007.pdf](http://www.probation.homeoffice.gov.uk/files/pdf/PC35%202007.pdf).
- 2 Harrison K. Legal and ethical issues when using antiandrogenic pharmacotherapy with sex offenders. *Sexual Offender Treatment* 2008;3. [www.sexual-offender-treatment.org/2-2008\\_01.html](http://www.sexual-offender-treatment.org/2-2008_01.html).
- 3 Bancroft JHJ. Human sexuality and its problems. 3rd ed. Churchill Livingstone, 2009.
- 4 Heim N, Hirsch CJ. Castration for sex offenders. Treatment or punishment? A review and critique of recent European literature. *Arch Sex Behav* 1979;8:281-304.
- 5 Prentky RA. Arousal reduction in sexual offenders: a review of antiandrogen interventions. *Sex Abuse* 1997;9:335-47.
- 6 Grubin D. Medical models and interventions in sexual deviance. In: Laws DR, O'Donohue WT, eds. *Sexual deviance: theory, assessment, and treatment*. 2nd ed. Guildford Press, 2008:594-610.
- 7 Maletzky B, Tolan A, McFarland B. The Oregon depo-provera program: a five-year follow-up. *Sex Abuse* 2006;18:303-16.
- 8 Lösel F, Schmucker M. The effectiveness of treatment for sexual offenders: a comprehensive meta-analysis. *J Exp Criminol* 2005;1:1-29.
- 9 Rösler A, Witzum E. Pharmacotherapy of the paraphilias in the next millennium. *Behav Sci Law* 2000;18:43-56.
- 10 Briken P, Hill A, Berner W. Pharmacotherapy of paraphilias with long-acting agonists of luteinising hormone-releasing hormone: a systematic review. *J Clin Psychiatry* 2003;64:890-7.
- 11 Alexander M. Should a sexual offender be allowed castration? Ethical considerations in using orchidectomy for social control. *BMJ* 1993;307:790-4.
- 12 Kafka MP. The monoamine hypothesis for the pathophysiology of paraphilic disorders: an update. *Ann NY Acad Sci* 2003;989:86-94.



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## Management of polymyalgia rheumatica

New guidelines are a step forward, but many unanswered questions remain

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Evidence is lacking on the management of polymyalgia rheumatica.<sup>1</sup> The recent guidelines published by the British Society for Rheumatology (BSR) and the British Health Professionals in Rheumatology (BHPR) are a brave attempt to give some structure to the diagnosis and treatment of this condition.<sup>2</sup>

Polymyalgia rheumatica is one of the most common inflammatory rheumatic diseases in elderly people. It is characterised by pain and stiffness, usually of sudden onset, affecting the limb girdle areas (shoulder and hip), neck, and torso.<sup>3</sup> Its prevalence in people aged over 50 is about 700 per 100 000.<sup>4</sup> It has many non-specific features and a wide differential diagnosis. No “gold standard” diagnostic test is available, so the diagnosis is often made on clinical grounds. This can lead to diagnostic error.

Polymyalgia rheumatica is managed mainly in primary care but also in secondary care by rheumatologists and other specialists.<sup>5</sup> It is one of the most common indications for long term steroid use in the community, accounting for 22% of prescriptions.<sup>6</sup> Despite being so common, there is surprisingly little sound evidence from randomised controlled trials on which to base diagnosis and management.

The new guidelines are aimed at healthcare practitioners in primary and secondary care, and they are intended to be used in the evaluation of patients with new symptoms of proximal bilateral shoulder or hip pain. A framework for the subsequent management of patients in primary care with regard to treatment, monitoring, and indications for early specialist referral is also outlined.

The guidelines recommend that the diagnosis of polymyalgia rheumatica is based on the presence of the following criteria: the patient is over 50 years of age, duration of symptoms is longer than two weeks, presence of bilateral shoulder or pelvic girdle aching, morning stiffness lasting longer than 45 minutes, and evidence of an acute phase response. It is crucial to exclude active infection, cancer, and other inflammatory conditions. Giant cell arteritis should always be considered because it occurs in 16-21% of patients with polymyalgia rheumatica.<sup>7</sup>

The suggested treatment regimen is prednisolone 15 mg for three weeks, which is then gradually tapered. Intramuscular methylprednisolone may also be used. Treatment usually lasts for one to two years. However, this guidance should not be regarded as absolute because it is supported by only grade B evidence.

