Clinical Progression and Genetic Analysis in Hereditary Spastic Paraplegia With Thin Corpus Callosum in Spastic Gait Gene 11 (SPG11)

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Background: Hereditary spastic paraplegia (HSP) with thin corpus callosum (CC) is a rare neurodegenerative disorder classified as a complicated form of spastic paraplegia. Some patients with HSP with thin CC have previously been described in Japanese families, and the genetic locus was linked to chromosome 15q13-15.

Objective: Our objective was to further clinically and genetically characterize HSP with thin CC.

Patients: We describe the clinical, structural, and functional follow-up and the genetic characterization of 2 sisters aged 26 and 31 years who had severe spastic paraplegia and cognitive impairment.

Results: Magnetic resonance imaging revealed a thin CC with progressing frontoparietal cortical atrophy paralleled by cognitive decline. Using transcranial magnetic stimulation, we delineated a lack of transcallosal inhibition. Images obtained with 18fluorodeoxyglucose positron emission tomography showed reduced cortical and thalamic hypometabolism that decreased further within 4 years. Additionally, combined axonal loss and demyelinating sensorimotor polyneuropathy were present. Because other family members were not affected, autosomal recessive inheritance was considered likely. Genetic analysis of this autosomal recessive HSP was consistent with the linkage to 15q13-15 (markers D15S971, D15S118, D15S659, and D15S994). No mutation was found within the SLC12A6 gene.

Conclusion: Progressive axonal degeneration occurs in the corticocortical projections, corticospinal tract, and peripheral nerves in HSP with thin CC linking to chromosome 15q13-15 in a German pedigree.

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HEREDITARY SPASTIC paraplegia (HSP) is a heterogeneous group of familial neurodegenerative disorders characterized by progressive lower limb spasticity. It is clinically divided into pure and complicated forms and genetically into autosomal dominant, autosomal recessive (AR), and X-linked recessive forms. Complicated HSP with linkage to chromosome 15q13-15 is associated with mental impairment, a thin corpus callosum (CC), and AR inheritance, and it starts in the second decade of life. Most patients with HSP with a thin CC (24 cases in 13 families) were previously described in Japan; cases in whites were only rarely reported.

We describe the clinical progression and genetically characterize AR HSP with a thin CC linked to chromosome 15q13-15 in a German pedigree. On the basis of the phenotypical similarity and the genetic linkage of the Andermann syndrome to 15q14, we screened this family for mutations within the potassium chloride (K+Cl-) cotransporter KCC3 (cation-chloride cotransporter) region.

METHODS

Index patients II:9 and II:10 (Figure 1A) were seen every 4 months for neurological examination during 5 years. Comprehensive laboratory analyses were performed, including analysis of cerebrospinal fluid for the presence of oligoclonal bands and blood testing for electrolytes, hormones, fats, vitamins, and infectious and metabolic diseases (adrenoleukodystrophy and metachromatic leukodystrophy).

Cerebral and spinal magnetic resonance (MR) imaging was performed during the course of the disease. Functional analysis was performed by means of transcranial magnetic stimulation, nerve conduction studies, concentric needle electromyography, 18fluorodeoxyglucose positron emission tomography (FDG-PET), and the Hamburg-Wechsler Intelligence Test for Adults.

Blood samples from the index patients and nonaffected family members were obtained af-
ter participants provided informed consent. Analysis of linkage to chromosome 15q13-15 was performed as previously described by using the following markers: D15S994, D15S659, D15S971, and D15S118. The SLC12A6 gene, located on chromosome 15q14, was screened for mutations by means of polymerase chain reaction and subsequent sequencing.

RESULTS

Two German sisters (Figure 1A) were affected by a complicated form of HSP. Patient II:9, a 31-year-old woman, developed a slowly progressive spastic paraplegia starting at the age of 24 years. In addition, she had increasing urinary urge incontinence and slow cognitive decline (IQ: 60). Patient II:10, her 26-year-old sister, had spastic paraplegia at age 20 years. She was less severely affected and still able to walk 3 km. Both sisters achieved normal motor milestones during childhood. However, their performance at school was low, as compared with that of their siblings. Moreover, they were obese; patient II:9 had a body mass index of 35.5, and patient II:10 had a body mass index of 34.7. They also both had lymphangiomatosis of the lower extremities.

Neurological examination revealed bilateral proximal pronounced weakness of the lower limbs, with patient II:9 more severely affected. The sisters had profound proximal spasticity and hyperreflexia of the lower limbs, and they had extensor plantar responses. They both had a slow, spastic, and slightly ataxic gait that wors-
ened across time. Progressive cognitive impairment was observed in both patients. Blood test and cerebrospinal fluid analysis results were within normal limits. Inflammatory and metabolic diseases were excluded.

Cerebral fluid-attenuated inversion-recovery (FLAIR), T1-weighted, and T2-weighted MR images showed severe thinning of the rostral part of the CC, which appeared as a thin band in the midsagittal T1-weighted images (Figure 2A and F). There was a tendency toward progressive atrophy of the rostral CC (Figure 2B). Frontoparietal atrophy and enlargement of the lateral ventricles were observed, and it progressed across 4 years (Figure 2C and D). Symmetrical white matter lesions were seen, as previously described in HSP with thin CC (Figure 2E).9 The MR images of the spinal cord were normal. In a combined muscle and nerve biopsy in patient II:9, signs of both axonal loss and demyelination were found.

