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Peripheral and central hypomyelination with hypogonadotropic hypogonadism and hypodontia

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Abstract

We identified four unrelated patients (three female, one male) aged 20 to 30 years with hypomyelination, pituitary hypogonadotropic hypogonadism, and hypodontia. Electron microscopy and myelin protein immunohisto-chemistry of sural nerves showed granular debris-lined clefts, expanded axonal space, outpocketing with vacuolar disruption, and loss of normal myelin periodicity. Reduced galactocerebroside, sphingomyelin, and GM1-N-acetylglucosamine and increased esterified cholesterol were found. This is a clinically homogeneous progressive hypomyelinating disorder. The term 4H syndrome is suggested.

We describe a dysmyelinating leukodystrophy that we characterized using clinical features, neuroimaging, peripheral nerve pathology, and biochemistry. The homogeneous abnormalities of these patients strongly suggest a combination of dysmyelination and a selective pituitary gland endocrine defect.

Methods

Patient description

All patients had a delay in teeth eruption with hypodontia of the permanent teeth (see details in table).

Laboratory testing

Results were normal for urinalysis, blood cell count, electrolytes, liver enzymes, cholesterol, triglycerides (elevated in patient 3), amino acids (blood), organic acids (urine), lactate (blood and CSF), CSF protein and glucose levels, blood very-long-chain fatty acids, lysosomal enzymes, and skeletal bone survey. Proteolipid protein gene dosage and sequencing were normal. Karyotype (except patient 3) and screening for SCA 1–3, 6–8, 10, 14, 17, DRPLA,

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FRDA1, and AOA1 showed no abnormalities. Patient 3 also had familial hypertriglyceridemia, hypercholesterolemia, and balanced chromosomal translocation (46, XX, t(6;14)) that showed no loss of genetic material compared with the unaffected mother and a healthy brother and that was thought to be unrelated to the leukodystrophy.

On standard luteinizing hormone (LH)–releasing hormone (RH) stimulation test, no patients had significant LH and follicle-stimulating hormone (FSH) responses, and all patients had normal responses to thyrotropin-releasing hormone and corticotropin-releasing hormone. No other hormonal abnormalities were found.

All patients had virtually identical abnormalities on neuroimaging, suggesting hypomyelination and cerebellar atrophy (figure 1). Magnetic resonance spectroscopy was done only in patient 3, and it showed decreased choline-containing compounds as the only abnormality (not shown). Brainstem auditory responses were normal, but cortical peaks were absent on somatosensory-evoked potentials. Background pattern was continuously slowed with symmetric 6- to 8-Hz activity. EMG and nerve-conduction velocity were normal in all patients.

The patients at NIH participated in a research protocol on leukodystrophies. The protocol was approved by the institutional review board of the National Institute of Neurological Disorders and Stroke. All patients or their legal guardians gave their written informed consent, including permission for the nerve biopsies.

Nerve biopsy

Care was taken by the neurosurgeon to avoid compression, devascularization, or drying of the nerve during removal of the biopsy segment. Immediately after its removal, fine double-bladed razor blades were used to delicately cross-section the nerve biopsy into several segments. These segments were fixed using freshly prepared solutions or frozen within the operative suite. Age-matched control sural nerve tissue was obtained from University of Maryland Brain and Tissue Bank for Developmental Disorders through National Institute of Child Health and Human Development contract NO1-HD-8-3284. Sural nerve tissue was processed using standard methods for electron microscopy.

For methods for immunohistochemistry and lipid analysis of nerve, see appendix E-1 on the *Neurology* Web site (www.neurology.org).

Results

Sural nerve biopsy

The five main ultrastructural findings were deposits of granular material, diagonal clefts across the myelin sheath, expanded abaxonal space filled with granular and cellular debris, outpocketings of cellular and membranous debris (outlines of lipid crystalloids), and focal loss of major and minor dense lines (figure 2).

