Letters to the editor

'Normal MRI neuroimaging and acute dancing eyes syndrome'
SIR–Dancing eyes syndrome DES (otherwise known as opso-clonus myoclonus syndrome) is a disabling neurological con-dition characterized by acute or subacute onset of eye opsoclonus, myoclonus, ataxia, and irritability. Although eye signs often resolve, significant cognitive and motor sequelae are typical. DES is often associated with neuroblastoma tumours, although non-specific infectious illnesses may also herald onset. Postinfectious and paraneoplastic associations have supported the theories that DES is immune-mediated.[1] This hypothesis is also supported by the use of immune modu-lating therapies, although a controlled trial to determine the most effective therapies has not been undertaken.

The clinical characteristics of DES suggest the involvement of cerebellar and brainstem neural circuits, however, more widespread neural dysfunction is possible. Antineuronal anti-body studies have demonstrated antibodies directed against components of the cerebellum in one study,[2] although a fur-ther study showed inconsistent findings of anti-neuronal anti-bodies in acute DES.[3]

The exact disease localization remains unknown due to the lack of pathological studies. Neuroimaging is considered to be normal by most paediatric neurologists. However, two case reports on this disorder have described focal inflammatory lesions in the pons and cerebellar vermis, respectively. [4,5] In view of this discrepancy, we examined retrospectively the brain MRI of 10 sequential patients (7 females, 3 males; mean age 32 months [SD 19], range 12 to 60 months) presenting with acute DES at Great Ormond Street Hospital, UK between 1995 and 2000. All patients had MRI within 4 weeks of disease onset. Four patients had an associated neuroblastoma and six were postinfectious without evidence of neuroblastoma (despite extensive investigation). T_1- and T_2-weighted images were reviewed in all 10 patients. Two neuroradiologists were blind-ed to the clinical details and purpose of the study. Both inde-pendently reported no abnormalities in all 10 images.

We conclude that acute MR neuroimaging is usually nor-mal in DES using conventional techniques, and that novel approaches are required to understand the pathogenesis of the disorder. Neuroimaging may still play an important role, possibly using MR spectroscopy techniques in acute DES, or regional volumetric analysis of chronic DES. Further immunological investigation is required to see whether cell mediated or humoral immunity is primarily involved in DES pathogenesis. Collaboration is likely to be important in future investigations of this rare but disabling condition.

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'Visual impairment due to a dyskinetic eye movement disorder in children with dyskinetic cerebral palsy'
SIR–We read with great interest the article by Jan and col-leagues[1] reporting 14 children (age range 4 months to 13 years) with dyskinetic cerebral palsy (CP) whose visual impairment was attributed to a dyskinetic eye movement disorder which had first been misdiagnosed as cortical visu-al impairment. It remains unclear to us, however, how corti-cal visual impairment was ruled out and we wonder whether dyskinetic eye movement disorder and cortical visual impairment can coexist and if this, in fact, accounted for the children's visual problems.

Dyskinetic CP is often the result of perinatal asphyxia which can also affect the central visual pathways or visual cor-tex resulting in cortical visual impairment. Children with cor-tical visual impairment have major problems with visual attention, pursuit, and voluntary and saccadic ocular move-ments, which are very difficult to study. They use unusual strategies when attempting to explore objects visually (e.g. tilting the head, deviation of eyes to one side). On the other hand, children with 'primary' congenital supranuclear eye movement disorders, such as oculomotor apraxia or congeni-tal motor nystagmus, do not have major problems with visual perception and often have good visual acuity.

Eye movement disorders may have consequences for spa-tial attention and other situations where body and/or envi-ronmental motion require coordinated, high level visual discrimination and eye movement on specific targets, but do not appear to have a major impact on visual acuity and visual perception in less demanding circumstances. Control of eye movements in children with dyskinetic CP is often remark-ably preserved, allowing these children to use computers and other visual devices effectively.

We wonder, then, whether Jan and colleagues described a particular subgroup of patients who had mainly an oculomo-tor pathology. We are not sure that this is the main explanation

in all children reported in their study, in whom cortical visual impairment could not be specifically ruled out.

We would appreciate comments from the authors who, indeed, have been pioneers in highlighting the still neglected problem of cortical visual impairment in children.[2]

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'Jan et al. reply'

SIR–The letter written by Drs Roulet-Perez and Deonna raises some interesting points, but it is the definition of cortical visual impairment which is at the root of the matter.

Good and colleagues describe cortical visual impairment as having the following features: decreased acuity, abnormal neurological imaging, and abnormal electrophysiological testing consistent with bilateral damage to posterior pathways including the occipital lobes. This definition focuses on the posterior pathway and does not involve other structures.

In our study, the presentation of children with dyskinetic eye movements was similar to that of children with cortical visual impairment, but there were important differences. Patients with dyskinetic eye movements had near normal or normal visual acuity, based on forced choice acuity cards, normal peripheral field testing, and EEG results that were inconsistent with cortical visual impairment. Further, these children's clinical presentations were different: they could identify targets more easily than cortically impaired children would but dyskinetic eye movements, which arose while attempting to reach or maintain fixation, resulted in a functional inability to use their vision.

