Inclusion Body Myopathy-Like Changes in a Family with Cerebellar Atrophy, Mental Retardation and Abnormal Pupils

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Dear Sir,

The presence of rimmed vacuoles and intranuclear tubulofilamentous inclusions in muscle fibers is characteristic of disorders such as inclusion body myopathies (IBM) [1–3], oculopharyngeal muscular dystrophy [4] and distal myopathies [5]. Autosomal recessive and dominant forms of the above syndromes, in which the central nervous system (CNS) is not usually involved, have been reported [1–3, 5].

Here we describe an apparently autosomal dominant syndrome of mental retardation, cerebellar atrophy and abnormal pupils, associated with muscle biopsy evidence of rimmed vacuoles and tubulofilamentous inclusions.

Case Report

Case 1. This 33-year-old woman was the first child of unrelated parents, with a 28-year-old brother in good health. Pregnancy and delivery were normal. The mother reports that the girl always had clumsy gait. At age 5 years, behavioral problems occurred and the child tended to avoid her peers and lost interest in playing. Learning disabilities became evident at school and the girl was assigned a special teacher.

At age 20 years, dysarthria with nasal voice and occasional dysphagia began; unsteady gait with frequent falls became evident. A brain CT scan showed cerebellar atrophy and cerebral cortical atrophy. Clinical manifestations progressed and by 25 years of age, speech could hardly be understood, dysphagia had worsened, cognitive function had deteriorated and the patient was no longer self-sufficient.

On hospitalization in our department at age 28 years, neurological examination showed severe mental retardation (IQ 48), ataxic gait, diffuse hypotonia and mild muscle hypotrophy, unintelligible speech and hypernasal voice, dysphagia, slight upward gaze palsy, strabismus, anisocoria with unreactive pupils, slight dysmetria, and hypoactive deep tendon reflexes. Routine blood chemistry, including CK, LDH, pyruvic and lactic acid, carnitine, vitamin E, and thyroid hormones, was normal. Electrocardiography showed partial right branch block. Echocardiography and chest x-ray were normal. Tilting test showed significantly reduced heart rate variability and very high vagal tonus. Brain MRI confirmed severe cerebellar atrophy (fig. 1 A) and small areas of signal hyperintensity in the olivary nuclei. EMG showed myopathic alterations. Peripheral nerve conduction velocities were in the normal range.

Two years later, the patient was readmitted to our department for recurrent episodes of severe constipation lasting 2–3 weeks. Neurological examination was substantially unchanged apart from absent deep tendon reflexes. Abdominal x-ray and intestinal transit studies showed marked slowing (96 h to reach sigma and 148 h to reach rectum). The patient was successfully treated with intravenous prostigmine and repeated enemas (evacuation took 1 week to occur). Since age 32 years, the patient has had progressively deteriorating symptomatic neuromuscular involvement associated with severe fatigue and dyspnea even after mild efforts. Neurological follow-up at age 33 years showed diffuse muscle weakness and marked proximal limb atrophy, more accentuated in the legs. Muscle CT scan showed proximal muscle atrophy of pelvic and shoulder girdles, triceps and biceps brachii, and quadriiceps muscles bilaterally. Paravertebral and calf muscles were substantially normal. No adipose substitution was evident. Respiratory functions showed severe obstructive deficit. Chest x-ray showed middle lobe atrophy. The patient was treated with antibiotics. She died a few months later of acute respiratory failure. The family did not authorize autopsy.

Case 2. This 62-year-old man was the father of case 1. He was the only child of unrelated parents. His father, who died of myocardial infarction at 70 years of age, was reported to have cognitive impairment. No further information about other family members was available. The patient was admitted to our department for slowly progressive cognitive impairment and psychic changes including obsessive-compulsive and aggressive behavior. He was reported to be of slightly subnormal intelligence. At age 30 years, he stopped working due to cognitive deterioration.
Neurological examination showed severe cognitive impairment (IQ 62), clumsy gait, bradykinesia, mild dysarthria with nasal voice, occasional dysphagia, anisocoria with unreactive pupils, generalized hypotonia and areflexia. Mild shoulder atrophy was evident. Routine blood chemistry, including muscle enzyme activities, lactate and pyruvic acid, carnitine, thyroid function, circulating autoantibodies, and inflammatory markers, was in the normal range. Electrocardiogram showed partial right branch block. Slight mitral and aortic valve insufficiency was evident at echocardiography. X-ray skull was normal. Tilting test showed very reduced heart rate variability and vagal hypertonus at rest. Respiratory function is reported to be normal.