Other findings included a few atrophic axons and axons with increased neurofilaments (not shown). Widely spaced myelin, uncompacted myelin, and onion bulbs were not identified. The findings were essentially identical in the sural nerve biopsies of the three patients studied.

Standard peripheral nerve stains, Bielschowsky, luxol fast-blue, and Masson's trichrome did not disclose abnormalities. A mild to moderate decrease in number of myelinated and unmyelinated axons on toluidine blue semithin (1µm) sections was identified (not shown).

Immunostaining for P0 protein demonstrated clefted disruption of myelin sheaths (figure E-1, A and B) and dark granular laminar deposits in a circumferential, curvilinear distribution (figure E-1A). The P0, myelin-associated glycoprotein (MAG) immunohistochemical stain light microscopic findings seem to correlate with and corroborate the ultrastructural pathology. Myelin basic protein staining was similar to that of P0, but the morphologic findings were less distinct and not definitive (not shown).

Lipid analysis of peripheral nerve

We found a reduction of galactocerebrosides and sphingomyelin in the patients compared with controls (figure E-2A). Unesterified cholesterol was definitely not increased (probably decreased) in the patients' specimens, but there was a small increase in cholesteryl esters, particularly in patient 3, who also had the lowest amount of cerebrosides and generally low lipid content compared with the other patients (figure E-2B). A reduction in GM1-N-acetylglucosamine, a glucosamine-containing ganglioside particularly enriched in peripheral nerve, was observed in the three patients.¹ Representative profiles obtained in patient 1 and controls are shown in figure E-2C.

Discussion

We describe four unrelated patients with the sporadic association of a progressive hypomyelinating leukodystrophy of unknown origin affecting central and peripheral nerve myelin with progressive cerebellar ataxia, hypogonadotropic hypogonadism, and hypodontia. Distinguishing features are the peripheral nerve abnormalities on electron microscopy and corroborative findings on P0 protein and MAG by immunohistochemistry despite normal nerve-conduction studies. This homogeneous leukodystrophy syndrome is probably autosomal recessive or de novo dominant disease.

The most unusual changes consist of a disorganization of the myelin sheath with incomplete or absent periodicity and myelin debris, some of which may be cholesterol crystals. Lipid analysis of sural nerve biopsies showed a reduction in galactosylcer-amides and sphingomyelin, both major myelin lipid components, and a small increase in esterified cholesterol, often seen in demyelinating diseases. The significance of the observed decrease of the most prevalent ganglioside in the peripheral nerve system is not known.¹

A search of the medical literature failed to reveal similar peripheral nerve findings.^{2,3} Abnormalities of the intraperiod line have been described in proteo-lipid protein and mannose-binding protein mutations, but these differ from the ones seen in the patient described here. In the peripheral nervous system, P0, a major myelin protein, stabilizes the intraperiod line by homophilic binding between extracellular domains on adjacent layers created through interactions of both the protein and oligosaccharide moieties.⁴

The occurrence of pituitary hypogonadotropic hypogonadism in this leukodystrophy syndrome may be an important clue. A number of patients with the combination of cerebellar ataxia and hypogonadotropic hypogonadism have been previously described, some of which have been categorized as belonging to the heterogeneous Holmes–Adie syndrome.⁵ Three patients of a consanguineous family of Palestinian origin with pituitary hypogonadotropic hypogonadism, associated with progressive ataxia and dementia beginning in the third decade of life, have been recently described.⁵ There was no neurophysiologic or pathologic study of the peripheral nerves. Although the white matter was involved in these patients, other neuroimaging characteristics were different from those of our patients.⁵ Another recent paper described four patients with cerebellar ataxia, hypodontia, and the MRI picture of hypomyelination.⁶ These patients were all prepubertal and were more severely affected than the patients of the present paper. It cannot be excluded that they had the same disease as our patients.

