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Azathioprine treatment in multiple sclerosis; pretreatment assessment of metaboliser status

Azathioprine is a cytotoxic immunosuppressant drug used widely in clinical neurology as an adjunct to steroid treatment for autoimmune and inflammatory conditions. As a result of the relatively high cost and modest benefit of the newly licensed immunomodulatory therapies in the treatment of multiple sclerosis there has been a resurgence of interest in the possible benefits of azathioprine. A meta-analysis in 1997 suggested that it was as effective as newer treatments in increasing the proportion of patients who remain free of relapse at 2 years.¹

The mode of action of azathioprine at the immune cell level remains unclear. It is converted rapidly in vivo to 6-mercaptopurine, which is extensively metabolised along three competitive routes (table 1).² Methylation catalysed by thiopurine transferase (TPMT) leads to the production of 6-methyl mercaptopurine. Wide variations in TPMT activity exist between patients and are determined by a common genetic polymorphism; 89% of the population have high TPMT concentrations, 11% intermediate concentrations, and 1 in 300 low or absent TPMT concentrations. A second catabolic route is oxidation with xanthine oxidase, which exhibits little interindividual variation in activity. The third route, catalysed by hypoxanthine guanine phosphoribosyl transferase, results in the formation of active thiopurine metabolites including 6-thioguanine nucleotides (6-TGN) which are thought to be responsible for the cytotoxicity of azathioprine.

In 1980 Weinshilboum and Sladek³ proposed that the inherited variation in TPMT activity might represent one factor in individual variations in sensitivity to thiopurine drugs. The importance of a low activity of TPMT with an associated increase in 6-TGN in red blood cells in patients with bone marrow failure treated with azathioprine was reported by Leonard *et al*⁴ in 1989. Since 1963 61 fatalities suspected to be associated with azathioprine have been reported to the Committee on Safety of Medicines (personal communication); 25 of these were classed as haemopoietic disorders. The importance of

an inherited deficiency in thiopurine methyltransferase is mentioned specifically in the data sheet for Imuran (Glaxo-Wellcome).

Full blood count is a poor method of detecting early bone marrow toxicity as by the time changes have occurred dangerously high concentrations of 6-TGN may have accumulated. An alternative which allows this complication to be anticipated is the measurement of TPMT activity in red blood cells. This is a relatively cheap test (~ £26), performed on an EDTA blood sample, and genotypic testing may soon be clinically available. Late onset myelosuppression has a more gradual onset and can be detected by changes in blood counts.

The overview of azathioprine treatment in multiple sclerosis published as a meta-analysis in the *Lancet* in October 1991⁵ showed that the probability of freedom from relapse during the first, second, and third year of treatment was significantly greater in the azathioprine group, but the change in the expanded disability status scale (EDSS) was not significantly different. The authors concluded that it was debatable whether the slight clinical benefits outweigh side effects and that it is still not possible to predict which patients are likely to benefit from treatment with azathioprine. Although studies included in the Cochrane database mention morbidity in terms of decreased haematological indices and three mortalities said to be unrelated to multiple sclerosis or azathioprine, TPMT concentrations were not measured in any of the trials included in the meta-analysis.

Individual variation in TPMT may explain the variable toxicity and treatment response with azathioprine in multiple sclerosis. In addition, knowledge of TPMT status in patients with multiple sclerosis could identify those unsuitable for azathioprine treatment and those in whom the dose could be increased to the top of the therapeutic range secure in the knowledge of a very low probability of toxicity. It has been suggested that studies using azathioprine may fail to detect a therapeutic effect due to underdosage—if TPMT is measured this can be avoided.

Anticipation of azathioprine related toxicity and the tailoring of dose to the metaboliser status of individual patients might have considerable implications in routine clinical practice.

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Migrainous brain stem disturbance in Norrie disease: case report

Norrie disease (or Norrie-Warburg syndrome) is a rare X linked disorder characterised by congenital blindness due to retinal hypoplasia. A third of patients may additionally have deafness and/or mental subnormality.¹ The gene has been mapped to Xp11.4-p11.3, in close proximity to the monoamine oxidase A and B (MAO-A and MAO-B) loci.²

We report a possibly unique case of Norrie disease in a man who described paroxysmal attacks of deafness, slurred speech, and somnolence from his late teens. The character of the attacks, in addition to their marked response to β blockade, argue for the enlargement of the phenotypic character of the disease to include migrainous aura affecting the brain stem.

