

TABLE 1. Comparison of CSF pterin and monamine transmitter metabolites before and after attack

CSF metabolite	Before attack	1 hr after attack	Normal values (nmol/L)
Total neopterin	6	7	7–65
Tetrahydrobiopterin	18	19	9–39
Dihydrobiopterin	2.6	3.2	0.4–13.9
Homovanillic acid	86	196	71–565
5-HIAA	44	97	58–220

CSF, cerebrospinal fluid; 5-HIAA, 5-hydroxyindoleacetic acid.

transmission contributes to the abnormal movements seen in these disorders. We report on a similar twofold increase in CSF HVA and 5-HIAA after an attack in a patient with PED, and propose that, at least at a biochemical level, these two conditions may share a common pathophysiological mechanism. Our patient also had a history of marked exacerbation of his movement disorder after commencing levodopa therapy.

The essentially normal pterin profile before and after the attack in our patient is of interest. Changes in the CSF biopterin concentration may reflect ongoing demands for dopamine synthesis or indeed synthesis activity.⁶ Failure to detect an increased concentration of CSF BH4 in this patient may relate to the intermittent nature of the attacks. Alternatively, changes in BH4 metabolism may not be reflected in CSF sampled 1 hour after an attack.

Although dramatic, these results represent a single observation and, therefore, must be interpreted with caution. The potential confounding effect of exercise and diet on CSF dopaminergic metabolites is unknown. In addition, the specimens were collected on separate days, although they were taken at approximately the same time. CSF analysis in further patients with hyperkinetic movement disorders may clarify the role of the altered monoaminergic transmission in the pathogenesis of these disorders.

Legend to the Videotape

Large-amplitude dystonic movements of the upper and lower limbs and trunk induced by walking.

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Forty-One-Year Follow-Up of Childhood-Onset Opsoclonus-Myoclonus-Ataxia: Cerebellar Atrophy, Multiphasic Relapses, and Response to IVIG

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Abstract: We report on an adult with opsoclonus-myoclonus-ataxia syndrome experiencing widely spaced neurological relapses, who was followed for 41 years. His responses to treatment are described. © 2002 Movement Disorder Society

Key words: ACTH; cerebellar ataxia; dancing eyes; IVIG; Kinsbourne syndrome; myoclonus

Opsoclonus-myoclonus-ataxia syndrome, though rare, affects children and adults. Despite age-related differences in the tumor types found in paraneoplastic cases, the clinical features are similar, and both adults and children may be steroid-responsive. Because the autoantibodies reported in adults are seldom found in children with opsoclonus-myoclonus-ataxia, the biological relation between the childhood-and adult-onset groups is unknown. Although opsoclonus-myoclonus-ataxia is a monophasic disorder in some children,¹ in others it is not, as indicated by relapses with illnesses. There has been little long-term follow-up into adulthood. We report on an adult with widely spaced neurological relapses, who was followed for 41 years, and describe his responses to treatment.

Case Report

The patient is a 42-year-old, African-born, Indian male who was diagnosed in England at 11 months of age with opsoclonus-myoclonus-ataxia 1 week after DPT immunization and apparent viral illness. He was a patient of Dr. Paul Sandifer, at one point seen by Lord Brain, and was the third case in Dr. Marcel Kinsbourne's original study.² Opsoclonus was a presenting sign. Myoclonus not only made his limbs unable to

A videotape accompanies this article.

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reach their targets, but it interfered with his ability to swallow and he lost his ability to sit. For at least 6 months he was bedridden, required a feeding tube, and he remained hospitalized for 1 year. There were no seizures. Both opsoclonus and myoclonus were completely suppressed by ACTH, beginning at 60 IU daily, and later by corticosteroids, which were tapered over 11 years. He began to speak at age 3 and learned to walk, but had slow speech and never achieved normal comprehension. Recovery of function was substantial but not complete. The remission lasted 10 years.

At age 22 years, the patient developed a flu-like illness with acute ataxia severe enough to confine him to a wheelchair within 3 weeks. His relapse was so unexpected that he was evaluated for other etiologies of ataxia, such as demyelinating disease. Neurological abnormalities included gait ataxia, limb dysmetria, but no opsoclonus, reflex abnormality, or weakness. Although he could stand with feet together, he wasn't steady and preferred them to be 6 to 8 inches apart. His speech was slightly dysphonic with a tendency to run together syllables of large words. He displayed irregular saccades with quickly attenuating nystagmus to horizontal gaze in either direction. Rapid alternating movements were slow. IQ testing showed borderline intelligence to mild mental retardation. Neuropsychological testing showed deficits in frontal function with poor understanding of concepts, low visual motor ability, poor impulse control, and disinhibition. A head computed tomography (CT) scan showed mild cerebellar atrophy, particularly of the vermis. He was treated with 30 IU ACTH daily, which was tapered over 5 years, and physical therapy. Although he improved greatly, he did not return to his previous level of function.