As neurological damage can be variable, it would not be unusual to see a spectrum of different neurological causes of visual impairment within the same patient. We have seen patients with a combination of cortical visual impairment and dyskinetic eye movements. As cortical visual impairment clinical features increasingly appear, such as poor visual attention, it becomes more difficult to tease these apart from the neurological features of dyskinetic eye movements. Further, patients with 'combined' impairments often have other severe neurological problems which make the assessment more difficult. But in our study, the cortical visual impairment features were minimal, so the apparent visual problems were attributed to dyskinetic eye movements.

We would advise caution when describing dyskinetic eye movements with other forms of eye movements. In congenital motor nystagmus, there is a minor reduction in acuity, without specific neuroanatomic anomalies and a normal electrophysiologic testing. In ocular motor apraxia, the cerebellar vermis appears to be affected. Patients with dyskinetic eye movements have different features leading to functional visual impairment which is due to erratic fixation and pursuit behaviour. Although patients with dyskinetic cerebral palsy can use assistive devices, our patients required significant adaptations due to their clinical severity.

These patients may have 'central' or 'cerebral' visual impairment. But, in our opinion, 'cortical' visual impairment is not the same as a 'cerebral' visual impairment, which we feel is a broad term that encompasses issues related to visual acuity, attention, processing, eye movements, and many others. The term 'cerebral' is problematic as it encompasses many disease states, some of which are not in the realm of visual impairment. We feel that the term 'cerebral' leads to greater misunderstanding.

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'Congenital disorders of glycosylation syndromes'

SIR–The congenital disorders of glycosylation (CDG) syndromes are genetic disorders characterized by a defective glycosylation of glycoconjugates.[1] CDG syndrome type 1a (CDG1a) is the most common; it is due to the deficiency of phosphomannomutase (PMM). The PMM2 gene, that is involved in most of the patients with CDG1a, has been mapped to chromosome 16p13 and molecular analyses have already defined a number of different mutations.[2] CDG1a is a multisystemic disorder with a well defined neurological picture that comprises alternating internal strabismus, abnormal (roving) eye movements, axial hypotonia, psychomotor retardation (usually severe), ataxia, and often hyporeflexia.[3] After infancy, retinitis pigmentosa, joint contractures, stroke-like episodes (in about 50% of patients), epilepsy in some individuals, and in females hypergonadotrophic hypogonadism commonly appear. Only rarely do these patients achieve walking without support, but there is no regression. The most pronounced and most easily detected carbohydrate deficiency has been found in serum transferrin.[4] Due to the specificity of this marker of the disease, investigation of serum asialotransferrin levels is the first step to a more specific biochemical study of this disorder.

From the neuroradiological point of view, CDG1a shows severe cerebellar atrophy and a small brainstem, these findings have also been known as features of olivopontocerebellar atrophy.[5]

In 1940, Norman[6] described an unusual form of familial cerebellar atrophy, occurring in early life, that showed primary granular cell layer atrophy of the cerebellum.[7] The main clinical features were: autosomal recessive inheritance, non-progressive ataxia, learning disability*, dysarthria with language delay, strabismus, and hypotonia. Given that the confirmation of the pathology had to be made

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*North American usage: mental retardation.

on the basis of the histological findings, only isolated cases of atrophy of the granular layer of the cerebellum or Norman's ataxia have been reported since this syndrome was described.

In 1994, we reported a series of 14 patients with Norman's ataxia on the basis of the clinical and neuroradiological features in all, and the histological findings in three autopsied patients. [8] Four years ago, one 10-year-old patient of the series presented with acute headache and obtundation caused by intracranial venous sinus obstruction due to a coagulation defect of factor 3. The clinical picture improved after treating with heparin and factor 3, and the patient was investigated for CDG1a. He showed a very high level of serum asialotransferrin (45%). PMM activity[3] measured in fibroblasts disclosed heterozygous molecular PMM2 deficit. The sister of this patient had been studied because of psychomotor delay but she died at two years of age due to respiratory problems. An autopsy was carried out that showed severe cerebellar atrophy, and the histological study revealed loss of granular cells and diverse abnormalities of Purkinje cells, especially focal swellings of 'asteroid bodies' or 'cactus-like' type. This suggested to us that Norman's ataxia and CDG1a, also known as carbohydrate-deficient glycoprotein syndrome type 1a (CDGS1a) or Jaeken disease, could be the same pathological entity.

This led us to investigate the patient in our series who had been diagnosed with possible Norman's ataxia. There were 24 patients but only 10 patients were studied as some lived too far from Madrid to travel to the hospital; also some felt that no cure would be found through the study and various other reasons). Seven of the 10 patients had highly raised serum concentrations of asialotransferrin. All seven patients showed heterozygous molecular PMM2 deficit (CDG1a). One of these seven was the patient whose sister had histological cerebellar changes corresponding to Norman's ataxia.

The findings observed in our series suggest the CDG1a is the biochemical basis of the histological changes of the cerebellum in Norman's ataxia.

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