Peripheral Nerve Involvement in Spinocerebellar Ataxias

Bart P. C. van de Warrenburg, MD; Nicolette C. Notermans, MD, PhD; Helenius J. Schelhaas, MD; Nens van Alfen, MD; Richard J. Sinke, PhD; Nine V. A. M. Knoers, MD, PhD; Machiel J. Zwarts, MD, PhD; Berry P. H. Kremer, MD, PhD

Background: In autosomal dominant cerebellar ataxias (ADCAs), it is unclear whether the associated peripheral nerve involvement is always a typical length-dependent axonopathy rather than primary neuronopathy due to neuronal degeneration in the spinal anterior horns and/or dorsal root ganglia.

Objective: To study the nature and extent of peripheral nerve involvement in patients with ADCA.

Patients and Methods: Standardized clinical and electrophysiologic studies of 27 genotyped patients with ADCA were conducted prospectively, with special emphasis on the distinction between primary neuronopathy and dying-back axonopathy.

Results: Electrophysiologic evidence of involvement of the peripheral nervous system was present in 70% of patients. Findings were compatible with dying-back axonopathy in 30%, while in 40% of patients, neuronopathy was diagnosed. Patients with spinocerebellar ataxia (SCA) 1 and SCA2 mostly displayed features of neuronopathy, while patients with SCA3 and SCA7 displayed both neuronopathy and axonopathy. In SCA6, no significant peripheral nerve involvement was demonstrated. We did not observe an influence of age, disease duration, or ataxia severity on the presence or type of peripheral nerve involvement.

Conclusions: Peripheral nerve involvement in ADCA manifests not only as distal axonal neuropathy, but also as primary neuronopathy. Electrodiagnostic studies in this group of patients should be conducted in such a way that primary neuronopathy is detected.

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Autosomal dominant cerebellar ataxias (ADCAs) share features of progressive, usually adult-onset spinocerebellar degeneration, including gait and limb ataxia, dysarthria, and oculomotor control impairment. Genetic studies have identified 21 genetic loci (spinocerebellar ataxia 1-8, SCA10-19, and SCA21-23) and 10 of the corresponding genes (http://www.gene.ucl.ac.uk/nomenclature). Still, about two thirds of Dutch ADCA families map to 1 of the 5 most common loci: SCA1, SCA2, SCA3, SCA6, and SCA7. In these 5 genes, the common mutation is an expanded coding CAG repeat that results in an elongated polyglutamine (polyQ) tract in the encoded proteins. How this polyQ-sequence induces neuronal loss in selected regions is currently unknown.

Although the cerebellum is predominantly affected, the mutated gene also causes dysfunction of other neuronal populations. The presence of peripheral nerve involvement in ADCAs has been reported, suggesting that disease mechanisms are not solely confined to the central nervous system compartment. However, none of these studies was developed to systematically investigate whether the peripheral nerve involvement is a typical distal-dominant axonopathy or a primary neuronopathy due to the degeneration of neurons in the anterior horns and/or dorsal root ganglia.

To study the nature and extent of peripheral nerve involvement in ADCAs and to obtain electrophysiologic data that support the presence of either a neuronopathy or a dying-back axonopathy, we prospectively conducted standardized clinical examinations, nerve conduction studies, and electromyography (EMG) in 27 genotyped ADCA patients.

METHODS

PATIENTS AND CLINICAL EVALUATION

Twenty-seven patients with ADCA with a mutation in the SCA1, SCA2, SCA3, SCA6, or SCA7
genes were recruited from our outpatient clinic and gave informed consent. Age at ataxia onset, disease duration, and the presence of symptoms that suggested involvement of the peripheral nervous system (paresthesias, pain, numbness, muscle cramps, weakness, fasciculations, and muscle wasting) were recorded. To quantify ataxia severity, the International Cooperative Ataxia Rating Scale was used, which ranges from 0 (no ataxia) to 100 (very severe ataxia).