Three years later, he developed an acute duodenal ulcer and uveitis of the left eye, which were thought to be steroid-induced and were treated successfully. An abdominal CT scan with specific attention to the suprarenal or adrenal area was negative for tumors. He had occasional vascular headaches, allergies, and required corrective lens for astigmatism. A spectral mapping of the electroencephalogram (EEG) was normal. He took diazepam and desipramine to manage stress that seemed to decrease his energy level.

Between the ages of 22 and 31 there were at least three other illness-induced relapses. On one occasion he became too ataxic to walk. Again he responded to increases in ACTH. Head MRIs also showed cerebellar atrophy and slight cerebral sulcal prominence. An EEG was normal.

The patient came to the National Pediatric Myoclonus Center at 36 years of age (see Videotape). He exhibited a pancerebellar syndrome, the main feature of which was gait ataxia, with inability to perform tandem walking or to stand on one foot without holding on. He drank from a cup without spilling and used a spoon well with either hand. Truncal titubation and action myoclonus were minimal and opsoclonus was absent, but his saccades were irregular. Handwriting was labored and poor (Fig. 1). Finger and foot tapping were slow and sequential finger movements were awkward. He had finger agnosia and acalculia, but no left-right confusion, aphasia, or apraxia. Touch and position sense were intact. Deep tendon reflexes were brisk with crossed adductors, but plantar responses were flexor. Strength was slightly decreased. Speech, like mental processing, was slow but fluent, although he was affable and engaging. He was seronegative for anti-Hu, anti-Ri, and anti-Yo autoantibodies. ESR, T4, TSH, CMP, and CBC were all

normal with the exception of mildly increased cholesterol of 232 and triglycerides of 264. Lyme antibody testing was negative. Head MRI showed significant cerebellar atrophy, which was most severe in the vermis (Fig. 2).

We recommended using intravenous immunoglobulins (IVIG) rather than steroids. He received a monthly infusion of 2 g/kg for 6 months. The improvement in ataxia was immediate and dramatic, with only transient headache as a side effect. His gait became steadier and he felt more confident in performing activities of daily living. As a result, he has continued on IVIG for 5 years, receiving treatments 6 months of each year when he is in the US. His family felt he improved in cognitive as well as motor function since being on a regular IVIG program. The IVIG dose was reduced to 1.5 g/kg.

Within the last few years he contracted malaria during his travels. In addition to chloroquine, he received IVIG. In a few days, he was up and about, a much quicker recovery than expected, and without relapsing neurologically.

The youngest of 3 children, the patient married at the age of 35, speaks four languages, drives in Africa, and sometimes jogs or swims. A brother and sister are in good health. He was schooled in the United States from age 8 to 24, acquiring the English language at the age of 12. After completing high school, he took some business and computer classes. The patient uses a computer but cannot do mathematics. He enjoys painting as a hobby. By mid-afternoon he becomes very fatigued and must take a nap. He has difficulty persevering with most tasks, and despite vocational planning and counseling, has not been able to work or live independently of the family.

Discussion

Our patient is one of the first reported cases of childhood opsoclonus-myoclonus-ataxia. Not only did he have relapses, indicative of a multiphasic disorder, but he has remained responsive to ACTH or corticosteroids. At the time of his first major relapse, there was nothing in the literature to suggest that such late events were possible in childhood-onset opsoclonus-myoclonus-ataxia. He is similar to a woman described in a recent case report,³ who presented with opsoclonus-myoc-

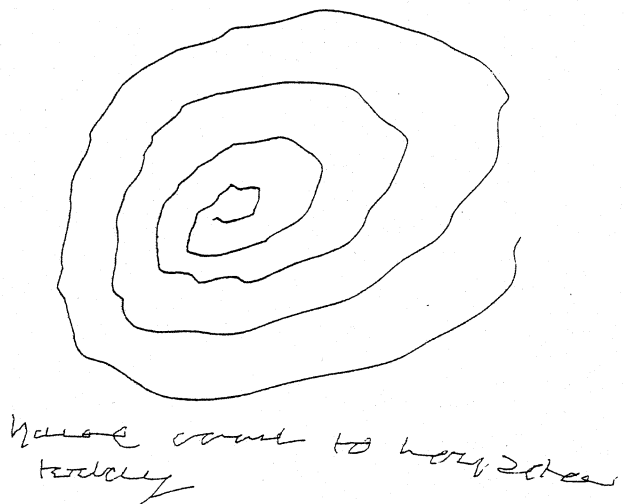


FIG. 1. Handwriting sample and Archimede's spiral at age 36 years. The patient was instructed to write "I have come to the hospital."

