Atypical Rigid Form of Huntington’s Disease: A Case with Peripheral Amyotrophy and Congenital Defects of a Lower Limb

Naomi Kanzato, Mineki Saito*, Takashi Horikiri*, Yukihiro Komine**, Masanori Nakagawa* and Toshio Matsuzaki*

We describe a patient showing an atypical phenotype of Huntington’s disease (HD), including prominent generalized dystonia, peripheral amyotrophy of the legs with an inverted champagne bottle configuration and pes equinus. The patient also had congenital defects of the lower left leg. Chorea and psychiatric symptoms were not prominent. Polymerase chain reaction assessment revealed 51 CAG repeats in gene IT 15. Magnetic resonance imaging of the brain demonstrated mild atrophy of the pons and cerebellum, and hyperintensity of the transverse pontine fibers and neostriatum on spin-echo images. Peripheral amyotrophy in this case might have resulted from axonal degeneration related to neuronal damage in the central nervous system, although at the present time we cannot confirm it as a new HD phenotype.


Key words: dystonia, neuronopathy

Introduction

Huntington’s disease (HD) is a progressive neurodegenerative disorder inherited as an autosomal dominant trait, characteristically with onset at middle age, manifesting as choreiform movements, cognitive decline, and psychiatric symptoms. Clinically atypical HD have been reported, such as HD with rigidity but little or no chorea (Westphal variant, usually seen in children); prominent bradykinesia noted in black patients (1); senile onset (2); tourettism (3); and myoclonus (4). Such variable features of atypical HD can lead to misdiagnosis, for example as olivopontocerebellar atrophy (OPCA) or Parkinson’s disease (5), unless a family member is known to have typical HD.

The Huntington’s Disease Collaborative Research Group (6) showed that CAG trinucleotide repeats on IT 15, the gene responsible for HD, are expanded and unstable in the disease. Normal subjects have repeats ranging from 11 to 34, while patients with HD have 42 or more repeats. While the diagnostic value of trinucleotide repeat expansion is high in HD, molecular mechanisms underlying a typical phenotype of HD without CAG expansion, and atypical phenotypes with CAG expansions have not been investigated adequately (7, 8).

Here, we describe a patient with an atypical phenotype of HD with CAG expansion, who had prominent generalized dystonia, and peripheral amyotrophy of the leg with an inverted champagne bottle configuration and pes equinus.

Case Report

The patient was born with the absence of the left lower leg and foot, although the delivery itself was normal. As he matured he showed no other developmental problems, and wore a prosthetic left leg. His father had began to have delusions of persecution at the age of 38 years, and committed suicide 2 years later, when the patient was 16 years old (no medical records were available). After graduation from a college, the patient worked as an architect. Since the age of 33, he had been aware of atrophy of the right leg and gait unsteadiness, and also his family began to note diminution of intelligence. At the age of 35, he developed delusions of persecution and auditory hallucinations, and was treated with chlorpromazine. He was admitted to our hospital at age 36.

Although his Wechsler Adult Intelligence Scale (WAIS) IQ

From the Department of Neurology, National Okinawa Hospital, Okinawa, *the Third Department of Internal Medicine, Kagoshima University, Kagoshima and **the Third Department of Internal Medicine, Ryukyu University, Okinawa

Received for publication March 16, 1998; Accepted for publication August 11, 1998

Reprint requests should be addressed to Dr. Naomi Kanzato, the Department of Neurology, National Okinawa Hospital, Ganeko 3-20-14, Ginowan-shi, Okinawa 901-2214
Atypical Rigid Form of Huntington’s Disease

was 77, his overall behavior appeared normal. His eyelids were retracted, giving his face a frightened appearance. Slight limitation of upgaze without nystagmus was noted. His neck was slightly hyperextended, and his sternocleidomastoid muscles were moderately tense. His speech was slurred, and chorea was evident in the tongue and the soft palate. His right leg showed an inverted champagne bottle pattern of muscle atrophy and pes equinus, with choreiform movement apparent in one toe. The left thigh was small, and distally the limb was absent (Fig. 1). His motor power was almost normal, but muscle rigidity of the arms and rigospasticity of the right leg were evident. His gait was stiff accompanied by prominent dystonic posturing of head, shoulder, and the arm. All deep tendon reflexes were brisk. No pathologic reflexes were elicited. All modalities of sensation were mildly impaired in the legs. Motor decomposition and bradykinesia was evident.

Results of routine hematologic and laboratory studies, including serum copper and ceruloplasmin were all normal. Cerebrospinal fluid (CSF) examination disclosed a normal opening pressure, cell count, and sugar content, but the protein content was mildly increased (74 mg/dl). CSF concentrations of amino acids were normal, as were levels of biogenic amine metabolites such as homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylethylene glycol (MHPG), but γ-amino butyric acid (GABA) was low (110 pmol/ml; normal range, 144–530 pmol/ml). Chromosomal analysis demonstrated normal male 46XY karyotype with no deletions or translocations. Although the patient’s clinical findings were reminiscent of Machado-Joseph disease (MJD, SCA III) or spinocerebellar ataxia type 1 (SCA I), polymerase chain reaction (PCR) study of genomic DNA extracted from his leukocytes, revealed no expansions indicative of these diseases. Instead, CAG repeat expansion was demonstrated in the HD gene (IT 15); repeat numbers were 51/17 in the two alleles. No family members studied showed such an abnormality.

Roentgenograms of his left leg revealed a residual fibula, 20 mm in length, and a shorter tibia (Fig. 2); this finding argued against causation by an intrauterine complication, the so-called congenital constriction band syndrome, since the band is thought to amputate the bones at the same length.

