Progressive Central and Peripheral Demyelinating Disease of Adult Onset in a Norwegian Family

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Objective: To describe the clinical features of a Norwegian family with a combined central and peripheral demyelinating disease.

Design: Multiple case report.

Subjects and Materials: Three generations of a Norwegian family. Medical records were available for all 9 members of the second generation and 5 affected members in the third generation.

Results: At least 5 members had clinical features, neuroimaging findings, and electrophysiologic signs indicating a chronic progressive disorder affecting both the central and peripheral nervous systems. The clinical symptoms developed between the ages of 30 and 70 years in affected family members, who gradually developed sensory loss, muscle deterioration, and distal weakness in all extremities, unsteady gait, and dysarthria. Five of 9 persons in the second generation had strokes and experienced mental deterioration. The initial stroke episodes were recognized between the ages of 54 and 68 years, and death occurred between the ages of 62 and 75 years. In 7 subjects, cerebrospinal fluid protein levels were increased, and in 3 agar gel electrophoresis indicated blood-brain barrier dysfunction. Seven family members had neuroimaging signs of a widespread white matter disorder. In 4 subjects, neurophysiological investigations indicated a polyneuropathy, and in 3 subjects, results from a sural nerve biopsy showed a demyelinating neuropathy. There was no evidence of coinheritance with genetic markers of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (19p), PMP22 (17q), APP (21q), CMTX1 (Xq), or PLP (Xq).

Conclusions: Progressive central and peripheral demyelinating disease seems to be a distinct type of hereditary adult-onset demyelinating disorder affecting both the peripheral and central nervous systems. Its exact nature remains unknown.

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REPORT OF CASES

SUBJECT II-14

Since adolescence, this individual experienced several episodes of syncope, and she had a euthyroid nodular nonoperated goiter.

At age 61 years, the subject had a transient episode of mental confusion, headache, and vomiting for approximately 24 hours. Results from a physical examination revealed loss of balance, dysarthria, and a slight loss of control in the upper left limb. One year after this episode, the patient had another episode with more severe dysarthria, transient palsy on the left side of her face, confusion, and loss of balance.

From age 63 years, the patient had permanent urinary incontinence, dysarthria, slow speech, and prolonged latency in responding to questions and commands. Her gait was unsteady, and the movements of her limbs were retarded. The patient had brisk knee jerks, but nearly absent ankle jerks and bilateral Babinski signs. She had moderate dementia (Mini-Mental State Examination score, 23/30) and was unable to take care of herself.
MATERIALS

The family pedigree is shown in Figure 1. Medical records were available for all 9 members in the second generation and 5 members in the third generation. No consanguinity was on record.

SUBJECT III-3

At age 15 years, this individual developed acute nephritis and chronic proteinuria. From age 30 years, he experienced sensory loss and gradual loss of control in both arms. At age 38 years, he developed a slight atrophy of the small hand muscles and a mild spasticity in the lower extremities. All sensory modalities were diminished in both arms, and deep sensation was impaired in the lower extremities. All tendon reflexes were nearly absent in both arms. In the lower extremities, the subject had hyperreflexia with ankle-jerk clonus. Syringomyelia was suspected, but findings from cervical magnetic resonance imaging at age 54 years did not confirm this diagnosis.

At age 54 years, the subject was unable to work. Results from a neurologic examination showed intention tremor, atrophy of the small hand muscles, and distal atrophy in both legs. He had impaired coordination in both arms, reduced motor function in all extremities, an unsteady gait, hyperreflexia in the lower extremities, and extensor plantar responses.

At age 58 years, the subject had slow speech, dysarthria, severe loss of balance, and slightly impaired short-term memory; however, his Mini-Mental State Examination score was 27.

SUBJECT III-8

At age 31 years, this individual gradually developed distal weakness in both legs 2 months after giving birth. Previously, she had had several spontaneous abortions in the first trimester. Findings from a physical examination revealed that she had slight horizontal nystagmus on gazing to both sides, bilateral foot-drop, and unsteady gait. All sensory modalities were normal and all tendon reflexes brisk, but plantar responses were nonreactive.