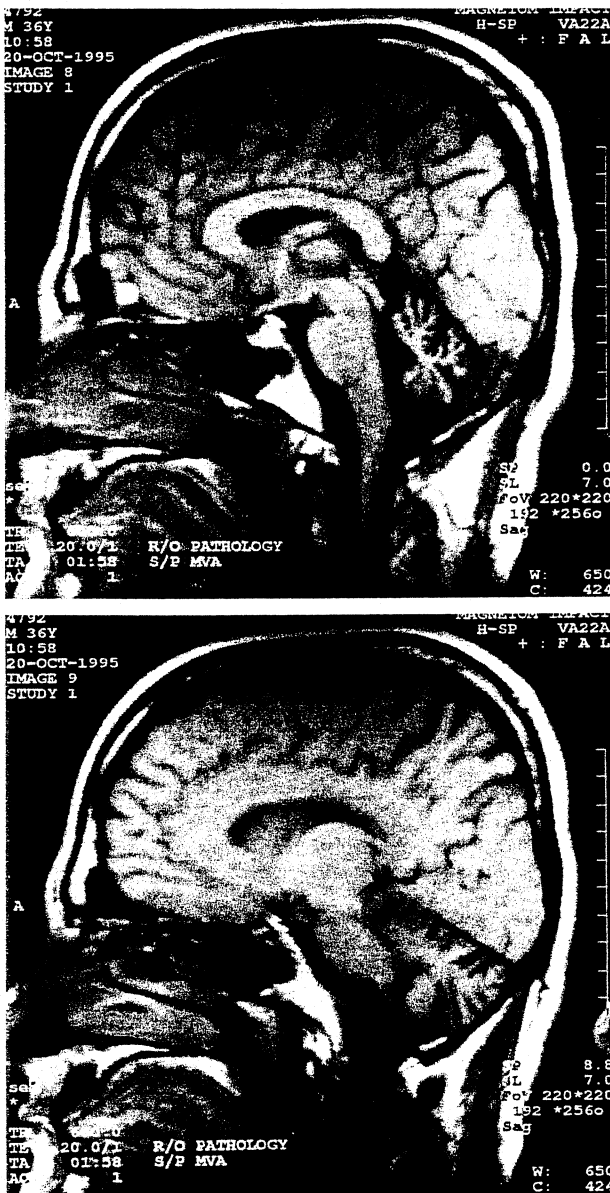


FIG. 2. Head magnetic resonance imaging scan. Sagittal, T1-weighted image in the plane of the cerebellar vermis (top) and cerebellar hemisphere (bottom).

lonus-ataxia at 20 months and relapsed with subacute cerebellar ataxia at 29 years of age. Just as she had responded well to corticosteroids as a child, remaining on betamethasone for 6 years, she improved on them as an adult. In 3 of 5 other patients with childhood opsoclonus-myoclonus-ataxia followed into adulthood, 4 of whom had reduced cognitive function and language capabilities, symptoms still worsened with episodes of minor illness.⁴

Our study substantiates the existence of a protracted, life-long, steroid-responsive syndrome and furthers the observation by demonstrating IVIG-responsiveness and cerebellar atrophy. Collectively, these reports indicate that prolonged follow-up is necessary to achieve a true picture of the incidence of relapse.

Our patient was doing so well one might have thought relapse was unlikely. Perhaps a predictor of relapse was the severity of his initial presentation, which is more severe than usual, but not rare. Some infants with profound hypotonia do require a feeding tube. A high incidence of relapses has been reported in cases in which neuroblastoma is found.⁵ The duration of treatment illustrates how long children with the disorder are kept on ACTH or steroids to avoid relapse.

The clinical significance of our observations depends on the veracity of the diagnosis. How certain can we be that the relapses during adulthood were a recrudescence of the initial disorder and not a nonspecific effect of illness or the appearance of some other disease? Our patient's worsening was more severe than expected from a stressor-induced mechanism and it did not improve until immunotherapy was instituted. His neurological manifestations did change over time, from opsoclonus and myoclonus to more predominant ataxia, behavioral, and cognitive impairment, but such a transition has been reported previously.⁶ As to other diseases, relapsing remitting multiple sclerosis can be considered, but the clinical features were dissimilar and the MRI was not diagnostic despite four decades of illness. This patient had no optic neuritis, internuclear ophthalmoplegia, or posterior column related findings. There were no demyelinating lesions. Vasculitis was ruled out by laboratory screening. Metabolic disorders do not respond to immunotherapy, tend not to be confined to a single system over multiple decades, typically do not cause opsoclonus-myoclonus-ataxia, and tested negative in this patient. We believe that other plausible disorders have been ruled out and the evidence fits best with relapses due to the underlying immunological disorder of opsoclonus-myoclonus-ataxia.

