Neurologic disorders occur in approximately 8% of patients with celiac disease but their etiology remains uncertain. Encephalopathy, progressive multifocal leucomalacia, dementia, and epilepsy were described in association with gluten sensitivity; and myelopathy, peripheral neuropathy, and myopathy were also reported in isolated cases.

The association between celiac disease and myoclonus was reported on several occasions. In each of these individuals, the neurologic features began in middle adult life, often many years after the diagnosis and successful treatment of the gluten sensitivity. We describe a case of progressive myoclonus, ataxia, and epilepsy (the Ramsay Hunt syndrome) that began in childhood. Although the patient had no clinical, hematologic, or biochemical evidence of malabsorption, extensive investigations revealed both serologic and histologic evidence of celiac disease and the presence of antigliadin antibodies in the patient's CSF.

Case report. A 20-year-old woman was admitted for investigation of progressive disability and cognitive decline. She had a normal birth and development but at the age of 8 years her parents noted irregular jerking movements in both of her arms. During the subsequent 2 years, she had numerous absence episodes and one generalized tonic-clonic seizure while asleep. At the age of 11 years, her verbal IQ was 78 and her performance IQ was 60. Throughout her teenage years she became increasingly ataxic and from the age of 18 was confined to a wheelchair.

During the 18 months before our assessment, the patient’s speech deteriorated, her cognitive function declined further, and she was no longer able to transfer from chair to bed unaided. Throughout this period she had maintained a good appetite for food, her weight had progressively increased, and she had no gastrointestinal symptoms nor any dermatologic complaints. There was no family history of neurologic disease or consanguinity. She was treated with clonazepam (2 mg tid) and sodium valproate (200 mg tid).

She was obese (80 kg, height 1.61 m) but general examination was otherwise unremarkable. She had spontaneous, stimulus-sensitive and action myoclonus. Cranial nerve examination was unremarkable apart from hypometric saccadic eye movements. Optic fundi were normal. She had a symmetric increase in tone in all four limbs but no weakness. Her reflexes were pathologically brisk but both plantar responses were flexor. She had marked truncal, appendicular, and gait ataxia, and cerebellar dysarthria. Formal psychometric analysis confirmed global cognitive impairment (IQ 50).

Clinical investigations including a full blood count, ESR, coagulation screen, urea and electrolytes, glucose, albumin, bone biochemistry, liver function tests, creatine kinase, and thyroid function tests were normal. She had a polyclonal elevation of the three major immunoglobulin classes on serum electrophoresis (IgG 19.9 g/l, IgM 2.4 g/l, IgA 4.8 g/l).

Serum copper, ceruloplasmin, and 24-hour copper excretion were within the normal range, and vitamin E, B₁₂, and folate levels were normal. After an 18-hour fast her blood lactate level was within the normal range. She had a normal urinary excretion of organic and amino acids and her blood acylcarnitines were normal. An EEG revealed slow wave bursts associated with small sharp waves and an evoked potential study revealed conduction delay in the central somatosensory pathways. Cranial MRI was normal. Her CSF opening pressure, glucose, protein, and cell count were normal and no oligoclonal bands were present. A muscle biopsy revealed normal morphology and histocytochemistry, and mitochondrial DNA analysis excluded the A8344G MERRF, A3243G MELAS, or 8993 NARP mutations in her blood and muscle. Histologic examination of a skin biopsy specimen was unremarkable.

A routine serum autoantibody screen was negative and anti-Purkinje cell antibodies were not detected. However, she had strongly positive titers for antigliadin IgA, IgG, and endomysial IgA. A duodenal biopsy revealed features of gluten-sensitive enteropathy.
typical of celiac disease with short, widened villi, crypt hyperplasia, and an inflammatory infiltrate in the lamina propria associated with increased numbers of intraepithelial lymphocytes (figure). Further CSF analysis revealed a polyclonal increase in IgG (0.075 g/l, 28% of total CSF protein) with no unmatched oligoclonal bands. Antiparkinje and anti-dorsal root ganglion antibodies were not present, but antigliadin IgA and IgG were detected in the CSF. The duodenal biopsy was repeated after 11 months on a gluten-free diet confirmed the diagnosis of celiac disease with the resolution of villous atrophy.

Discussion. This case illustrates two major points: first, the Ramsay Hunt syndrome can occur in association with celiac disease in the absence of any preceding clinical, hematologic, or biochemical features of malabsorption. Second, this neurologic syndrome may begin in childhood.

It is surprising our patient had normal cranial MRI. Although areas of high signal intensity on T2-weighted MRI in association with cerebellar atrophy were described in less severely affected patients with celiac disease,8,9 even in severe cases cranial imaging may be normal,7 as may the gross appearance of the brain at post mortem.9

The pathogenesis of the neurologic associations of celiac disease remains uncertain. Conventional biochemical indices of malabsorption may be within normal limits, and malabsorption of an unidentified factor may be responsible for the syndrome. However, in the majority of the reported cases myoclonus and ataxia developed in the presence of histologically normal small intestinal mucosa.1

Celiac disease in an immunologic disorder that is triggered by the ingestion of gliadin. An isolated vasculitis of the CNS was described in one patient with celiac disease; this responded to prednisolone and cyclophosphamide.10 In the absence of evidence to support a generalized breakdown of the blood-brain barrier, the presence of antigliadin antibodies in this patient's CSF would support an autoimmune etiology and the local production of antigliadin IgA and IgG within the CNS. Although these findings may have both diagnostic and pathophysiologic significance, the prevalence of CSF antigliadin antibodies in asymptomatic individuals with serum antigliadin antibodies is not known, and it is possible that they are an epiphenomenon.