At age 32 years, the subject was diagnosed as having chronic inflammatory demyelinating polyneuropathy (CIDP). She had no response to parenteral corticosteroid therapy, and at age 40 years was unsuccessfully treated with corticosteroids for approximately 1 year. Findings from a physical examination at that time showed weakness and atrophy in her small hand muscles and the distal muscles in both legs. She had distal sensory loss of all modalities in all extremities, hyperreflexia in the upper extremities, and knee jerks, but nearly absent Achilles reflexes. The subject had severe loss of balance and was unable to work. Results from a neurologic examination at age 56 years showed dysarthria and cognitive slowness; however, her Mini-Mental State Examination score was 27.

FIGURE 1. Pedigree of the family with progressive central and peripheral demyelinating disease. Markers for the CADDASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) (notch 3) locus on chromosome 19 are given. Numbers indicate observed DNA fragment size (in base pairs) of each polymorphic marker. Haplotypes are ordered in subject II-14 (see “Haplotype Analysis” subsection of the “Results” section), and recognizable haplotypes are indicated by a letter above the haplotype. Squares indicate male; circles, female.

Records of Deceased Family Members

Subjects II-9 and III-1 were examined in a neurologic hospital service. With onset of combined central and peripheral demyelinating disease in their 30s and 50s, respectively, they both gradually developed atrophy and weakness of their extremity muscles, distal sensory loss in both arms and legs, unsteady gait, and loss of control in both arms. Their speech was slow and dysarthric, and eventually they had retarded movements in their limbs and urinary incontinence. After ages 60 and 54 years, respectively, they also had several episodes of cerebral ischemia. They died at ages 62 and 70 years, respectively.

Five of 9 individuals in the second generation had strokes and developed cognitive impairment. The initial episodes of cerebral ischemia were recognized between the ages of 54 and 68 years, and the median age at death was 70 years (range, 62-75 years).

In the second generation, 4 members (subjects II-5, II-10, II-11, and II-12) died of myocardial infarction at ages 47 to 62 years. Prior to death, all of them had angina, 2 had type 2 diabetes mellitus, and 1 had elevated total cholesterol levels. Five sisters in the second generation had a nodular goiter.

In the first generation, subject I-1 was in good health until his death at the age of 85 years. His wife (subject I-2) had diabetes and died at 59 years, possibly of a myocardial infarction. Further information is not available.

Subjects III-13 and III-16 both developed slight dysarthria and unsteady gait after 40 years of age. Findings from a neuropsychological examination of subject III-13 at age 45 years revealed cognitive slowness, including psychomotor slowing and deficits in cognitive flexibility and organizing ability.
RESULTS

CEREBROSPINAL FLUID

All 7 members examined in a neurologic service underwent lumbar puncture and testing of cerebrospinal fluid (CSF) (Table). They had increased levels of CSF protein, and agar gel electrophoresis showed increased levels of serum proteins (transudative patterns) in 5 of 6 subjects examined. One individual (subject III-3) had oligoclonal bands, and 2 had increased gamma traces. All 7 individuals had a normal cell count except for subject III-16 (white blood cell count, 0.011 \( \times 10^9 \text{L} \)).

In 2 subjects, a cytological analysis of CSF was performed. Subject III-8 had an elevated fraction of 60% monocytes and 22% macrophages, whereas subject III-3 had 14% monocytes and 85% lymphocytes.

NEUROIMAGING

Five family members underwent magnetic resonance imaging of the brain (subjects II-14, III-3, III-8, III-13, and III-16). All had high-density areas in periventricular white matter, and 2 also had high-density areas in the cerebellum (Figure 2).

Subjects II-9 and III-1 were examined with cerebral computed tomography, which showed bilateral diffuse periventricular hypodensity and low-density areas in the cerebellum.

