A 20 year old woman had a four year history of MG. The disease manifested itself with horizontal diplopia, ptosis and fluctuating proximal weakness. (Osserman grade - II).⁴ Diagnosis of MG was supported by high levels of antiacetylcholine receptor antibodies of 22.8 pmol/ml (normal range 0-5 pmol/l), and decremental response on repetitive nerve stimulation with improvement after Edrophonium chloride (Tensilon). The patient had thymectomy in 1988 due to thymic hyperplasia and since then was treated with anticholinesterase medication with a partial response. Due to progressive weakness in the last months, she was admitted to hospital in October 1992 for IVIg treatment.

On admission her general examination was normal, neurological examination revealed mild ptosis, proximal muscle weakness without bulbar signs or respiratory difficulties. ESR, anti nuclear factor, rheumatoid factor, immunoglobulin levels, thyroid function, and chest x ray were normal.

The patient was treated with IVIg (Gamimune, Miles Inc, USA) 4.5%-5.5% solution in 9%-11% maltose without preservative in dosage of 0.4 gr/kg/day. On the third day of treatment her temperature rose to 37.8°C and she complained of severe headache with photophobia, nausea and she vomited once. She had nuchal rigidity, positive Brudzinsky sign, normal fundi and no focal neurological signs. Lumbar puncture revealed clear CSF, with a pressure of 200 mm H₂O. Cell count was 80 μ l, 50% lymphocytes and 50% neutrophils. CSF protein was 0.97 g/l and glucose 2.5 mM/l (blood glucose 3.9 mM/l). Gram stain, bacterial and viral cultures, cryptococcal antigen, and acid fast staining were negative. IVIg infusion was discontinued and the patient recovered after 72 hours without antibiotics or any specific treatment. Lumbar puncture was repeated after 10 days and showed 10 μ l lymphocytes, normal protein (0.19 g/l) and glucose (3.1 mM/l) levels.

As IVIg therapy was considered an important mode of therapy in this young patient, it was necessary to establish whether the meningitis was associated with IVIg or coincidental.

We therefore obtained informed consent and started a challenge with IVIg infusion increasing the dose from 0.1 gr/kg/day to 0.4 gr/kg/day. On the fifth day her temperature rose to 38.6°C and she developed severe headache with photophobia. Nuchal rigidity with positive Brudzinsky and Kernig's signs were again noted. IVIg treatment was discontinued and after 48 hours the fever, headache and signs of meningeal irritation disappeared. The patient refused a third CSF examination. Side effects of IVIg treatment are usually mild, consisting mainly of allergic reactions in IgA deficient patients, hepatitis, and transient vasomotor symptoms with chills, nausea, flushing, chest tightness and wheezing.⁵ Transient headache, vomiting, altered consciousness associated with fever had been described in several patients.⁶

Drug induced meningitis has been reported with trimethoprim-sulfamethoxazole, nonsteroidal anti-inflammatory agents, azathioprine, isoniazide, OKT3 and others.⁷ Most reports were in patients with underlying connective tissue diseases such as systemic lupus erythematosus, but not in MG patients.

The mechanism of drug induced meningitis is presumed to be an acute hypersensitivity reaction limited to the leptomeninges without systemic anaphylaxis. Our case adds to the previous four cases of aseptic meningitis associated with IVIg, it is the first described in an MG patient and proved with challenge. As the use of IVIg in the treatment of neurological disorders will increase in the future, the phenomenon of associated aseptic meningitis should be anticipated.

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ZEEV MEINER
TAMIR BEN-HUR
YARON RIVER
AVINOAM RECHES
Department of Neurology,
Hadassah University Hospital,
Jerusalem, Israel

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Paraneoplastic opsoclonus-myoclonus in Hodgkin's disease

Opsoclonus is rapid, irregular, chaotic and conjugate eye movements that occur in all directions. It may be part of a syndrome with myoclonus of the trunk and limbs, and may also be associated with cerebellar dysfunction.