At transcranial magnetic stimulation, both patients showed a lack of transcallosal inhibition, which indicates the absence of inhibitory responses across the CC (Figure 3). The low amplitude of the contralateral responses to transcranial magnetic stimulation was indicative of lesions of the corticospinal tract. Results of nerve conduction studies and concentric needle electromyography were characteristic of sensory nerve fiber dysfunction (Figure 4A). Demyelination of motor nerve fibers was indicated by delayed F waves (Figure 4B). Fibrillation potentials and positive sharp waves were found at concentric needle electromyography, and motor unit action potentials were of increased duration, amplitude, and firing rate, which indicates loss of motor axons (Figure 4C). Moreover, autonomic neuropathy was indicated by reduced heart rate variability in patient II:9 (Figure 4D). The FDG-PET images showed hypometabolism in the frontoparietal and temporal cortices and in the thalamus. Progressive hypometabolism occurred in patient II:9 during 4 years (Figure 5).

Other than the index patients II:9 and II:10, the remainder of the 17 family members were neurologically normal (Figure 1A). Body mass index and the size and shape of the CC, as well as of the cortex, were normal on sagittal MR images. No evidence of consanguinity was found.

Because of the AR inheritance and clinical phenotype of a complicated form of HSP, we performed a segregation analysis for markers at chromosomal locus 15q13-15 in this family. In the pedigree, 4 of the 4 examined markers (D15S971, D15S118, D15S994, and D15S659) were informative and indicated linkage to 15q13-15. Both index patients II:9 and II:10 were concordant for the same alleles, whereas all other family members were discordant (Figure 1B). However, no mutation was found on the solute carrier family 12, member 6 gene SLC12A6 that maps to this region and encodes the potassium chloride cotransporter KCC3.

**COMMENT**

**PROGRESSIVE AXONAL DEGENERATION PRECEDES CORTICAL ATROPHY**

Both index patients fulfill the diagnostic criteria for AR HSP with mental impairment and a thin CC. The slow
clinical progression correlates with the structural and functional findings. Interestingly, comparison of the clinical and structural data in index patient II:9 indicates that thinning of the CC may already be present at an early stage of the disease. Apart from these structural changes, our electrophysiological data demonstrated a pronounced functional deficit in inhibitory responses across the CC, which correlates to dysfunctional corticocortical projection. Transcallosal inhibition physiologically reflects suppression of ongoing voluntary electromyographic activity in the ipsilateral distal hand muscles after transcranial magnetic stimulation\(^{10,11}\) and is present in patients with pure HSP with CC of a normal size.\(^{12}\)

Progressive cortical atrophy paralleled by increasing cerebral and thalamic hypometabolism was present in patient II:9, who was the more severely affected. Cognitive performance was consistent with MR imaging and FDG-PET findings. Cortical and thalamic hypometabolism and decreased cerebral blood flow were previously described in spastic gait gene 11.\(^{6,13}\) Moreover, a case of AR HSP with thin CC that was neuropathologically analyzed\(^{14}\) also had cortical and thalamic degeneration. However, cortical and thalamic degeneration are not specific for complicated HSP but have been described in many degenerative diseases with cognitive impairment such as Niemann-Pick disease type C,\(^{15}\) sporadic Creutzfeldt-Jakob disease,\(^{16}\) and Alzheimer disease.\(^{17}\)

Skull size and shape were normal in both index patients, and early clinical history was not remarkable for any obvious neurological deficits, which suggests normal prenatal and postnatal brain development. Patterns of callosal atrophy are different among neurodegenerative diseases, and CC atrophy may correlate with cortical atrophy.\(^{16}\)

Long-projecting axons appear to be more susceptible to degeneration in HSP with a thin CC, which results in severe gait impairment and impaired mental performance. Some of the spastic gait gene loci have already been characterized, and the neurobiological function of these gene products indicates a function in axon and myelin maintenance (eg, L1 cell adhesion molecule and spastin).\(^{19-21}\)

**GENES MAPPING TO CHROMOSOME 15q13-15**

Several other loci for AR HSP are described; however, to our knowledge, AR HSP with a thin CC has been

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Figure 4. Axonal loss and demyelinating polyneuropathy in patient II:9. A, Near-nerve recording from the left sural nerve. The arrows point to abnormal late components that indicate demyelination of sensory nerve fibers. B, F-wave recordings from the right tibial nerve. Delayed F waves (60.2 ms) and an increased number of A waves (arrows) both indicate demyelination of motor nerve fibers. C, Concentric needle electromyograms from the hypothenar muscles. The upper trace shows positive sharp waves, and the lower trace shows motor unit action potentials with increased amplitude of 4.1 mV and a maximal discharge rate of 30 discharges per second that indicate chronic axonal damage. D, Electrocardiographic recording of 30 consecutive R-R intervals. The heart rate variability was less than 60% of the lower limit of normal.

Figure 5. Images obtained with \(^{18}\)fluorodeoxyglucose positron emission tomography in patient II:9 demonstrate frontoparietal cortical and thalamic hypometabolism (arrows). Note the increasing hypometabolism during follow-up. A, Initial images. B, Images obtained 4 years later. The color bars refer to the level of glucose metabolism: red indicates high metabolism; green, low. The horizontal arrows indicate the confidence level of metabolic activity.
reported with linkage to chromosome 15q13-15. This finding is in accordance with ours. This locus is associated with the Andermann syndrome, an AR disease characterized by partial or complete agenesis of the CC, sensorimotor neuropathy, and mental retardation.\textsuperscript{8,22} 

Andermann syndrome maps to chromosome 15q14 and is associated with mutations in the gene SLC12A6, which encodes KCC3.\textsuperscript{8} In the present and previously published studies, AR HSP with a thin CC maps closely to the Andermann syndrome region and shares major clinical features. The hypothesis, however, that AR HSP with a thin CC and Andermann syndrome are allelic disorders\textsuperscript{8} cannot be supported by our genetic analysis. Once the underlying genetic defect is delineated, it may lead from an improved understanding of the disease to the development of therapeutic strategies to ameliorate the underlying neurodegenerative process.

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