Response to steroids is widely used as a defining feature of polymyalgia rheumatica. Vigilant monitoring and evaluation of the response to corticosteroids is recommended, and in typical cases at least a 70% improvement in symptoms is expected. The response is assessed after one to three weeks by evaluating the global response to relevant symptoms (proximal pain, stiffness), and the diagnosis is confirmed after four to six weeks.<sup>2</sup>

Early referral to a specialist is advised in cases with atypical features such as age less than 60 years, chronic onset, lack of shoulder involvement or inflammatory stiffness, or



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“red flag” features such as prominent systemic symptoms (weight loss or night pain). In addition, specialist input is suggested in patients with a normal or very high acute phase response and when encountering treatment problems such as lack of response to steroids or contraindications to steroids.<sup>2</sup>

No other validated international guidelines are available for the diagnosis and treatment of this condition. Diagnostic and classification criteria are currently being developed.<sup>5,8,9</sup> Clinical and patient oriented outcomes have been defined but still need validation by good quality trials.

The current guidelines simplify the approach to the diagnosis and management of patients presenting with polymyalgic symptoms, although they are not supported by good scientific evidence—most of the recommendations are graded at level B or C. Until further research is available, many unanswered questions remain.

- Dasgupta B, Hutchins A, Matteson E. Polymyalgia rheumatica: the mess we are now in and what we need to do about it. *Arthritis Rheum* 2006;55:518-20.
- Dasgupta B, Borg FA, Hassan N, Barraclough K, Bourke B, Fulcher J, et al; BSR and BHPR Standards, Guidelines and Audit Working Group B. BSR and BHPR guidelines for the management of polymyalgia rheumatica. *Rheumatology (Oxford)* 2010;49:186-90.
- Dasgupta B, Kalke S. Polymyalgia rheumatica. In: Isenberg D, Maddison P, Woo P, Glass D, Breedveld F, eds. *Oxford textbook of rheumatology*. 3rd ed. Oxford University Press, 2004:977-82.
- Siebert S, Lawson TM, Wheeler MH, Martin JC, William BD. Polymyalgia rheumatica: pitfalls in diagnosis. *JR Soc Med* 2001;94:242-4.
- Dasgupta B, Matteson EL, Maradit-Kremers H. Management guidelines and outcome measures in polymyalgia rheumatica (PMR). *Clin Exp Rheumatol* 2007;25(6 suppl 47):130-6.
- Walsh LJ, Wong CA, Pringle M, Tattersfield AE. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. *BMJ* 1996;313:344-6.
- Pipitone N, Hazleman B, Salvarani C. Polymyalgia rheumatica. In: Bijlsma JWJ, ed. *EULAR compendium of rheumatic disease*. BMJ Publishing Group, 2009:556-73.
- Leeb BF, Bird HA, Neshor G, Andel I, Hueber W, Logar D, et al. EULAR response criteria for polymyalgia rheumatica: results of an initiative of the European Collaborating Polymyalgia Rheumatica Group (subcommittee of ESCISIT). *Ann Rheum Dis* 2003;62:1189-94.
- Dasgupta B, Salvarani C, Schirmer M, Crowson CS, Maradit-Kremers H, Hutchings A, et al; members of the American College of Rheumatology Work Group for Development of Classification Criteria for PMR. Developing classification criteria for polymyalgia rheumatica: comparison of views from an expert panel and wider survey. *J Rheumatol* 2008;35:270-7.

## Maternal age and diabetes in childhood

The higher risk of type 1 diabetes in the offspring of older mothers is well known but still unexplained

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Two recent meta-analyses of early life influences on the risk of early onset type 1 diabetes largely confirm what previous studies have shown.<sup>1,2</sup> The first found that childhood onset diabetes is associated with increasing birth weight, equivalent to a 7% increase in risk for every 1000 g in weight,<sup>1</sup> and the second reported that caesarean section increases the risk by around 20%.<sup>2</sup> A third more recent pooled analysis of five cohort studies and 25 case-control studies provides formal confirmation that the risk of childhood onset diabetes increases with maternal age: 5% for each five years of age.<sup>3</sup> The studies included were heterogeneous, so interpreting the results is a challenge.

Why should the age of the mother at delivery influence the risk of diabetes in the child? There is much speculation, but the main explanations are that biological programming of the child is in some way affected by the age of the mother, or perhaps the father, and that the difference is caused by environmental or social confounders encountered before birth or in early childhood. Older women may, for example, be more likely to have complicated pregnancies and require caesarean section. Statistical adjustment for this and other potential confounders did not, however, affect the outcome in the pooled analysis described above.<sup>3</sup>

Other conditions, including childhood cancer, are influenced by maternal age. A recent pooled analysis found an odds ratio of 1.08 (95% confidence interval 1.06 to 1.10) per five year increase in maternal age for the 10 most frequently diagnosed childhood cancers. Possible explanations include germline mutations (more common in sperm than in oocytes); alterations in oocyte gene expression as a result of promoter DNA methylation or age related hormonal changes; more prolonged maternal exposure to environmental carcinogens; and other unexamined potential confounders.<sup>4</sup>

