HEREDITARY SPASTIC PARAPLEGIA TYPE 8 – NEUROPATHOLOGICAL FINDINGS

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Letter to the Editor

Sir,

An interesting report is presented by de Bot et al. (2012) (4) on a rare type 8 autosomal-dominant form of hereditary spastic paraplegia (HSP) caused by a mutation in the VCP gene. Here we present, for the first time we believe, the neuropathological findings in an HSP type 8 (SPG8) case with a confirmed KIAA0196 mutation.

HSP is clinically and genetically a heterogeneous group of disorders with more than 72 loci and 55 genes known to be involved so far (12). SPG8 has been described in 13 families (2, 5, 8, 10) and presents as a pure spastic paraplegia without associated neurological abnormalities in all families but one (2). SPG8 is caused by mutations in the strumpellin gene KIAA0196. Eleven different missense mutations (2, 5, 10) and one large deletion in intron 10 – exon 15 of KIAA0196 (10) have been identified so far in patients with SPG8 (www.hgmd.cf.ac.uk). Strumpellin knockdown experiments in human neuroblastoma cells demonstrated reduced axonal outgrowth, and knockdown studies in zebrafish revealed severe contractile cardiac dysfunction, tail curvature, and impaired motility, implying a strumpellin loss-of-function pathogenesis of SPG8 (3).

The major neuropathological finding in pure HSP is axonal degeneration, maximal in the terminal portions of the longest descending and ascending tracts (1). A case-control study quantifying corticospinal tract axon number showed reduced cross-sectional area and axonal density in the corticospinal tracts with a more pronounced axonal loss in the distal neuraxis in HSP patients. The cross-sectional area and axonal density of the sensory tracts were reduced only in the upper regions of the spinal cord. This is consistent with a “dying back” axonal degeneration (6).

The proband presented here is a 46-year-old male with a slowly progressing spastic paraplegia. He was healthy until the age of 37, where he had onset of pain in the lower limbs,
intermittent dropfoot, foot clonus, and slight ataxia. At age 45 he had an unaided walking
distance of 200 m, spasticity and exaggerated deep tendon reflexes in the lower limbs, foot
clonus and slight paresis of the hip corresponding to an estimated Spastic Paraplegia Rating
Scale (SPRS) score of 19. He had no symptoms from the bladder, and no cognitive or
psychiatric symptoms. MRI of the brain and spinal cord was normal.

The proband’s mother was healthy until her first pregnancy at 25 years of age, where she
exhibited slight paresis and spasticity of the legs. A neurological examination at age 34
revealed slight eye movement ataxia, ataxia of the legs, and exaggerated patellar and heel
tendon reflexes corresponding to an estimated SPRS score of 15. She was suspected of
having multiple sclerosis, but the diagnosis was never confirmed. She was re-evaluated at age
42 due to urine incontinence and progression of the spastic paraparesis – signs and symptoms
corresponding to an estimated SPRS score of 20. At the age of 61 she suffered from severe
depression and complained of cognitive deficits. Her unaided walking distance was 25 m
(estimated SPRS score 25). She died 70 years old following a hemicolectomy due to stage T3
colon cancer. Her medical history also included surgical treatment and radiotherapy for
advanced breast cancer, hyperthyroidism, and atrial fibrillation. An autopsy was performed to
determine the cause of the patient’s symptoms. Informed consent for performing the autopsy
and related analyses as well to publish this article was obtained from the son of the deceased
woman.

There are no other known affected family members. A 43-year-old brother of the proband
has no symptoms of spastic paraplegia. The maternal grandfather died suddenly and
unexpectedly 65 years old and the maternal grandmother had unconfirmed Parkinson’s
disease and died 89 years old.

Mutational analysis of genomic DNA from a peripheral blood sample from the proband
revealed a missense mutation in the gene for strumpellin (KIAA0196) in exon 16:
c.1876G>T; p.(Val626Phe) previously found to be heterozygously present in a British family and three large North American families with European ancestry thus confirming the clinical diagnosis of SPG8. The presence of the KIAA0196 mutation in the proband’s deceased mother was confirmed on DNA extracted from frozen normal colon tissue. The mutation was absent in DNA extracted from peripheral blood from the proband’s younger brother.