A 22 year old female presented with a three month history of shortness of breath, left-sided pleuritic chest pain, weight loss, pruritus and night sweats. On examination there was a lymph node mass in the left supraclavicular region, hepatosplenomegaly and a left-sided pleural effusion. A biopsied lymph node showed lymphocyte depleted Hodgkin's disease (BNLI Grade II). CT scan of the chest and abdomen showed a large mediastinal mass, left-sided pleural effusion and marked hepatosplenomegaly, and she was staged IV B Hodgkin's disease. Treatment consisted of alternating courses of LOPP (chlorambucil, vincristine, procarbazine, prednisolone) and EVAP (etoposide, vinblastine, adriamycin, prednisolone). After 8 courses of chemotherapy she continued to have generalised itching, persistent mediastinal widening and elevated erythrocyte sedimentation rate. Bilateral posterior iliac marrow trephines were disease-free, and it was decided to treat her with high dose BEAM chemotherapy (BCNU, etoposide, cytarabine, melphalan) and autologous bone marrow transplant (ABMT), 18 months after presentation. During the subsequent pancytopenic phase she required support with antibiotics (piperacillin, gentamicin, ceftazidime, vancomycin), platelets and parenteral nutrition.

Seven weeks after BEAM chemotherapy she developed tremors, headaches and an unsteady gait. On examination she had severe opsoclonus, and myoclonic movements of the head and limbs. There were no cerebellar signs. Blood glucose, electrolytes, urea, creatinine, bilirubin, haemoglobin, white cell count and immunoglobulins were normal. There was no increase of CSF pressure, and normal CSF total protein, glucose, cell counts and immunoglobulins. CT and MRI scans of the head were normal. A CT scan of the chest showed persisting but decreased mediastinal lymphadenopathy. She received 1g methylprednisolone intravenously daily for 3 days and localised radiotherapy to the mediastinal mass.

Her neurological symptoms improved gradually over the next 3-4 weeks and she remains well and free from any neurological symptoms approximately 12 months after BEAM chemotherapy and ABMT.

The term opsoclonus was first used by Orzechowski¹ in 1927 to describe rapid irregular conjugate eye movements in several patients with non-epidemic encephalitis. Opsoclonus can be diagnosed at the bedside by the presence of spontaneous, large-amplitude conjugate saccades occurring in all directions of gaze without a saccadic interval. The combination of opsoclonus and myoclonic movements of the head and upper limbs without evidence of cerebellar dysfunction found in our patient are typical of previously reported cases of the OM syndrome.² These patients differ from those with paraneoplastic cerebellar degeneration by more rapid onset, predominance of truncal over appendicular ataxia, presence of myoclonus, a tendency for remission, and preservation of cerebellar Purkinje's cells.³

Opsoclonus occurs in association with a wide variety of aetiological factors,⁴ including viral and bacterial infections of the CNS, intracranial tumours (for example, glioblastoma), thalamic haemorrhage, hydrocephalus, multiple sclerosis, intoxication with lithium and amityptiline, and in non-ketotic hyperosmolar diabetic coma.⁵ Most published cases of OM syndrome have been described in children as a paraneoplastic manifestation of neuroblastoma.⁶ OM as a "remote effect" of cancer in adults is much less common and has been described as a series of single case reports over many years⁴ and the associated tumours have included carcinoma of the uterus, bladder, breast, lung and thymus. Our report is the first of OM in a patient with Hodgkin's disease.

The site of the lesions causing opsoclonus is unknown. It may occur as a result of an abnormality in the tonic inhibitory control of horizontal and vertical saccadic burst-neurons by "pause cells" in the pontine paramedian reticular formation (PPRF). The most likely site of the lesion is the pretectal region of the midbrain.⁷ In our case, CT and MRI scans did not reveal any abnormality in this or any other region.