Magnetic resonance imaging (MRI) of the brain demonstrated mild atrophy of the cerebrum, cerebellum, pons, and middle cerebellar peduncle (Fig. 3A). The transverse pontine fibers (B), caudate nuclei and putamen (C) showed moderate hyperintensity on spin-echo images. Spinal MRI showed no
abnormal findings within cord and nerve roots.

Electroencephalography disclosed normal background activity and no paroxysmal features. Nerve conduction studies revealed normal motor conduction velocities. However, the threshold stimulus intensity required to excite the axons in the leg was several times above the normal limit. Electromyography in the leg revealed chronic reinnervation but no active denervation. Somatosensory evoked potentials (SEP) on stimulating the posterior tibial nerve showed the P37 latency to be prolonged to 41.5 msec (normal 36.41 ± 1.83 msec); the central conduction time of P37-N20 was also prolonged to 20.9 msec (16.76 ± 0.41 msec). The blink reflex showed prolongation of latencies of ipsilateral and contralateral R2 components to 51.8 msec (30.5 ± 3.4 msec) and to 52.0 msec (30.5 ± 4.4 msec), respectively. Right supraorbital nerve stimulation did not evoke a contralateral R2.

Discussion

The patient was diagnosed as having HD based on CAG repeat expansion in IT15 despite atypical clinical features. Because the frequency of new HD mutations is considered exceedingly low (9, 10), the patient probably inherited the disease from his father, who had psychiatric symptoms. The patient's prominent generalized dystonia, muscular rigidity, cerebellar ataxia, and localized chorea were consistent with the characteristics of the rigid variant of HD (11). The inverted champagne bottle pattern of leg amyotrophy has not been reported in HD, although only one sporadic HD with axonal neuropathy who received surgery for her pes equinus exists (12).

Disorders such as hereditary motor and sensory neuropathy (HMSN) type II and adult-onset spinal muscular atrophy (SMA) should be considered in the differential diagnosis of this patient's characteristic peripheral amyotrophy. HMSN type II is a clinically and genetically heterogeneous disorder with a late onset of manifestations such as amyotrophy in the lower limbs but relatively little or no involvement of hand muscles (13). While the description resembles the present case in a number of ways, the patient had no relative who demonstrated such a hereditary neuropathy, and essentially no evidence was seen of the active denervation in the peripheral nervous system that one would expect in HMSN type II. Adult-onset SMA (14) was excluded because our patient had hyperreflexia and lacked lower motor neuron bulbar involvement.

Considering the various possible explanations, we concluded that this patient's peripheral amyotrophy may have resulted from axonal degeneration related to neuronal damage in the central nervous system (so-called neuronopathy). A hereditary defect in synthesis and maintenance of structural proteins may have resulted in manifestation of neuronopathy in

Figure 3. A: T1-weighted (TR 500/TE 20), B and C: proton-weighted (TR 2000/TE 110) magnetic resonance images of the brain. Mild atrophy of the cerebellum, pons, and middle cerebellar peduncle, and moderate hyperintensity of the transverse pontine fibers, caudate nuclei and putamen are evident.
adult life. This kind of peripheral amyotrophy has been reported in MJD (15), which is a multisystem neurodegenerative disorder due to CAG repeat expansion in another gene. However, we cannot easily conclude this peripheral amyotrophy as a new HD phenotype at the present time, because we cannot confirm the direct evidence that his father had the same phenotype of peripheral amyotrophy.

Savoiardo et al (16) reported the rigid variant of HD in seven patients with MRI findings of markedly increased signal intensity in the neostriatum as in the present case, but none showed increased signal intensity from transverse pontine fibers. Zweig et al (17) reported two variant HD cases with autopsy findings including significant atrophy of the brainstem and spinal cord. The present patient showed the MRI features of pontocerebellar atrophy. Furthermore, prolonged latency of R2 of the blink reflex and prolonged central conduction time of SEP were features of our case, suggestive of disturbed impulse conduction in the brainstem and spinal cord.

Concerning the absence of the left lower leg and foot, no history of consanguinity or maternal medication or infection during pregnancy was obtained. The feature was distinct from phacomelia, a well-known complication of thalidomide syndrome which had broken out in 1958, the patient’s birth year. Roentgenographic findings ruled out the congenital constriction band syndrome, the most common cause of congenital defects of extremities (18–20). Considering these, we suspect that the defect of our patient’s leg might have been caused by mutations affecting regional development (21). However, we should consider this congenital leg defect as an incidental anomaly rather than HD phenotype, because expression of CAG repeats expansion is speculated as ‘gain of function’ at the protein level followed by neuronal death (22). The prevalence of HD in Japan is approximately 4 per 10 million population, which is low in comparison with that of Western countries where it ranges from 49 to 72 per million (23). Furthermore, the rigid variant type of adult HD occurs rarely, in less than 5% of cases. The rigid variant is considered a heterogeneous group, possibly related to allelic variation at the HD locus or to unlinked autosomal modifying loci (5, 17, 24). Further investigation of distinct subgroups of atypical HD phenotypes, including the present case, should provide clues to susceptibility factors in multisystem neuronal degeneration and to the function of the HD gene.

Acknowledgements: We thank Dr. Y. Sasaki, Brain Research Institute of Niigata University, for the genetic analysis. We are grateful to Prof. K. Fukiyama, Third Department of Internal Medicine, Ryukyus University, for critical reading of our manuscript.

References