We did not attempt to identify an additional sensory component of the ataxia. Examination of the peripheral nervous system was carried out by the same investigator (B.P.C.V.) in all patients and performed according to a standardized protocol. The Medical Research Council scale (0-5) was used to measure the muscle strength of 7 muscles or muscle groups in both arms and legs. Summation of muscle strength could result in a maximum Medical Research Council sum score of 140. Sensory function was examined in all extremities and included rating of pinprick, touch, vibration, and joint position sense according to a distal to proximal distribution. Summation of all sensory modalities could lead to a maximum sensory sum score of 56. Clinically, involvement of the peripheral nervous system was considered in case of (spinthalamic) sensory disturbances, muscle weakness, amyotrophy, and/or markedly decreased or absent tendon reflexes.

**ELECTROPHYSIOLOGIC STUDIES**

A Medelec Synergy EMG system (Oxford Instruments, Surrey, England) was used for neurophysiologic studies. Nerve conduction studies were conducted according to standard techniques. Motor nerve conduction studies included the median, peroneal, and posterior tibial nerves, and sensory nerve conduction studies encompassed antidromic stimulation of the left median, radial, and ulnar nerves, and both sural nerves. Compound muscle action potentials (CMAPs) less than 7 mV in the upper extremities and less than 5 mV in the lower extremities were considered abnormal; for sensory nerve action potentials (SNAPs), these values were 10 μV and 5 μV, respectively. The CMAPs and SNAPs of all nerves examined were summated into a sum score. The sural/radial amplitude ratio was calculated by dividing the highest sural nerve SNAP by the left radial nerve SNAP. In our laboratory, a sural/radial amplitude ratio greater than 0.30 was found to have a predictive value of 90% (females) and 100% (males) for the absence of a dying-back axonal neuropathy (B.P.C.V., M.J.Z., unpublished data, 2003). Concentric needle electrode EMG studies were performed in the left extensor hallucis longus and rectus femoris muscles, using a standard method of visual, semiquantitative measurement of insertion activity and spontaneous activity at rest, and assessment of motor unit morphologic characteristics (duration, amplitude, and recruitment pattern) during slight, intermediate, and maximum voluntary contraction.

Axonal neuropathy was considered to be present when there was a reduction of CMAPs and/or SNAPs, with or without neurogenic muscle changes and spontaneous muscle fiber activity, all in a distal to proximal gradient. Neuronopathy was defined as electrophysiologic evidence of axonal neuropathy without a distal to proximal gradient. A sural/radial amplitude ratio greater than 0.30 was used as an additional tool to demonstrate the absence of such a gradient.

**STATISTICAL ANALYSIS**

The means of the group with and the group without EMG abnormalities were compared with a t test. Multiple comparisons of means per SCA subtype were corrected with the Bonferroni rule. Linear regression analysis was applied to assess the correlation between the sum of CMAPs and SNAPs and age, disease duration, or International Cooperative Ataxia Rating Scale score. All analyses were carried out by using the SPSS computer package, version 9.0 (SPSS Inc, Chicago, Ill).

**RESULTS**

**CLINICAL CHARACTERISTICS**

Patient characteristics are presented in the Table. Symptoms or complaints that suggested peripheral nervous system involvement were present in 78% of patients. The presence of distal paresthesia and/or numbness was reported by 8 patients. None of the 6 patients with subjective muscle weakness reported predominant involvement of proximal muscles, although 1 patient did notice wasting of proximal leg muscles. Eight patients observed fasciculations that (also) occurred in the proximal muscles of arms and legs in 3 of them. Fifteen patients complained of muscle cramps, which involved proximal muscles in 4.

At examination, vibration sense was found to be abnormal in 22 patients. In 3 patients, a total absence of lower extremity vibration sense was observed. Joint position sense was diminished but preserved in 5 patients. Other findings compatible with peripheral nerve involvement were present in 56% of patients. Muscle weakness was found in 9 patients. Proximal muscle weakness was present in 2 patients, with weakness of the quadriceps femoris and ilopsoas muscles in 1 SCA1 patient and weakness of only the intrinsic hand muscles in 1 SCA7 patient. In 13 patients, decreased or absent tendon reflexes were observed, which affected only the ankle jerks in 5. Sensory disturbances, when present, always showed a distal to proximal gradient.