The pathogenesis of opsoclonus, with or without an associated neoplasm is also unclear. There has been the occasional report linking viral infection of the CNS to OM.⁸ This is unlikely in our case as there was no clinical evidence of viral infection, and CSF/MRI examination was normal. Gentamicin administration during the pancytopenic phase was a possibility since streptomycin, a similar aminoglycoside, has

been implicated in the past, but symptoms appeared approximately four weeks after the last dose of gentamicin. It is possible that one or more of the previously administered cytotoxics may have been responsible but this has not been reported before, and the last course of treatment was eight weeks before the onset of her neurological symptoms. A further possibility is that our patient developed OM as a direct manifestation of Hodgkin's disease, but at the time of development of OM the extent of her disease had considerably reduced following high dose chemotherapy. Furthermore, before the onset of neurological symptoms she had had clinical and radiological evidence of regression of her disease. Normal CT and MRI scans of her brain excludes a diagnosis of cerebral Hodgkin's disease. A metabolic abnormality resulting from destruction of Hodgkin's disease tissue is also unlikely, although it has been previously postulated that production of neurotoxic amines and/or peptides might be responsible.⁹ This report, however, failed to show any correlation between the presence or severity of OM and the routinely available measurements of catecholamine secretion. The discovery of antineuronal antibodies in patients with other paraneoplastic syndromes has led to the suggestion that these diseases may have an autoimmune aetiology. Support for an autoimmune basis to paraneoplastic OM has come from reports of a specific antineuronal autoantibody (anti-Ri) in the serum of patients with opsoclonus and breast carcinoma.¹⁰ The presence of the Ri antigen in tumour tissue of these patients suggests that it is the body's immune response to a tumour antigen that elicits the antibody response. Although there was no specific autoimmune serological data to support such a response in our patient, it is possible that breakdown of lymphomatous tissue resulting from effective chemotherapy led to the production of antineuronal antibodies and the subsequent development of OM.

Treatment for opsoclonus from whatever cause remains uncertain. While some authors recommend ACTH or steroids,⁴ this is by no means of proven benefit. At the very least, it is imperative to treat the underlying condition.

C L KAY
G A B DAVIES-JONES
The Royal Hallamshire Hospital, Glossop Road,
Sheffield S10 2JF, UK
Department of Haematology
R SINGAL
D A WINFIELD

Correspondence to: Dr Davies-Jones

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Very late onset X-linked recessive bulbospinal neuronopathy: mild clinical features and a mild increase in the size of tandem CAG repeat in androgen receptor gene

X-linked recessive bulbospinal neuronopathy (X-BSNP) is an adult-onset hereditary motor neuronopathy characterised by bulbar symptoms, slowly progressive proximal dominant muscular atrophy, and endocrinological abnormalities.¹⁻⁴ Generally, the age at onset of X-BSNP ranges from the third to fifth decade,^{1,2,5} and activities of daily living of most patients with this disease significantly decline within fifteen years of onset.⁵ Recently, patients with X-BSNP were found to have an abnormally elongated tandem CAG repeat in the first exon of androgen receptor (AR) gene.⁶ The increased number of CAG repeats in AR gene is, however, considerably variable among patients. We report a very late onset and very mild case, and the abnormal elongation in his AR gene was also mild.