Electromyogram showed myopathic changes in the proximal arm muscles. CVs were normal. Brain MRI showed marked cerebrocortical and cerebellar atrophy. MRI of the cervical tract did not reveal any signal abnormalities. Muscle CT scan showed bilateral atrophy of biceps and triceps muscles without adipose substitution. Muscles in other districts were normal. Molecular analysis for SCAs 1, 2, 3, 6 and 17 resulted as being normal.

Muscle Biopsy

In both patients, muscle biopsy from quadriceps was performed. Frozen sections were stained by standard methods including Congo red stain. Immunocytochemical analysis was performed using an antibody against β-amyloid (rabbit anti-amyloid-β, 20–40, Chemicon).

**Case 1.** Findings included slight variation in fiber size, about 6% hypotrophic basophilic fibers containing rimmed vacuoles (fig. 1B).

**Case 2.** Findings included moderate variation in fiber size, about 8% hypotrophic and often basophilic fibers containing rimmed vacuoles. Occasional inflammatory cells, surrounding and sometimes invading necrotic muscle fibers, were observed.

In both cases, ultrastructural examination showed 3–4% nuclei with intranuclear aggregation of filaments (fig. 1C). The rare vacuoles observed contained myeloid bodies, filamentous material, cellular debris and degraded organelles. Immunocytochemistry and Congo red stain failed to demonstrate β-amyloid in rimmed vacuoles.

**Discussion**

We describe a familial syndrome characterized by cerebrocortical and cerebellar atrophy, progressive cognitive impairment, autonomic dysfunction and myopathy with rimmed vacuoles and intranuclear filamentous inclusions.

In the present family, muscle biopsy findings define mild myopathy, more accentuated in case 2, with a low percentage of hypotrophic fibers containing rimmed vacuoles and some nuclei with filamentous inclusions. The low percentage of affected fibers distinguishes this type from other defined myopathies characterized by rimmed vacuoles and intranuclear filamentous inclusions [1–5]. Moreover, β-amyloid was not found in vacuoles. Clear clinical signs of muscle involvement were only observed in case 1, whose clinical course was rapidly progressive, leading to disability and death from respiratory failure. However, both patients had CT evidence of proximal limb muscle hypotrophy and electromyographic signs of mild myopathy. For many years, muscle pathology was overshadowed by CNS symptoms in both patients; in the father, CNS symptoms are still the only clinically significant manifestations.

Besides classical distal myopathy, a few dominant myopathies with rimmed vacuoles have been genotyped. A dominant form of IBM with limb girdle phenotype, bone Paget disease and frontotemporal dementia as additional symptoms is caused by a mutant valosin-containing protein [6]. This syndrome did not have cerebellar atrophy. A chromosome 14 locus seems involved in a dominant distal myopathy with infantile onset [7]. Hereditary IBM, ophthalmoplegia and congenital joint contractures in a large Swedish family were mapped to chromosome region 17p13.1 [8, 9]. In all cases, there was histological evidence of rimmed vacuoles and tubulofilamentous inclusions. Our patients did not resemble any of these families in phenotype.

The association of brain abnormalities, cognitive impairment and autonomic dysfunction has never been reported in rimmed vacuole-related myopathies. Abnormal pupils have been described in a familial tubular aggregate myopathy [10].

Many disorders with mental deterioration and cerebellar atrophy have been described, ranging from the relatively common spinocerebellar atrophies (SCA) to...
single reports of rare syndromes. However, to our knowledge, none of them were associated with muscle biopsy changes like those reported in our patients. A SCA syndrome segregating independently from myopathy should be also considered, but the most common forms were ruled out by molecular analysis.

Our data suggests that the present syndrome may be an IBM-like disorder with unusually severe CNS involvement and intrafamilial variability of muscle phenotype. An alternative explanation is that all three features belong to a hitherto undescribed syndrome.

References