NERVE CONDUCTION STUDIES

In 3 subjects (III-1, III-3, and III-8), peripheral nerve conduction velocities indicated a predominantly motor polyneuropathy, with reduced motor conduction velocities in the lower extremities. For subject II-9, nerve conduction velocity was in the low to normal range. All 3 subjects tested had notably prolonged distal latencies (Table).

HISTOPATHOLOGIC STUDIES ON SURAL NERVE BIOPSY SPECIMENS

Biopsy of the sural nerve was performed in 3 subjects (II-14, III-1, and III-8) and revealed in all cases features compatible with a demyelinating or dysmyelinating neuropathy. Results of the biopsies revealed characteristics of remyelination in 39% of all teased fibers in subject III-8, 9% in subject III-1, and 12% in subject II-14. In all biopsy specimens, 3% to 8% of the teased fibers also showed excessive variability of myelin thickness with paranodal globules. All had onion-bulb formations and Pi granules (of Reich) in the Schwann cells. Findings from electron microscopy also showed hypermyelinated fibers (Figure 3), which were most pronounced in subject III-8. There was no axonal degeneration, metachromatic material, or cytoplasmic accumulation of polyglucosan bodies. Arterioles did not show granular deposits in the vessel walls.
Figure 3. Electron micrograph from sural nerve showing myelinated fibers with abnormalities. The most characteristic formation is the hypermyelinated fiber in the lower right corner, formed by folding of spiraled redundant myelin loops. The rest of the fibers reveal thickening of the myelin sheath with intramyelinic vacuoles and myelin splitting.

HAPLOTYPE ANALYSIS

Blood samples for genetic analysis were obtained from 6 living individuals with combined central and peripheral demyelinating disease (subjects II-7, III-14, III-3, III-8, III-13, and III-16). Samples from subject II-13, the healthy spouse of subject II-14, and their adult children were used to construct unequivocal haplotypes of subject II-14. If the disorder affecting this family is caused by alterations in the gene loci we examined, which are then inherited as autosomal dominant traits, affected family members should share haplotypes. Even if crossover occurs within the examined region, at least the part of the haplotypes containing the gene in question should be the same. The hypothesis of sharing a mutated gene from a common ancestor would be refuted if at least 2 affected individuals did not share with the other affected members haplotypes containing the candidate gene locus.

The alleles of 8 polymorphic markers spanning both sides of the cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (notch 3) locus on chromosome 19q were determined using fluorescent fragment-size analyses performed with a capillary electrophoresis instrument (ABI310, Applied Biosystems, Foster City, Calif). The markers tested are shown in Figure 1. Based on evidence from the shared haplotype, a mutation at the CADASIL locus is an unlikely cause of combined central and peripheral demyelinating disease.

Similarly, no indication of consistent haplotype sharing was found for the peripheral myelin protein 22 locus on chromosome 17 (markers D17S122, D17S955, D17S1336, D17S1337, and D17S1338), the amyloid precursor protein locus on chromosome 21 (intragenic markers APP.PCR1 and 222/223, D21S1270, D21S263, and D21S1910), the X-linked Charcot-Marie-Tooth (CMTX1 and CX23) locus (markers DXS991, DXS1273, DXS983, and DXS8092), or the myelin proteolipid protein locus on the X chromosome (markers DXS178, DXS101, DXS1191, and DXS1120). (Data not shown, available from the authors on request.)

OTHER INVESTIGATIONS

In subjects III-3 and III-8, findings from enzyme studies of blood leukocytes, arylsulfatase A, α-β-galactosidase, and galactocerebrosidase ruled out metachromatic leukodystrophy, Fabry disease, and Krabbe disease. The determination of plasma long-chain fatty acids ruled out adrenoleukodystrophy.

