Attention deficits following ADEM ameliorated by guanfacine

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ABSTRACT

The authors report here the case of a patient with severe deficits in arousal and sustained attention, associated with hemispatial neglect. These impairments were secondary to acute disseminated encephalomyelitis, with bilateral involvement of the medial nuclei and pulvinar of the thalamus. Treatment with the noradrenergic agonist guanfacine, previously used for attention deficits in attention deficit/hyperactivity disorder and stroke, was associated with a significant amelioration of both the spatial and sustained attention impairments in neglect. Guanfacine may prove to be a useful tool in the treatment of disorders of attention associated with neurological conditions.

Acute disseminated encephalomyelitis (ADEM) is a relatively rare neuroinflammatory disorder associated with multifocal lesions, frequently preceded by a viral prodrome. It is usually a monophasic illness, with many patients recovering well, although up to half followed up long-term have been reported to have persistent neurological deficits.1 MRI usually reveals asymmetrical subcortical white-matter involvement. However, the deep grey-matter nuclei, such as the thalamus and basal ganglia, may also be affected.2

There are few studies documenting the cognitive and neuropsychological sequelae of ADEM,3 4 with most focussing on motor disabilities. Here, we report a patient with thalamic lesions secondary to ADEM, causing persistent left-sided hemispatial neglect (failure to attend to stimuli in contralesional space) and difficulty sustaining attention. These deficits were subsequently ameliorated by administration of the noradrenergic agonist guanfacine, a drug that has been shown to have positive effects in children with attention deficit/hyperactivity disorder,5 as well as sustained and spatial attention deficits in some patients with neglect secondary to stroke.6

CASE REPORT

A 38-year-old male presented with a right-sided facial droop and hemiparesis following a 2-week prodrome of headache, fever, cough and right hemisensory symptoms. Soon after admission, he developed tonic–clonic seizures, necessitating treatment with phenytoin, intubation and ventilation. MRI revealed patchy signal changes in the thalamus, cerebellum, temporal and occipital lobes bilaterally, while MR angiogram revealed normal extra- and intracranial blood flow. Cerebrospinal fluid examination, vasculitic blood screen and transoesophageal echocardiogram were normal. Electroencephalography demonstrated features consistent with encephalopathy, and a diagnosis of ADEM was made. He subsequently received two courses of intravenous methylprednisolone, intravenous immunoglobulin, plasma exchange and antibiotics. He was also anticoagulated for a deep venous thrombosis and required surgical treatment for an associated compartment syndrome.

The patient remained in intensive care, due to persistent epileptiform activity, for 4 months, when seizures were stabilised on a regimen of levetiracetam 2 g, phenytoin 700 mg and prednisolone 30 mg. He was then transferred to a rehabilitation unit, at which time he had a tetraparesis, with predominant left-sided weakness.

Neuropsychological testing also revealed significant cognitive impairments, including left-sided neglect (with intact visual fields on confrontation), reduced arousal and difficulty sustaining attention. In addition, there were significant impairments in verbal memory (chance performance on the short and easy Recognition Memory Test for verbal material and low average performance on the Wechsler Adult Intelligence Scale—Revised (WAIS-R) Digit Span subtest) and naming (5/15 correct on Graded Naming Test). There was also evidence of dysfunction on tests of executive function (concrete performance on Proverb Interpretation and perseveration on Single Letter Reading and the Similarities subtest of the WAIS-R). On the basis of educational and occupational background, he was estimated to have been functioning in at least the superior range premorbidly and had therefore suffered severe intellectual deterioration.

Admission for reassessment occurred 2 years later, at which time anticonvulsant medication consisted of levetiracetam 750 mg and gabapentin 300 mg both twice daily (the total daily dose of levetiracetam was 1250 mg at 6 months’ follow-up, with a further reduction to 1000 mg 10 months later). Cranial nerve examination was normal, except for a mild left-sided facial weakness. Examination of the limbs revealed a severe hemiparesis with increased tone on the left and a pyramidal distribution of weakness, worse distally. The limb reflexes were all brisk with bilaterally extensor plantar responses. There was severe left hemispatial neglect and impairments in sustained attention and arousal, with the patient spending 20 h a day in bed due to drowsiness. A decision was taken to trial the alpha-2-noradrenergic agonist guanfacine, with the hypothesis that this might improve these cognitive impairments.

