

ringed sideroblasts is generally many fewer than 15%. The white cell and megakaryocyte series are not affected. Occasionally, patients develop severe sideroblastic anaemia secondary to drug therapy or severe alcohol abuse which may reverse on stopping the offending drug.<sup>7-9</sup> In the case of isoniazid, the mechanism is thought to be inhibition of pyridoxine related haem synthesis; isoniazid binds pyridoxine and the complex is excreted via the kidney.<sup>9</sup> Penicillamine may have a similar mode of action.<sup>10</sup>

A number of haematological side effects of penicillamine therapy have been reported. Sullivan *et al*<sup>10</sup> reported a case of sideroblastic anaemia in a patient with biliary cirrhosis who was taking 1000 mg of penicillamine a day. The features of sideroblastic anaemia developed over 12 months and resolved after cessation of penicillamine and introduction of pyridoxine treatment. The patient later recommenced taking penicillamine with pyridoxine cover, without further problems. This patient had abnormal liver function and this may have contributed to the situation.

Ramselaar *et al*<sup>8</sup> reported a patient who developed aplastic anaemia secondary to penicillamine. The leucopenia resolved, but the patient remained anaemic and thrombocytopenic with bone marrow features of sideroblastic anaemia. The patient did not respond to pyridoxine therapy and subsequently died of a septicaemic episode.

In our patient, the development of sideroblastic anaemia was closely associated with the introduction of penicillamine therapy and his rheumatoid arthritis was relatively quiescent as judged by clinical and laboratory parameters. On introduction of pyridoxine, the patient's anaemia resolved and the abnormal sideroblasts disappeared from the bone marrow. Thus the sudden onset of anaemia and the response to withdrawal of penicillamine strongly implicate penicillamine as the causal agent. The follow up bone marrow analysis showed only minor dysplastic features—a frequent finding in pyridoxine sensitive sideroblastic anaemia.

We believe that this is the first reported case of acquired sideroblastic anaemia which was reversible with pyridoxine, in a patient with rheumatoid arthritis. As many of the adverse effects of penicillamine are dose dependent,<sup>4</sup> it may be possible to reintroduce penicillamine under pyridoxine cover, particularly if a smaller dose controls the joint disease.

This report highlights the need for vigilance in patients with rheumatoid arthritis who are receiving maintenance penicillamine. The development of anaemia whilst on penicillamine treatment warrants careful investigation, including consideration of a bone marrow aspirate if other more common causes are excluded.

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## Homozygous complement factor deficiency and primary antiphospholipid syndrome: a clinical and serological study

Complement factor 2 (C2) deficiency is the most common inherited complement deficiency.<sup>1</sup> In 60% of cases the disorder is associated with a lupus-like disease, and to a lesser extent with recurrent bacterial infections. An isolated form of glomerulopathy is described in about 25% of patients.<sup>2</sup> Here, we describe a patient with homozygous C2 deficiency and primary antiphospholipid syndrome (PAPS). The main PAPS manifestation was repeated cerebrovascular disease; another relevant feature was hypertensive nephropathy without overt nephritis.

Bilateral cataracts were diagnosed in a 40 year old man in 1986; simultaneously, he was discovered to be hypertensive. There was no previous history of renal calculus or urinary symptoms. Blood analysis revealed creatinine 0.247 mmol/l, urea 27.8 mmol/l, triglycerides 226 mg/dl as the only altered parameters. Urinary sediment was normal; protein excretion was 0.2 g/24 h. The patient was treated with captopril 50 mg/day, with good blood pressure control.

Nine months later, the patient suffered a convulsive seizure without any residual neurological deficit.

Laboratory studies showed low haemolytic complement activity (< 8 U/ml) with normal C3 and C4 concentrations. Antinuclear antibodies and antibodies to double stranded DNA, extractable nuclear antigens and rheumatoid factor were negative.

A percutaneous renal biopsy showed a segmental and focal glomerulosclerosis, without acute occlusive changes by fibrin thrombi or fibrinoid necrosis of the vessel wall. Immunofluorescence showed a weak positivity with IgA, C3, C4, and Clq antisera.

In 1987, the bilateral cataracts were surgically removed. Subsequently, the patient became aware of a right visual field defect.