Biopsy of the quadriceps muscle was performed in subjects II-14, III-3, and III-8. Frozen sections were processed for staining with hematoxylin-eosin, modified Gomori trichrome, nicotinamide adenine dinucleotide–dehydrogenase (preincubation at pH 4.3, 4.5, and 9.4), acid phosphatase, periodic acid–Schiff, oil red O, nonspecific esterase, succinate dehydrogenase, and cytochrome c oxidase. In 2 subjects (II-14 and III-3), atrophy of both fiber types was seen in single fibers as well as in small groups. There was also a tendency toward grouping of normally sized fibers. The biopsy specimen from subject III-8 did not reveal essential abnormalities. Findings from electron microscopy demonstrated no ragged red fibers, abnormal cytochrome c oxidase staining, or mitochondrial abnormalities compatible with mitochondrial myopathy. However, subject II-14 had a slightly augmented intracellular lipid accumulation of unknown origin.

Needle electromyography was performed in 2 subjects (III-3 and III-8). Fibrillation, positive denervation potentials, and a reduced interference pattern were found in distal muscles of the lower extremities and also to some extent in distal muscles of the upper extremities, indicating a peripheral neurogenic lesion. Somatosensory evoked potentials showed increased central conduction velocities in subjects III-3 and III-8. Electroencephalograms were recorded in 4 subjects; findings were normal for subject III-13, while in subjects II-9, III-1, and III-8, results revealed generalized slowing, most prominent on the left temporal side of the brain.

Total blood cholesterol levels were elevated in subjects II-14 (8.5 mmol/L [328.7 mg/dL]), III-8 (10.8 mmol/L [417.6 mg/dL]), and III-13 (7.1 mmol/L [274.6]). Subjects II-9 and III-1 had hypertension, and subject III-16 had hypothyroidism.

COMMENT

Many members of the Norwegian family in our study had similar unusual neurologic clinical features and laboratory findings. A hereditary disorder may thus be suspected. The disorder in this family is characterized by the following characteristics: (1) gradually developing distal sensory loss, distal atrophy and weakness of muscles in all extremities, unsteady gait, dysarthria, cognitive slowness, and memory impairment; (2) onset of disease in the fourth to seventh decades, with symptoms persisting for approximately 10 to 30 years before death; (3) recurrent episodes of cerebral ischemia with onset at ages 54 to 68 years; (4) neuroimaging findings revealing symmetrical, widespread lesions in white matter in
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of the hereditary leukodystrophies, X-linked adrenoleukodystrophy, autosomal recessive metachromatic leukodystrophy, and Krabbe disease are associated with specific central and peripheral neuropathologic findings. Metachromatic leukodystrophy was ruled out in this family based on the absence of metachromatic material in the sural nerve biopsy specimens and normal leukocyte arylsulfatase A levels in 3 subjects. Normal levels of plasma long-chain fatty acids and normal activity of the enzyme galactocerebroside in leukocytes ruled out adrenoleukodystrophy and Krabbe disease.

Most of the hereditary leukodystrophies that have been described are autosomal recessive or X-linked recessive disorders, with onset in infancy or childhood, although several have onset later in life. The observed pattern of inheritance in this Norwegian family did not support autosomal or X-linked recessive inheritance. In 1941, Camp and Lowenberg described an American family with an autosomal dominant inherited disorder morphologically similar to Pelizaeus-Merzbacher disease. The family members developed unsteady gait, dysarthria, mental deterioration, and episodes of stroke, all clinical features also seen in the Norwegian family we describe. However, they reported no clinical evidence of peripheral neuropathy and normal CSF protein levels. Nerve conduction velocities were not given.

In 1984, a large Irish-American kindred with an autosomal dominant pattern of inheritance was described with loss of fine motor control and gait disturbances beginning in the fourth to fifth decade of life. There was neuroimaging evidence of white matter changes, most prominent in the frontal and parietal lobes and in the cerebellum. Four patients had slightly elevated levels of CSF protein, but nerve conduction velocities were normal in all patients tested, and results from a sural nerve biopsy were normal in 1 patient.

In mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, recurrent strokes are typical. In contrast to findings in this Norwegian family, young age of onset, cortical infarcts, seizures, elevated levels of lactate in blood, and ragged red fibers revealed on muscle biopsy are also typical. Symptoms and signs of neuropathy, ataxia, and retinitis pigmentosa also differ from those observed in the family we report, regarding both clinical picture and the fact that patients with this condition are reported to have features of axonal neuropathy. Mutational tests for mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes and neuropathy, ataxia, and retinitis pigmentosa were not performed in the Norwegian family, but mitochondrial inheritance seems unlikely.

Since at least 6 members in this Norwegian family developed recurrent strokes, cognitive impairment, and abnormalities in white matter also seen in normotensive subjects on neuroimaging, we suspected CADASIL. However, we found no evidence of genetic linkage to CADASIL or vascular changes characteristic of this disorder in findings from the sural nerve biopsies.

Multiple sclerosis (MS) is one of the most common white matter diseases, and genetic factors seem to play an important role in the predisposition for MS. There are several case reports describing the occurrence of MS and peripheral neuropathy in the same patients. Our patients had many clinical features similar to those of chronic progressive MS. However, only 1 subject (III-3) had oligoclonal bands in CSF. Lesions in the areas typical for MS, such as the optic nerve and corpus callosum, were not seen in our patients. Furthermore, the feature least consistent with MS was the extensive family involvement. Transudative patterns revealed on agar gel electrophoresis and CSF protein levels above 100 g/L are also atypical in patients with MS.

There are several reports of the coexistence of MS and CIDP, but the occurrence of demyelinating lesions in the CNS is uncommon in CIDP. Subject III-8 was treated for supposed CIDP. However, this case did not satisfy the research criteria for the diagnosis of CIDP, and she did not respond to corticosteroid treatment. So far, there has been no evidence of a hereditary component of CIDP.

Although PNS myelin is derived from Schwann cells, and CNS myelin from oligodendrocytes, some protein molecules are present in both CNS and PNS myelin. Therefore, it is not surprising that in some individuals there may be immunologic cross-reactivity between the white matter of the PNS and CNS. For example, following the induction of experimental allergic encephalomyelitis, CNS demyelination may be accompanied by demyelination in peripheral nerves.

Differing susceptibilities to experimental allergic encephalomyelitis and neuritis between inbred strains of rats have been demonstrated. Dyck et al describe 7 patients who had CIDP and also had clinical features of hereditary motor and sensory neuropathy. They concluded that the observations may reflect a genetic susceptibility to inflammatory-demyelinating processes in kindreds with hereditary motor and sensory neuropathy.

The cause of increased CSF protein levels seen in the Norwegian family is unclear. Commonly, the electrophoretic findings of transudative change (increased levels of serum proteins in CSF) is considered to be an indication of blood-brain barrier dysfunction or a decrease in CSF flow rate. However, an intrathecal immunoglobulin synthesis due to prominent gamma trace was present in 2 subjects (II-14 and III-8), and no indi-
cation of blood-brain barrier dysfunction was found in subject III-13.

In the family we describe, 5 of 7 sisters in the second generation developed nodular goiter at a young age, and 5 family members had diabetes mellitus. Both observations may indicate an autoimmune disorder. A possible explanation for the predisposition for goiter could be iodine deficiency, previously a common condition in the inland area where the family lives. No antinuclear antibodies were detected in the family. The possibility remains, however, that there was an immunologic component to the family’s condition. Some of the patients who had strokes had other vascular risk factors such as hypertension (subjects II-2, II-7, II-9, and III-1), diabetes mellitus (II-2, II-7, and II-9), elevated cholesterol levels (subjects II-7, II-14, III-8, and III-13), and cigarette smoking (subjects II-14, III-1, and III-8). The strokes could therefore have a vascular origin, not being primarily related to the hereditary disease with central-peripheral demyelination. Furthermore, some of the cognitive impairments may be related to a vascular encephalopathy. However, none of the neurologically unaffected family members have had strokes. Recently, sensitivity to cerebral ischemic insult in a rat model of stroke was found to be determined by a single genetic locus.26 The occurrence of blood-brain barrier dysfunction was found in subject III-13.

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