ASSESSMENT MEASURES

MRI was repeated to determine the extent of lesions (figure 1A). Two standard bedside neuropsychological
tests were used to assess neglect, while a computerised task was used to measure the deficit in sustained attention. The neglect tests used were line cancellation, in which subjects are instructed to cancel all the lines they can find (total 40) distributed across an A4 sheet of paper and bisection of 17 cm horizontal lines, where the mean deviation rightwards from centre was taken from three attempts. The computerised task which has been used previously\(^7\) was presented on a Dell Latitude D820 laptop computer, and entailed the subject depressing the central button on a response box (RB-530 Cedrus Corp.), whenever an infrequently occurring black circle (8 mm diameter) occurred. The circle remained on the screen for 1 s and was presented on a grey background with interstimulus intervals of 1–7 s. 100 stimuli were presented over a total period of 8 min. Responses quicker than 100 ms were classified as anticipations, and therefore as commission errors, as were responses occurring more than 1600 ms after target onset. Perceptual sensitivity, or \(d'\), which is derived from signal detection theory\(^8\) and takes into account commission as well as omission errors, was the behavioural outcome measure of this task and calculated according to the formula below:

\[
\phi^{-1}(H) - \phi^{-1}(F)
\]

where \(H\) is the hit rate, and \(F\) is the false alarm rate. The higher this value, the better the subject was at accurately detecting targets.

These tests were performed on two consecutive days prior to commencing guanfacine, as well as at several time points after its introduction. The dose of guanfacine was titrated up slowly over 3 days in the following increments: 0.5 mg, 1 mg and 2 mg as single daily doses. The first on-guanfacine testing session was performed the day 2 mg was reached.

An additional testing session off-guanfacine was performed 2 months later (due to initial difficulty obtaining the drug locally) at which point the patient had not received guanfacine for 2 weeks. Three on-guanfacine testing sessions were performed 6 months after the initial commencement of 2 mg of guanfacine daily, and a final session occurred a further 10 months later. Therefore, in total, the patient underwent three testing sessions off and five on guanfacine. Testing was always performed during the afternoon.

Guanfacine has previously been well tolerated in studies investigating its efficacy in children and adolescents with attention deficit/hyperactivity disorder; however, the most commonly experienced side effects include drowsiness, sedation and dizziness.\(^5\)\(^9\) The patient reported here did not experience any side effects.

### RESULTS

Figure 1A demonstrates the thalamic lesions on T2-weighted MRI, along with performance on attention tests on and off guanfacine. The thalamic lesions localise to the medial thalamic nuclei (including the mediodorsal nucleus) and pulvinar on the left and to the pulvinar on the right.\(^10\) Lesions of the right pulvinar have previously been linked to the pathogenesis of neglect,\(^11\) while the patient’s remaining small lesions (in the cerebellum, temporal and occipital lobes) all lie outside areas commonly associated with the syndrome, such as the inferior parietal lobe, temporoparietal junction and inferior frontal lobe.\(^12\)\(^15\)

All three measures used to assess attention deficits improved on guanfacine. Permutation testing was used to investigate whether these effects were statistically significant. This established procedure has specifically been used in single-case designs.
DISCUSSION

The case presented here demonstrated severe hemispatial neglect and impairments in sustained attention, associated with bilateral thalamic lesions caused by ADEM. Initiation of the noradrenergic agonist guanfacine led to an improvement of these deficits, especially those involving the medial nuclei — including the medial pulvinar — are most frequently associated with deficits in arousal, which can be particularly severe following bilateral damage, as can occur following stroke. Hemispatial neglect is also often reported, again following strokes involving the medial thalamus and pulvinar, most frequently in the right hemisphere. In contrast, these impairments have rarely been referred to in the literature as a sequela of ADEM.

Difficulty with arousal or maintaining alertness, so that attention can be sustained on current goals, is increasingly accepted as a component of the neglect syndrome, capable in fact of predicting the severity of the spatial bias. It has been proposed that arousal is dependent on noradrenergic input from the locus coeruleus to inferior parietal and frontal cortex, and indirectly to these regions via the thalamus. Damage to these regions can also be associated with neglect.

Further evidence of the intimate link between arousal and the spatial orientation of attention comes from rehabilitation studies. Alertness training can improve neglect, while single doses of guanfacine have previously been shown to enhance sustained attention, in addition to ameliorating the spatial deficit. Although continued guanfacine use has been demonstrated to be efficacious in the treatment of inattentiveness in children and adolescents with attention-deficit/hyperactivity disorder, this is the first demonstration of a persistent amelioration of at least some components of the spatial deficit of neglect with a noradrenergic agonist.

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