Three years later (May 1990) he showed clinical features of intermittent claudication with inadequate blood supply to the lower extremity. In July 1990 he suddenly experienced dysarthria, right dismetria and lateropulsion with mild right hemiparesis and hemihypoesthesia. A right homonymous hemianopsia, matching the earlier visual complaint, was also detected. Antiplatelet drug treatment (aspirin) was started. Cranial computed tomography, performed 72 hours afterwards, showed a recent right cerebellar hemisphere infarct and an old left occipital lobe infarct. Angiographic examination showed abnormally dilated basilar and left vertebral arteries.

At this stage, anticardiolipin antibodies were detected by standard enzyme linked immunosorbent assay.<sup>3</sup> Their values were moderate positive for IgM and low positive for IgG (according to the international standards for that assay<sup>3</sup>); a year later IgG and IgM values were both moderate positive. Coagulation studies showed normal prothrombin time and activated partial thromboplastin time. Thrombocytopenia was not found. HLA typing was performed using microlymphocytotoxicity, and complotypes assayed: agarose electrophoresis, immunofixation and Coomassie staining for C4; cellulose acetate electrophoresis, immunofixation and nigrosin staining for factor B; and polyacrylamide isoelectrophoresis, immunofixation and silver staining for C2. The total haemolytic complement activity and C2 were undetectable, with normal C3 and C4 concentrations (table). Reconstitution of total haemolytic complement activity was possible by addition of C2. The results of complotype and haplotype analysis were also compatible with homozygous C2 deficiency (table).

The proband had a sister who suffered repeated migraines and died at the age of 30 years from cardiac infarction; the father also died (aged 64 years) from cardiac infarction. The mother was asymptomatic and had negative autoimmune serology.

We present here the first description (*Medline* 1987-April 94) of a patient with a homozygous C2 deficiency and PAPS. C2 deficiency is a molecular genetic deficiency with two variants;<sup>4</sup> in the proband, the HLA haplotype corresponded with the type I form, although the complotype was not typical.

### Immunochemical concentrations of components of the complement system, classical haemolytic complement activity (CH<sub>50</sub>) and class I, II, and III specificities in the family members

| Component               | Family member   |  | Normal range  |
|-------------------------|---|--|---------------|
|                         | Mother  | Proband  |               |
| CH <sub>50</sub> (U/ml) | 138   | 0  | 100-180 U/ml  |
| C2 (mg/dl)              | 1.9   | 0  | 1.5-5.7 mg/dl |
| C3 (mg/dl)              | 85  | 90   | 80-120 mg/dl  |
| C4 (mg/dl)              | 39  | 41   | 20-40 mg/dl   |
| HLA phenotype           |   |  |               |
| Class I                 | A2, A25, B7, B18  | A25, A-, B18, B-   |               |
| Class II                | DR2, DR4, DQw1, DQw3  | DR2, DR-, DQw1   |               |
| Class III               | C2* C, C2* Q0<br>B* S, B* S<br>C4A* 3, C4A* 3<br>C4B* 1, C4B* 2 | C2* Q0, C2* Q0<br>B* S, B* S<br>C4A* 3, C4A* 3<br>C4B* 2, C4B* 2 |               |

The patient showed some features common to C2 deficiency related nephropathy,<sup>2</sup> but lacked the usual histological features.

PAPS criteria<sup>5</sup> were fulfilled by our patient; he had a history of thrombosis and a moderate level of anticardiolipin antibodies without a primary cause. The association of antiphospholipid antibodies with thromboembolic disorders is well established.<sup>6,7</sup> In accordance with these reports, we believe that the existence of these antibodies in our patient increased the risk of cerebral ischaemic events, evidence of which was already present in the grossly dilated vertebral basilar anomaly. Here, renal disease seemed not to be directly related to antiphospholipid antibodies because thrombotic microangiopathy was not demonstrated.<sup>8</sup>

Antiphospholipid antibodies have already been related to the presence of null alleles of C4 in patients with systemic lupus erythematosus,<sup>9</sup> but not in PAPS patients.<sup>10</sup>

The basis for the association between inherited complement deficiency of early components and autoimmune disease is not understood. It may involve ineffective clearance of microbial or non-infectious antigens (such as cardiolipin) which might stimulate autoantibodies. In our patients, because of the rarity of homozygous C2 deficiency, it is likely that this condition was causally related to the antiphospholipid syndrome.

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## Might patients with HLA-B27 related diseases benefit from antiandrogenic treatment?