In contrast, asthma in childhood seems to be associated with younger maternal age. A postal questionnaire of 16 000 adults in northern Europe reported an 8% reduction in the risk of childhood asthma (adjusted odds ratio 0.92, 0.88 to 0.97) for each five year increment in maternal age, which persisted after adjustment for known confounders.<sup>5</sup> This provides yet another example of the curious reciprocal association between type 1 diabetes and atopic disorders. Both have increased in parallel over the past 50 years, especially in affluent populations of European descent, yet atopy reduces the risk of type 1 diabetes and diabetes reduces the risk of asthma.<sup>6</sup> This reciprocity has been explained in terms of the Th1-Th2 paradigm. Type 1 diabetes is characterised by T helper type 1 (Th1) CD4 positive T cells and the signature cytokine interferon  $\gamma$ , whereas atopic disorders are characterised by Th2 cells and interleukins IL-4, IL-5, and IL-13.<sup>7</sup> The axis is more complex than initially believed, but the polarity between Th1 and Th2 disorders seen at a population level remains highly suggestive.<sup>6,7</sup>

Infectious disease eliminated up to a third of the children born to our ancestors within the first few years of life, but recent generations have faced a much less challenging environment. One consequence, according to the hygiene hypothesis, is that an increasing number of children will fail to develop a healthy

“mixed” pattern of immune response and will instead remain as outliers at either end of the Th1-Th2 spectrum.<sup>8</sup> Hence the parallel rise in both types of immune disorder. But does the age of the mother influence the immune potential of the child, and if so, how? Once again we are left clutching at straws.

The rise of childhood type 1 diabetes is largely unexplained. The increase can be traced back to the middle of the 20th century, if not earlier, with a linear trend and an approximate doubling time of 20 years.<sup>9,10</sup> Prospective studies from birth confirm the dominant role of HLA associated susceptibility in conferring individual risk, such that early onset is associated with the highest risk alleles.<sup>11</sup> Paradoxically, it is equally clear that the global increase in type 1 diabetes must be driven by as yet unidentified non-genetic influences. To take one example, the increase in childhood type 1 diabetes over the past 50 years has largely been restricted to a subset of the population with HLA associated susceptibility, yet the ratio of intermediate to high risk alleles has increased substantially over the same period, implying that the environment has become progressively more favourable for the development of diabetes.<sup>12</sup>

Consistent with this interpretation, the increase in childhood onset diabetes has in some cases been mirrored by a reduced incidence in young adults, which suggests that we may be witnessing a “spring harvest” of genetically susceptible individuals rather than an overall increase in the lifetime incidence of type 1 diabetes. In all events, it is clear that the trend for women to delay their pregnancies into their 20s or 30s has made a modest contribution towards the rise of childhood onset type 1 diabetes, but is in no way responsible for it.<sup>3</sup>

- Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ, et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia* 2008;51:726-35.
- Harder T, Roepke K, Diller N, Stechling Y, Dudenhausen JW, Plagemann A. Birth weight, early weight gain, and subsequent risk of type 1 diabetes: systematic review and meta-analysis. *Am J Epidemiol* 2009;169:1428-36.
- Cardwell CR, Stene LC, Joner G, Bulsara MK, Cinek O, Rosenbauer J, et al. Maternal age at birth and childhood type 1 diabetes: a pooled analysis of 30 observational studies. *Diabetes* 2009; published online 29 October.
- Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, et al. Parental age and risk of childhood cancer. A pooled analysis. *Epidemiology* 2009;20:475-83.
- Laerum BN, Svanes C, Wentzel-Larsen T, Gulsvik A, Torén K, Norman E, et al. Young maternal age at delivery is associated with asthma in adult offspring. *Respir Med* 2007;101:1431-8.
- Cardwell CR, Shields MD, Carson DJ, Patterson CC. A meta-analysis of the association between childhood type 1 diabetes and atopic disease. *Diabetes Care* 2003;26:2568-74.
- Rabin RL, Levinson AI. The nexus between atopic disease and autoimmunity: a review of the epidemiological and mechanistic literature. *Clin Exp Immunol* 2008;153:19-30.
- Gale EAM. A missing link in the hygiene hypothesis? *Diabetologia* 2002;45:588-94.
- Gale EAM. The rise of childhood type 1 diabetes in the twentieth century. *Diabetes* 2002;51:3353-61.
- Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G; EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. *Lancet* 2009;373:2027-33.
- Bonifacio E, Hummel M, Walter M, Schmid S, Ziegler A-G. IDDM1 and multiple family history of type 1 diabetes combine to identify neonates at high risk for type 1 diabetes. *Diabetes Care* 2004;27:2695-700.
- Gillespie KM, Bain SC, Barnett AH, Bingley PJ, Christie MR, Gill GV, et al. The rising incidence of childhood type 1 diabetes is associated with a reduced contribution from high-risk HLA haplotypes. *Lancet* 2004;364:1699-700.