A 38 year old left handed male computer consultant with Norrie disease sought neurological attention because of episodes of being unwell. He was born with no vision and atrophic eyeballs (phthisis bulbi). At the age of 18 he developed hearing loss necessitating hearing aids; after a period of worsening his hearing stabilised. His paroxysmal attacks began at this age, initially at a frequency of once every 4 or 5 months. During the year before neurological consultation, they increased to once every 2 or 3 weeks. They were predictably associated with stress or stress release. An attack typically began with a gradual deterioration (over a few minutes) of balance with further worsening in the hearing in his right ear, associated with a sense of fuzziness in his head. Occasionally he would experience a loud banging noise. The symptoms progressed to slurred speech, drowsiness, and almost complete deafness in the right ear. Observers described him as appearing pale and in discomfort during these episodes. The attacks could be truncated if he took a tablet or two of Praxilene (100 mg naftidrofuryl oxalate) sufficiently rapidly after the onset of symptoms. Otherwise, they would pass off after a few hours sleep. He did not describe a headache at any time; there was a dislike for food during the attacks but no nausea or vomiting.

His medical history otherwise consisted of mild asthma, controlled by occasional bronchodilator inhaler use. He had a nephew with Norrie disease. There was a family history of migraine in his mother.

General physical examination was normal. Neurological examination disclosed an articulate, insightful man with intact higher mental function. Both eyes were prosthetic. There was mild sensorineural hearing loss, worse on the right. The remainder of the neurological examination was unremarkable.

Brain MRI was normal. Further investigation of his monoamine oxidase status (see below) with urinary catecholamine metabolites, whole blood serotonin, and CSF

Table 1 Pathway of azathioprine metabolism

serotonin and dopamine metabolites was unfeasible for logistical reasons.

The time course, circumstances of precipitation, and positive family history suggested an acephalgic migrainous disturbance. Despite his asthma, prophylaxis with β blockers was initiated (10 mg propranolol twice a day, building up to a long acting preparation (80 mg Inderal LA once daily). On review 6 months later, he reported a marked positive effect, having had only one, relatively mild attack during the period. His asthma remained well controlled on a more regular use of inhalers.

Norrie disease is a member of a family of disorders that result from mutations in genes occupying the proximal portion of the short arm of the X chromosome. The gene is flanked on either side by the MAO-A and MAO-B loci.² Point mutations in the Norrie gene lead to at least two other distinct clinical syndromes: familial and sporadic exudative retinopathy, and the retinopathy of prematurity.¹ More complex genetic defects arising from larger mutations including the Norrie locus have been described. Vossler *et al*³ described three boys with Norrie disease and cataplexy with REM sleep disorganisation. All three patients had absent serum MAO-B activity; serum serotonin was increased, and plasma catecholamines were normal. Collins *et al*⁴ reported on a male patient with a mutation spanning all three of the MAO and Norrie disease loci. The patient had severe mental handicap with myoclonus and stereotyped behaviour disorder; serum MAO activity was undetectable. Chen *et al*² drew attention to a family with pure MAO-A deficiency who had the phenotype of low normal intelligence, impulsivity, cardiovascular problems, and altered concentrations of amine metabolites.

To the best of our knowledge, there is no reported association between Norrie disease (and its genetic variants) and migraine. This is perhaps surprising considering what is the currently accepted wisdom on migraine pathophysiology.⁵ This strongly implicates the serotonin-MAO axis—migraineurs have increased serotonin and diminished MAO platelet activity between attacks. Our patient was not investigated genetically or with serum MAO determination, but we surmise that he harbours at least a partial defect of MAO-A activity (the relevant enzyme for serotonin degradation). This presumably (and perhaps in conjunction with his familial tendency to migraine) is the metabolic basis for his symptoms.

We conclude that patients with Norrie disease who experience intermittent neurological dysfunction may benefit from β blockade.

We thank the patient for permitting us to report his case and Dr Tony Fryer for helpful discussion.

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Acute deterioration in Chiari type 1 malformation after chiropractic cervical manipulation

Type 1 Chiari malformation consists of caudal displacement of the cerebellar tonsils through the foramen magnum. It may also be associated with displacement of the medulla and hydromyelia or syringomyelia. The natural history is variable, with most patients presenting between the 3rd to 5th decades.¹ In a reported series of 71 patients, 69% presented with pain, 56% had weakness, 52% had numbness, and 40% complained of unsteadiness.² Mohr *et al*³ classified patients' presentations into four main groups: syringomyelia, paraparesis, cerebellar, and "raised pressure". We describe a patient with a previously relatively asymptomatic complex Chiari 1 malformation who acutely deteriorated after chiropractic manipulation of the cervical spine.