An 84 year old Japanese man with no family history of any related disease, noted mild difficulty in climbing stairs when he was in his mid seventies. In 1991, at the age of 83, painful muscular cramp in the calves and difficulty in walking was more apparent, although he could ride a bicycle and work in the field. He was referred to our hospital in January 1992. A neurological examination showed diffuse muscular weakness and remarkable amyotrophy in his four extremities as well as in the truncal and facial muscles. The tongue was mildly atrophied, but there was no dysphagia. Deep tendon reflexes were generally absent and there were no pathological reflexes. Fasciculation was remarkable in his face, tongue, neck, anterior chest, arm and leg muscles, and was enhanced by mild voluntary contractions. There was neither apparent sensory disturbance, cerebellar ataxia, nor gynaecomastia. The plasma creatine kinase level was 75 IU/l (normal <110). Glucose tolerance was normal. There was no hyperlipidaemia nor liver dysfunction. The endocrinological studies showed that the steady-state level of plasma testosterone was normal but plasma oestrone and oestradiol were mildly elevated. The suppression test conducted by oral administration of fluoxymesterone for six days showed a normal suppression in plasma testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Needle EMG studies showed generalised high amplitude NMU potentials with reduced NMU interference in the muscles examined. A nerve conduction study showed normal motor conduction velocities in the median and tibial nerves, but no sensory action potential in the sural nerve. A sural nerve biopsy revealed moderate reduction of large myelinated fibre density, and a muscle biopsy of the vastus lateralis showed scat-

tered grouped atrophy, clusters of picnotic nuclear clumps, and hypertrophic fibres which often contained internal nuclei.

The number of tandem CAG repeats in the first exon of his AR gene was determined on genomic DNA obtained from his peripheral blood leukocytes, using polymerase chain reaction and cycle sequencing techniques.^{7,8} His number of CAG repeats was 40, which was the shortest in our series of patients with X-BSNP (45 cases with a range from 40 to 55; the normal range being from 17 to 24 in our series).⁸

The extremely late onset of illness and well preserved function were quite unusual for X-BSNP, although diffuse muscular wasting in the limb muscles, contraction fasciculation and mild tongue atrophy of this patient suggested motor neuron disease. Moreover, absence of familial inheritance, and lack of gynaecomastia, glucose intolerance, hyperlipidaemia and liver dysfunction were incompatible with this disease. However, detection of AR gene mutations with an abnormally increased size of a polymorphic tandem CAG repeat⁶ clearly confirmed a diagnosis of X-BSNP. Detection of AR gene mutations is beneficial not only for the pre-onset diagnosis or carrier detection of X-BSNP^{6,9} but for the clinical diagnosis of atypical patients as seen in the present case.

This is the oldest case in terms of onset of muscular weakness, and may be the mildest in severity of symptoms so far reported. Additionally, 40 repeats of tandem CAG is the shortest in our series of 45 cases of X-BSNP. The clinical severity of this disease is known to be varied among the patients. We have shown that the number of CAG repeats in AR gene is correlated with age at onset of muscular weakness and clinical severity of the age-adjusted muscular weakness,⁸ suggesting that the size of an abnormally elongated CAG repeat in AR gene is one of the factors determining the clinical severity of X-BSNP, as was recently documented in fragile X syndrome¹⁰ and myotonic dystrophy.¹¹ These correlations among age at onset, clinical severity and increased size of the tandem CAG repeat were confirmed in our case.

In a majority of patients with X-BSNP, plasma testosterone, LH and FSH are poorly suppressed after oral administration of fluoxymesterone (Morishima et al, unpublished data), in spite of a significant suppression being present in normal controls. Although the precise mechanism of the fluoxymesterone suppression on these gonadal and gonadotropic hormones is not clear, it may reflect some aspect of androgen target organ sensitivity.¹² The normal suppression pattern of plasma testosterone, LH and FSH in this patient could also be related to milder elongation of tandem CAG repeat in AR gene.

MANABU DOYU
GEN SOBUE
TERUNORI MITSUMA
Division of Neurology,
the Fourth Department of Internal Medicine,
Aichi Medical University
MASAO UCHIDA
TAMAKI IWASE
Department of Neurology,
Tosei General Hospital
AKIRA TAKAHASHI
Department of Neurology,
Nagoya University School of Medicine,
Japan

Correspondence to: Dr Sobue, Division of Neurology, the Fourth Department of Internal Medicine, Aichi Medical University, Nagakutecho. AICHI. 480-11 Japan.