Cerebellar involvement is a key feature of childhood opsoclonus-myoclonus-ataxia and may even contribute to cognitive impairment.⁷ Cerebellar atrophy, however, is uncommon early in the course of the disorder. There have been two reports of cerebellar vermis lesions in children with opsoclonus-myoclonus.^{8,9} Biopsy or autopsy reports in these cases and another child without atrophy showed Purkinje and granular cell loss with gliosis.¹⁰ Two of the children had ganglioneuroblastoma and at least 1 had been treated with chemotherapy. Greater involvement of the vermis in opsoclonus-myoclonus-ataxia is in keeping with its principal cerebellar manifestations of gait impairment and truncal titubation.

If cerebellar atrophy is a late feature of the disorder, why is its appearance delayed, whereas in paraneoplastic cerebellar degeneration (PCD), a different disorder affecting adults, it is an early and requisite finding?¹¹ There are several possible explanations, none of which have been confirmed in the absence of an animal model and the paucity of post mortem studies. It may have to do with the antigen or antigens and the nature or magnitude of the autoimmune response they trigger. Although significant cytotoxic injury might be expected to produce early atrophy, other types of injury, such as apoptosis, might not. Alternatively, an immunologically-induced neurophysiological derangement in opsoclonus-myoclonus-ataxia resulting in cerebellar overactivity could lead to gradual trophic changes, much in the same transsynaptic way that olivary degeneration occurs in palatal tremor.¹² Increased cerebellar blood flow identified by PET is associated with several forms of tremor, but there is no direct evidence that cerebellar hyperactivity causes tremor.¹³ A more worrisome and likely explanation is that the initial cerebellar injury is sublethal but ongo-

ing and cumulative. If this is the case, early, more specific and effective immunotherapy will be necessary to prevent the atrophy.

IVIG is being embraced more and used at higher doses since first reported as a treatment for opsoclonus-myoclonus-ataxia.¹⁴ Case reports suggest that children benefit from 1 g/kg/day.^{15,16} Our patient was fortunate in responding to three different, separately administered therapeutic agents which may work through different mechanisms.¹

Because the patient presented several years before an association was made between opsoclonus-myoclonus-ataxia and neuroblastoma,¹⁷ it is unclear if he had neuroblastoma. Despite modern imaging technology and increased awareness of the need to screen for neuroblastoma, diagnostic difficulties continue to plague clinicians due to the tumor's tendency toward spontaneous regression and the flu-like symptoms that have so often suggested a viral etiology in children later shown to have a tumor. In as many as half of the reported cases, no tumor is found despite repeated nuclear medicine scans or body CT. All that can be said is that he did not harbor three of the autoantibodies found in a minority of patients with a paraneoplastic syndrome.

The capacity of patients to respond for years to ACTH without loss of efficacy indicates a lack of tolerance or receptor down-regulation. This is of interest to models of pro-opiomelanocortin receptors, at which ACTH may bind,¹⁸ and should be an important clue to the mechanism of ACTH's action in opsoclonus-myoclonus-ataxia.

Our patient adds to the profile of neuropsychological dysfunction in opsoclonus-myoclonus-ataxia. His cognitive abilities were not uniform, as he seemed to have islands of preserved function surrounded by deficits. Finger agnosia and acalculia, although short of a Gerstmann's syndrome, suggest dominant hemisphere dysfunction. The pattern of abnormalities we reported previously in opsoclonus-myoclonus-ataxia was compatible with subcortical dysfunction.¹⁹ A cognitive-affective syndrome has been described in adults with lesions involving the posterior lobe of the cerebellum and the vermis.²⁰ These individuals have impairment of executive functions, spatial cognition, personality changes, and language deficits. How much of the cognitive impairment in children with opsoclonus-myoclonus-ataxia can be attributed to cerebellar involvement remains a fundamental question.

Note added in proof

Since this manuscript was submitted for publication, Hayward and colleagues [J Pediatr 2001;139:552-559] reported that cerebellar atrophy occurred in children with opsoclonus-myoclonus-ataxia and neuroblastoma several years after onset. These cases support our assertion that cerebellar atrophy in opsoclonus-myoclonus-ataxia of pediatric onset is caused by the paraneoplastic disorder.

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Hereditary Chin Trembling: A New Family with Exclusion of the Chromosome 9q13-q21 Locus

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