The dysmyelination and lipid abnormality observed are unlikely to have been caused by the hormonal abnormality because patients with idiopathic hypogonadotropic hypogonadism typically have no neurologic abnormalities.⁷ It may, however, be related to molecules such as pregnenolone and progesterone,⁸ but the progesterone-receptor knockout mouse has normal LH/FSH secreting cells and no brain abnormalities.⁹ Because the gonadotrophic defect in our patients is situated at the pituitary level, other disorders associated with hypothalamic-based hypogonadotropic hypogonadism can be ruled out. It is possible that an undetermined transcription factor causes the observed abnormalities in myelin, pituitary, and teeth reported here.¹⁰

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Figure 1.

Brain MRI of all four patients shows that the supratentorial white matter has a signal intensity close to that of the cortex on T1-weighted images, whereas the white-matter signal is hyperintense on T2 images, indicating hypomyelination. The cerebellum is atrophic and the corpus callosum is thin in all patients.

Figure 2.

Sural nerve abnormalities observed on electron microscopy. (A) Electron microscopy of peripheral nerve myelin at low magnification in patient 3 shows an overview of peripheral nerve myelin sheaths with pools of granular material tapering to curvilinear deposits, circumferentially and diagonally across the thickness of the myelin sheath (arrowheads; original magnification 4100 $\times$). (B) Pools of granular material (arrowhead) tapering to acuminate curvilinear deposits appear to track the myelin sheath circumferentially, traversing the myelin sheath diagonally and, on occasion, perpendicularly traversing the myelin sheath (arrow). Granular deposits line a transverse cleft cutting across the myelin sheath (arrow), extending from an expansion of the abaxonal region within the innermost myelin layers to a collection of myelin, cell debris, and paracrystalline material forming an outpocketing (O) just within the outer myelin layers. The axonal membrane and inner and outer myelin layers appear intact (patient 3, original magnification 9750 $\times$). (C) A perpendicular, granular debris-lined cleft forms a disruption across the myelin sheath and in continuity with an abaxonal expanded space containing cell and myelin debris (arrow). The cleft does not transect the outer myelin leaflets. Several diagonal and perpendicular deposits of granular material traverse the myelin sheath (arrowheads, patient 1, original magnification 7400 $\times$). (D) Small foci and larger regional loss of the major and dense lines (L) are noted in many of the myelin sheaths of cross-sectioned peripheral nerve. Although tangential orientation of the myelin may be a possible cause for this morphologic appearance in this cross-sectional high-power view, transitions (arrowheads) between the areas where the major and dense lines are distinct and where they are not visible (L) are documented (patient 1, original magnification 71000 $\times$).

Table

Clinical summary of patients

Patient/ age, y/sex	Early development	Pubertal development	Cognitive examination	Neurologic findings
1/27/ female	Normal until age 12 y; wheelchair dependent since age 15	No spontaneous puberty	FSIQ 64, VIQ 68, PIQ 62	Dysarthria, no pursuit, upbeat nystagmus; ataxia, dysmetria, and spasticity; DTR +2, +3 in knees, +1 in ankles, Babinski signs, normal sensory examination
2/30/male	Normal until age 12 y	No spontaneous puberty	FSIQ 72–60, VIQ 82–72, PIQ 64–52	Dysarthria, no pursuit, upbeat nystagmus; ataxia, dysmetria, and spasticity; DTR 0 to +1, normal sensory examination
3/30/ female	Normal until age 12 y	No spontaneous puberty	VIQ 59; PIQ 63 (estimate)	Dysarthria, saccadic pursuit, no nystagmus; ataxia, dysmetria, and spasticity; DTR 0 to +1, bilateral Babinski signs, normal sensory examination
4/23/ female	Normal until age 7 y	No spontaneous puberty, Tanner stage 1 or 2		Titubation, saccadic pursuit limited horizontal gaze, no vertical gaze, facial paresis, severe dysarthria, dysmetria; DTR normal, bilateral Babinski signs, normal sensory examination

FSIQ = full scale IQ; VIQ = verbal IQ; PIQ = performance IQ; DTR = deep tendon reflexes.

All patients first presented at Tanner stage 0 or 1 and developed Tanner stage 4 or 5 on hormone therapy.