The weight of the fixated brain was 1002 grams. The gross external appearance of the brain was normal and there were no signs of atrophy. Sections from the cerebrum, cerebellum, pons, mesencephalon and medulla oblongata appeared normal, without signs of atrophy, which was confirmed by histological examination. The spinal cord was 39 cm long. There was severe atrophy of the spinal cord between the cervical and lumbar enlargements, where the spinal cord consisted mainly of vessels and meninges (Fig. 1). Humped surfaces were found corresponding to the cervical enlargement and more widespread above, at, and below the lumbar enlargement. Grey matter was not readily distinguished on gross horizontal sections of the spinal cord in these areas. Cross sections of longitudinal vessels were present. Histological examination confirmed severe atrophy of the thoracic spinal cord with demyelination as demonstrated by luxol fast blue staining and loss of neurons. Although the overall number of motor neurons was preserved in the cervical and lumbar enlargements, what appeared to be remnants of motor neurons were found suggesting motor neuron degeneration in these spinal cord regions. Moreover the number of axons in the white matter was markedly reduced in these parts of the spinal cord. There was no increased number of inflammatory cells and no reactive gliosis (Fig. 2).

The early reports on the neuropathological changes in HSP were published before the genetic background of the HSP subtypes was known. With increasing knowledge of the molecular basis of HSP it is possible to relate the neuropathological findings for the different subtypes of HSP to the function of the proteins encoded by the corresponding genes. Caution
is necessary, however, as HSP often does not shorten lifespan, and neuropathological observations may be associated with age or age-associated diseases (7).

We found pronounced atrophy of the spinal cord, with only remnants of nervous tissue between the two enlargements in post mortem tissue from a woman with a confirmed mutation in KIAA0196. To our knowledge such severe atrophy has not previously been reported in HSP. Spinal cord atrophy is commonly found in SPG8 as well as in other types of SPG. SPG6 and SPG8 appear to have particularly severe spinal cord atrophy. A study using magnetic resonance imaging found a significantly higher degree of cord atrophy in SPG6 and 8 compared to SPG3A and 4 (9). Although a neuropathological study found no correlation between cross-sectional area and axonal loss in HSP of unknown genetic type (6), our findings do indeed indicate a high degree of spinal cord atrophy in SPG8. An autopsy case of HSP with thin corpus callosum had severe degeneration in the lateral and anterior corticospinal tracts, spinocerebellar tracts and posterior column as reported in a case study by Kuru et al. (2005). This was, however, not an HSP8 case, but a complicated type of HSP that was not subtyped (11). Another autopsy case compatible with a complicated form of autosomal recessive HSP, but not further subtyped, had severe atrophy of the ventral and lateral corticospinal tracts in the spinal cord (13).

From the SPG8 case presented here by us it appears that the almost complete atrophy of spinal cord nervous tissue, would be a characteristic neuropathological finding of HSP type 8.

Figure legends

Figure 1

Macroscopic appearance of the spinal cord. a) Spinal cord with severe atrophy. b) The portion between the cervical and lumbar enlargements consists mainly of meninges and vessels. c) Cervical enlargement. d) Lumbar enlargement.
Figure 2

Histological appearance of the medulla oblongata and spinal cord. a) Medulla oblongata. b-c) Cervical enlargement with reduction in number of axons as demonstrated at high magnification of a luxol fast blue stained slide (insert f). d) Severely atrophied spinal cord between the cervical and lumbar enlargements with marked reduction in number of axons. e) Lumbar enlargement with disorganized overall histology and reduction in number of axons demonstrated at high magnification of a luxol fast blue stained slide (insert g). Bars: a, b – 5mm; c-e – 2.5mm; f, g – 250µm

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References


Macroscopic appearance of the spinal cord. a) Spinal cord with severe atrophy. b) The portion between the cervical and lumbar enlargements consists mainly of meninges and vessels. c) Cervical enlargement. d) Lumbar enlargement.

Fig. 1
63x44mm (300 x 300 DPI)
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Bars: a, b – 5mm; c-e – 2.5mm; f, g – 250µm

Fig. 2

173x177mm (300 x 300 DPI)