Myoclonus and ataxia may begin up to 27 years after the initial diagnosis and successful treatment of the celiac disease. For this reason, we do not expect a major improvement in our patient's neurologic status on a gluten-free diet, but have modified her intake to reduce any subsequent risk of her developing intestinal neoplasia. Although immunosuppression with prednisolone, cyclophosphamid, or plasmapheresis have been tried in a number of patients, the results were not encouraging.11 We have not noted any objective change in her clinical signs after 10 months of this treatment, but her parents report improved concentration and a reduced nocturnal seizure frequency.

This case illustrates the diverse presentation of celiac disease and confirms that celiac disease should be considered in the differential diagnosis of myoclonus and ataxia, whatever the age of the patient and in the absence of any gastrointestinal signs.12 Antigliadin antibodies can be found in the serum of up to 12% of normal controls and 5% of patients with other specific neurologic syndromes.10 However, to our knowledge CSF antigliadin antibodies have not been documented before. Although their significance is uncertain at present, CSF antigliadin antibodies may have pathogenic significance and prove to be useful in identifying celiac disease in patients with unexplained ataxia and myoclonic epilepsy.

References
Machado-Joseph disease (MJD) is an autosomal dominant spinocerebellar degeneration originally described in Portuguese descendants from the Azores Islands.\(^1\)\(^2\) The disease locus was mapped to chromosome 14q32.1.\(^3\) The MJD gene has been recently expressed with substantial clinical variability and has been classified into four subphenotypes: type 1, an early-onset disease with cerebellar ataxia and pyramidal and extrapyramidal features; type 2, a middle-age-onset disease with cerebellar ataxia and pyramidal and extrapyramidal features; type 3, a late-onset disease with cerebellar signs and amyotrophy.\(^4\)\(^5\) In addition, a type 4, with parkinsonism and peripheral neuropathy, has also been described.\(^6\)

Neuropathologic lesions are widespread in MJD.\(^1\)\(^2\) There is extensive neuronal cell loss and gliosis in Clarke's columns, dentate nucleus, pontine nuclei, and vestibular nuclei. There is moderate to severe involvement of substantia nigra, anterior horn cells, and motor cranial nerve nuclei. Variable degrees of involvement of the striatum, subthalamic nucleus, and globus pallidus have also been reported.

Positron emission tomography (PET) using the tracer \(^{18}\)F-6-fluorodopa (6-FD) and \(^{11}\)C-raclopride (RAC) PET studies in six patients with Machado-Joseph disease (MJD) (age, 17 to 61 years; duration of illness, 3 to 10 years), normal controls (n = 10 in 6-FD-PET; n = 8 in RAC-PET), and patients with idiopathic parkinsonism (n = 15 in 6-FD-PET). The youngest patient with MJD had prominent dystonia and pyramidal features (type 1 MJD), whereas the remainder were prominently ataxic (types 2 and 3 MJD). Striatal RAC binding was normal in patients with MJD. Striatal 6-FD influx constants (Ki) were low in the range of idiopathic parkinsonism in two patients with MJD (youngest and oldest patients), whereas striatal Ki were normal in the remaining patients with MJD. The impairment of the nigrostriatal dopaminergic pathway did not correlate with the phenotype, CAG repeat length, disease duration, or age of onset of patients with MJD. Our results suggest that striatal D2 receptors are normal and the nigral damage is diverse in MJD.

**Fluorodopa and raclopride PET analysis of patients with Machado-Joseph disease**

**Article abstract**—We performed \(^{18}\)F-6-fluorodopa (6-FD) and \(^{11}\)C-raclopride (RAC) PET studies in six patients with Machado-Joseph disease (MJD) (age, 17 to 61 years; duration of illness, 3 to 10 years), normal controls (n = 10 in 6-FD-PET; n = 8 in RAC-PET), and patients with idiopathic parkinsonism (n = 15 in 6-FD-PET). The youngest patient with MJD had prominent dystonia and pyramidal features (type 1 MJD), whereas the remainder were predominantly ataxic (types 2 and 3 MJD). Striatal RAC binding was normal in patients with MJD. Striatal 6-FD influx constants (Ki) were low in the range of idiopathic parkinsonism in two patients with MJD (youngest and oldest patients), whereas striatal Ki were normal in the remaining patients with MJD. The impairment of the nigrostriatal dopaminergic pathway did not correlate with the phenotype, CAG repeat length, disease duration, or age of onset of patients with MJD. Our results suggest that striatal D2 receptors are normal and the nigral damage is diverse in MJD.