There are several rheumatic diseases which may be suspected of sharing the curious feature that both probands and their unaffected sibs have sex ratio biases that are in the same direction. For instance, rheumatoid arthritis (RA), early onset pauciarticular juvenile rheumatoid arthritis, and coxarthrosis are all conditions in which probands and their unaffected sibs seem to contain excesses of females, while ankylosing spondylitis (AS), Reiter's syndrome, and late onset pauciarticular juvenile rheumatoid arthritis are all conditions in which probands and their unaffected sibs seem to contain excesses of males.<sup>1,2</sup> The caution in the foregoing sentence is appropriate, because many of the data underlying these conclusions were gathered for other purposes and were therefore subject to possible volunteer bias or survivorship bias (both of which would be expected to lead to female excesses). However, these qualifications do not apply to the data on juvenile rheumatoid arthritis;<sup>2</sup> and they do not apply to recent reports of data explicitly gathered to test the sex ratio biases of sibs of RA and AS probands.<sup>3-6</sup> Tables 1 and 2 summarise these data; they suggest that the biases are real.

What may be inferred from this? One may propose that the same agent causes both the disease in probands and the unusual sex ratios in their unaffected sibs.

There is very substantial evidence that parental hormone levels at the time of conception partially control the sexes of human offspring at birth.<sup>7,8</sup> So I suggested that low testosterone levels are a cause of RA and of RA patients' excess of sisters, and that high testosterone levels are a cause of AS and of these probands' excess of brothers.<sup>1</sup> The suspicion in regard to RA was strengthened by the subsequent demonstration that RA patients may benefit from androgen treatment.<sup>9</sup> So the question arises if patients with HLA-B27 related diseases might, analogously, benefit from antiandrogen treatment. This resolves into the question: what evidence is there that HLA-B27 related diseases are partially caused by high levels of androgens?

For illustrative purposes, I shall consider AS (because there are more published data on this condition), but the following speculations may also apply to the other B27 related diseases. It is well established that patients with AS have high testosterone levels, on average.<sup>10-12</sup> Moreover, there is evidence that B27 is associated with high testosterone levels in healthy controls also.<sup>1,13</sup> Thus the high testosterone levels in AS patients may reasonably be interpreted as a genetically determined precursor of the disease, rather than its consequence. This conclusion is strengthened by the observation that disease, in general, causes men's testosterone levels to decrease, not increase.<sup>14</sup>

Table 1 Recently published data on the sexes of sibs of probands with ankylosing spondylitis

| Source                           | Brothers | Sisters |
|----------------------------------|----------|---------|
| Calin <i>et al</i> <sup>3</sup>  | 232      | 199     |
| Ploski <i>et al</i> <sup>4</sup> | 54       | 32      |
| Totals                           | 286      | 231     |

Tested against an expected white live birth sex ratio of 0.514,<sup>5</sup> the pooled data here yield a  $\chi^2$  value of 3.2 ( $p < 0.05$ , one way).

Table 2 Recently published data on the sexes of the sibs of probands with rheumatoid arthritis

| Source                             | Brothers | Sisters |
|------------------------------------|----------|---------|
| Calin <i>et al</i> <sup>3</sup>    | 280      | 294     |
| Ploski <i>et al</i> <sup>4</sup>   | 191      | 210     |
| Deighton <i>et al</i> <sup>6</sup> | 36       | 46      |
| Totals                             | 507      | 550     |

Tested against an expected white live birth sex ratio of 0.514,<sup>5</sup> the pooled data here yield a  $\chi^2$  value of 5.0 ( $p < 0.02$ , one way).

So there seem to be good grounds for supposing that some of the sex related rheumatic diseases are caused by unusual hormone levels which in turn are (partially) controlled by their associated HLA antigens. Accordingly, it seems reasonable to wonder if AS patients might benefit from antiandrogenic treatment.

This raises a moral problem which is illustrated in the predicament of the television playwright, the late Dennis Potter. His suffering from psoriatic arthritis (a B27 related condition) was dramatised in *The Singing Detective*. One may suggest that Potter's creativity and pervasive interest in sex may both have had a hormonal basis. Practitioners offering antiandrogen treatment should advise patients of their possible psychological side effects. Men who want relief from their B27 related diseases may nevertheless not be keen to risk compromising their masculinity in the process; so it might be preferable to consider treating female patients first . . .

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