This white woman first presented at the age of 47 years in August 1995. She had sustained a mild "whiplash" injury in April 1995, having been struck at low speed from behind while sitting in a stationary car. She developed neck pain a few days later and this became progressively more annoying over the next 2 months. She then attended for chiropractic manipulation of the neck. This included repetitive high velocity, low amplitude thrusting movements at the base of the neck. Immediately after the therapy session, her neck pain worsened, spreading to involve the occiput, vertex, and frontal head regions. It was made worse with coughing, lifting, and bending over. She became aware of diplopia and intermittent difficulty swallowing. She had progressive gait instability when walking longer distances. In retrospect, she had many years of poor balance, with difficulty walking on uneven ground when wearing high heels. There was no sphincteric or sensory disturbance. Her history was unremarkable apart from total gastrectomy for a benign peptic ulcer. She was receiving regular B12 injections.

Examination showed normal visual acuity and funduscopic findings. There was bidirectional horizontal gaze evoked nystagmus and mildly impaired horizontal vestibulo-ocular reflex suppression. Vertical pursuit was abnormal with markedly impaired vertical vestibulo-ocular reflex suppression. There was right hypertropia on right gaze. There was no facial weakness or sensory loss. She had a "nasal" quality to her speech, with mild dysrhythmia with rapid consonants. The jaw jerk was pathologically brisk. There was increased tone in the lower limbs. Deep tendon reflexes were increased with positive Hoffman's sign and bilateral extensor plantar responses. She had a wide based gait with moderate truncal ataxia.

Plain radiographs of the neck disclosed assimilation of the posterior arch of C1 into the occiput, and abnormality of the dens. Brain MRI showed prolapse of the cerebellar tonsils through the foramen magnum to the level of the base of C2, with basilar invagination of the peg and angulation of the upper medulla (fig 1). There was mild midline cerebellar abnormality and distortion of the vertebrobasilar system. The aqueduct seemed normal. Laboratory tests disclosed compensated hypothyroidism.

She continued to deteriorate over the next 12 months, developing vertical nystagmus in

the primary position, and became unable to walk unassisted.

In October 1996 she underwent a complex decompression procedure, with anterior removal of the anterior arch of C1, odontoid peg and clivus, and posterior removal of the occipital bone and attached occipitalised arch of C1. The surgery was complicated by development of pneumonia and a loculated empyema requiring a thoracotomy for decortication, and septic arthritis of a C1/C2 zygoapophyseal joint. She required a temporary percutaneous feeding gastrostomy.

Three years after surgery she has very mild residual cerebellar ataxia, eye movement disorder, and mild dysarthria. She is able to eat a normal diet and walks independently.

Various neurological complications have been described with head and neck manipulation. Case reports have most often documented vascular injuries and stroke syndromes.^{3,4} Cervical manipulation has also been associated with spinal cord injuries and paraparesis,⁵ phrenic nerve injury,⁶ and various nerve root disruptions.

The patient reported here represents a case of occult complex Chiari 1 malformation, which acutely decompensated after neck manipulation. The mechanism of injury is probably related to vigorous head rotation with direct traction on the markedly angulated medulla. It is also possible that the anterior compression at the craniocervical junction was worsened by transient subluxation of an already abnormal atlantoaxial joint.

The frequency of complications after spinal manipulation is not known, although the usual public perception is that it is relatively risk free. This patient, and the literature would suggest that there is a real, if small, complication rate with a substantial long term morbidity and disability.

Certain conditions would seem to be absolute contraindications to chiropractic manipulation, and ideally these would be identified before proceeding. Plain radiographs of the spine, with emphasis on the occipitocervical junction, have been suggested as screening tools before manipulation.³ If bony abnormalities or lytic changes are seen, then manipulation should be avoided. Certainly if this rule was followed, the patient would not have shown rapid deterioration. It should be emphasised however, that adult Chiari malformation is not uncommon and may not be associated with gross skeletal abnormalities.

Patients with previous symptoms of brain stem ischaemia should also avoid therapy. Others have also suggested that malignancy,

Figure 1 Preoperative T1 weighted sagittal MRI, showing cerebellar tonsillar invagination and angulation of the upper medulla, and abnormality of the dens and posterior arch of C1.