**ELECTROPHYSIOLOGIC STUDIES**

Electrophysiologic evidence of peripheral nerve involvement was found in 19 (70.3%) of 27 patients. In 8 patients, abnormalities were compatible with a typical dying-back axonal neuropathy, which was purely sensory in 1 and mixed sensorimotor in 7 patients. However, in 11 patients, the findings were indicative of a neuronopathy involving dorsal root ganglion and/or anterior horn cells.

In 4 of the 5 SCA1 patients, electrophysiologic findings were abnormal, indicating motor and sensory neuronopathy in 3 and an axonal sensorimotor dying-back neuropathy in 1 patient. Sensory neuronopathy was found in all 3 SCA2 patients. In 1 patient, neurogenic muscle changes without a distal to proximal gradient indicated additional involvement of spinal motor neurons. Only 1 of 8 SCA3 patients showed normal neurophysiologic findings. An axonal sensorimotor neuropathy was diagnosed in 4 and a neuronopathy in 3. The neuronopathy involved both motor and sensory neurons in 2, and only motor neurons in 1 patient.

Of the 7 SCA6 patients, electrophysiologic abnormalities were observed in 1 patient only and interpreted as axonal sensorimotor neuropathy. Electrophysiologic findings were considered abnormal in all 4 SCA7 patients studied. Mild axonal sensorimotor neuropathy and axonal sensory neuropathy were both diagnosed in 1 patient. Neuronopathy affecting motor neurons was deemed
likely in another patient, while findings were interpreted as an early-stage sensory neuronopathy in the fourth SCA7 patient. Overall, no signs of demyelinating peripheral nerve disease were present.

**CLINICAL CHARACTERISTICS VS ELECTROPHYSIOLOGIC FINDINGS**

That some patients without EMG abnormalities were found to have vibration sensory disturbances indicates that this can just as likely be due to posterior column degeneration as to peripheral nervous system degeneration. Therefore, in the following, we disregarded vibration sensory disturbances.

Some patients without electrophysiologically confirmed peripheral nerve involvement did, however, have signs and symptoms that suggested peripheral neuropathy clinically, which was most evident in the SCA6 group. Alternatively, several patients with electrophysiologic abnormalities had no peripheral symptoms or signs at all. Peripheral symptoms were present in 68% of patients with established peripheral nerve involvement, and peripheral signs were present in 68% as well. In patients with normal electrophysiologic findings, these percentages were 63% and 25%, respectively. Of all 11 patients with neuropathy, 4 did not have any symptoms, and 3 had no objective signs that suggested involvement of the peripheral nerves. In the 8 patients with an axonopathy, these numbers were 2 and 1, respectively.

**STATISTICAL ANALYSIS**

There was no significant correlation between the sum of CMAPs and SNAPs and age, disease duration, or ataxia severity, although the correlation between age and the sum of CMAPs and SNAPs ($r = -0.34$) almost reached significance ($P = .09$), indicating an age-related decline in nerve action potentials. Similar results were obtained by summing SNAPs only. There was no significant difference in age, disease duration, or ataxia severity between...
The issue of whether peripheral nerve involvement manifests as a typical distal-dominant axonopathy or as primary neuronopathy has not been systemically addressed. Solving this issue seems relevant to understand the pathophysiologic mechanisms of polyQ-induced neurodegeneration. In addition, the peripheral neuronopathy in SCA patients is a putative candidate surrogate disease marker for future therapeutic trials, which makes the determination of the true nature and pattern of peripheral nerve involvement even more important. Here, we confirmed the high prevalence (about 70%) of peripheral nerve involvement in ADCAs. Dying-back axonal neuronopathy was found in 29.6%, while neuronopathy was observed in 40.8% of patients.

Some findings deserve comment. Our SCA2 patients all had abnormalities compatible with sensory neuronopathy, mainly affecting the upper limbs. That the axonal neuronopathy in SCA2 preferentially affected the arms was already known, and it has been suggested that this most likely resulted from motor and sensory neuronopathy. The axonal neuronopathy in only one 72-year-old SCA6 patient may not represent disease-related polyneuropathy, but rather chronic idiopathic axonal polyneuropathy. Although the presence of axonal neuronopathy has been reported in SCA6, the fact that the sensory neuronopathy in SCA6 population was found to be significantly higher compared with the other SCA subtypes strengthens our idea that peripheral nerve involvement is not a prominent disease feature, if at all, in SCA6. There is accumulating evidence that SCA6 behaves differently from the other SCAs that carry a CAG repeat expansion.

In a previous study of 5 SCA7 patients, electrophysiologic abnormalities were not observed, while the 4 patients we studied all showed peripheral nerve involvement. Remarkably, some patients with electrophysiologically confirmed peripheral nerve involvement were found not to have any accompanying sign or symptom, suggesting that the peripheral nerve involvement is often mild and subclinical. The slow progression of disease may also contribute to this observation. In the ADCA patients studied here, neuronopathy and axonopathy were clinically almost indistinguishable, and in only 2 cases, weakness of predominantly proximal muscles provided a clue for a lower motor neuron lesion.

Neuropathologic examinations have revealed degenerative changes and reductions in the number of neurons in the anterior horns and/or dorsal root ganglia of patients with SCA1, SCA2, SCA3, and SCA7, and we are not aware of such findings in those with SCA6. Based on these observations, one would expect the peripheral nerve involvement to manifest as neuronopathy and not as a typical dying-back axonopathy.

On the other hand, recent studies on cell and animal models of polyQ diseases show that neuronal cell death is preceded by neuronal dysfunction that involves dendrites and axons. In this way, the presence of dying-back axonopathy is to be expected, with neuronopathy representing end-stage disease. However, the findings in SCA2 patients, in whom sensory neuronopathy was mainly observed in the upper extremities, argue against this sequence of events. We also did not observe a difference in disease duration between the neuronopathy and axonopathy groups.

In agreement with others, we hypothesize that the primary event in peripheral nerve involvement in ADCAs is dysfunction of motor neurons in the anterior horn and sensory neurons in the dorsal ganglions. This is supported by the fact that the primary site of degeneration in trinucleotide repeat expansion diseases is supposed to be nuclear. The dysfunction thus involves the soma itself but can then result in either motor and/or sensory neuronopathy or in length-dependent (dying-back) distal axonopathy. In which of these 2 downstream disease pathways the neuron finds itself is probably related to the SCA gene and gene product characteristics and to yet unidentified modifying genes or environmental factors. Such contributing factors might also explain the possible absence of peripheral nerve involvement in some patients.

We did not find any correlation between the sum of SNAPs and age and ataxia severity. Previously, the severity of axonal polyneuropathy in SCA3 patients was found to be related to age and not to CAG repeat length or disease duration. Moreover, in SCA3 patients, the CAG repeat was shown to be shorter in those with axonal neuropathy. Patients with SCA2 with a later age at onset (>40 years) and small CAG repeat expansions, both suggesting milder disease, were found to display more severe peripheral neuropathy. We recently reported an SCA3 family, carrying intermediate repeat expansions, with a syndrome encompassing restless legs, fasciculations, and sensorimotor axonal polyneuropathy. Apparently, peripheral nerve involvement, both neuronopathy and axonopathy, can be an early disease feature, can occur in patients with relatively small repeat expansions, and is not related to disease progression. This would suggest that the pathways resulting in dorsal root and anterior horn neuronal dysfunction differ from the disease mechanisms in the central nervous system, or that the vulnerability of the peripheral and central nervous system for polyQ toxicity differs.

Peripheral nerve involvement in SCA patients manifests not only as distal axonal neuropathy, but also as primary neuronopathy. Electrophysiologic studies in this group of patients that aim to examine additional peripheral nerve involvement should include nerve conduction studies of upper extremity nerves and EMG studies in proximal muscles to detect neuronopathy. One might argue that the distinction between axonopathy and neuronopathy is rather trivial in this group of diseases, but we believe that it is essential for understanding disease...
mechanisms and for the accurate evaluation and follow-up of patients with ADCA.

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Corresponding author: Bart P. C. van de Warrenburg, MD, University Medical Center Nijmegen, Department of Neurology, PO Box 9101, 6500 HB Nijmegen, the Netherlands (e-mail: b.vandewarrenburg@neuro.umcn.nl).


