The first chronic polyneuropathy with r

A patient that changed my practice

Chronic inflammatory demyelinating neuropathy patient to be treated with intravenous immunoglobulin

Marinus Vermeulen

Department of Neurology, Academic Medical Centre, University of Amsterdam, PO Box 22700, 1100 DE Amsterdam, the Netherlands; email: M.Vermeulen@amc.uva.nl

Practical Neurology, 2002, **2**, 354–357

After completing my neurological training my main field of interest was in cerebrovascular disorders. However, my practice changed in several ways in 1982 after I gave intravenous immunoglobulin (IVIg) to a 16-year-old boy with chronic inflammatory demyelinating polyneuropathy (CIDP) and he improved. Similar patients started to be referred to me and I began to see many types of peripheral neuropathy and so learned a lot about diseases of the peripheral nervous system in general, and the diagnostic strategies required to sort them out. That first patient undoubtedly had an impact on my whole neurological practice.

He had been admitted with a 2-month history of progressive weakness in his arms and legs, which became paralysed. There were no tendon reflexes apart from one depressed ankle reflex. There were no sensory signs, although he had some tingling in the hands and feet. Nerve conduction velocities were somewhat slow: 40 m/s in the peroneal nerve and 41 m/s in the median nerve. H-reflexes could not be elicited in the legs. In those days we did not look for conduction block and we had no neurophysiological criteria for demyelination. The demonstration of some slowing of conduction velocity was sufficient. The cerebrospinal fluid (CSF) protein was raised at 0.97 g/L. Sural nerve biopsy was performed because it was then the general view that before starting immunomodulating treatment the diagnosis had to be confirmed histopathologically. The biopsy showed demyelination and remyelination. We decided to treat him with fresh frozen plasma. The beneficial effects of this peculiar

treatment had been discovered in Rotterdam, where I was working at the time, by Professor Herman Busch and Andrew Maas, a neurosurgical resident. They had under their care a patient with CIDP who was being treated with plasma-exchange. One day the plasma-exchange machine was not working properly. Plasma from blood bank donors had been given but none had been removed, and yet the patient still had the same beneficial treatment response as was seen after plasma-exchange. This beneficial response to plasma infusion could be reproduced time and again. My patient also had a beneficial response to infusion of donor plasma. He did not respond to steroids. However, these infusions of plasma from bloodbank donors were not without the risk of transmitting viruses, for example hepatitis. At that time we were blissfully ignorant of the risk of HIV. Moreover, this treatment was labourious as 4 L of plasma had to be infused each week to maintain the improvements in the patient's condition. A year before, Imbach and colleagues had shown that patients with autoimmune thrombocytopenia may respond to donor plasma but they also demonstrated that the immunoglobulin fraction was the effective part (Imbach *et al.* 1981). The advantage of IVIg was, and still is, that much smaller volumes could be infused and the manufacturing procedure meant that the risk of transmitting viral diseases, even HIV as we appreciated later, was negligible. So I looked for some IVIg for administration to patients and found it at the Central Laboratory of the Dutch Red Cross, and treated my patient. He was probably the first neurological patient

Table 1 The final diagnosis in patients referred with chronic inflammatory demyelinating polyneuropathies in whom the diagnosis had to be changed

Chronic idiopathic axonal polyneuropathy (CIAP)
Hereditary motor and sensory neuropathy type 1
X-linked hereditary motor and sensory neuropathies
Hereditary liability to pressure palsies
POEMS syndrome
X-linked adrenoleucodystrophy
Diabetic plexopathy
Radiation plexopathy
Hypothyroidism
Amiodarone polyneuropathy
Non-systemic vasculitic neuropathy
Motor neurone disease
Tumour of the filum terminale

treated in this way, but I have heard that at approximately the same time a patient in Germany with myasthenia gravis was given IVIg.

The effects of IVIg impressed me and many of my Dutch colleagues. As a result, a lot of patients in the Netherlands were enthusiastically treated in those days with IVIg but often with less than impressive, or no results at all. Many of these ‘unresponsive’ patients were then referred to me with the questions ‘why have they not responded, and should a nerve biopsy be performed to confirm the diagnosis?’. Often the explanation was that the patients did not have CIDP at all, but other diagnoses, and doubts about the need for nerve biopsy began to arise.

Table 1 shows the final diagnosis in patients treated with IVIg and who were referred to me with the diagnosis of CIDP. The most frequent diagnosis in patients who did not respond was chronic idiopathic axonal polyneuropathy (CIAP), an entity which I later learnt to recognize from the work of my Dutch colleagues in Utrecht. It is a chronic axonal neuropathy. There should be no family history of hereditary neuropathies, and in pure sensory neuropathies, malignancies should be considered. CIAP has a mean age of onset of 60 years. Both sensory and motor symptoms are present but the sensory symptoms predominate at onset. Motor abnormalities are often only demonstrable at neurophysiological investigation. Usually both large and small fibres are affected leading to tingling, numbness or burning pains. This neuropathy may start asymmetrically but soon there is a symmetrical diminished sense of touch and vibration, and of proprioception. The sensory disturbances de-

velop first in the toes and extend to the feet and the lower legs in a stocking-like distribution. Late in the course the fingers and hands may become involved. Weakness, if present, starts in the toe extensors followed by ankle dorsiflexors and may extend later to the ankle flexors and intrinsic hand muscles. Tendon reflexes are diminished or absent in a distal to proximal distribution. In all patients the clinical features are slowly progressive but they do not lead to severe disability. We do not know the cause of this neuropathy but we do know the course so we may now reassure patients that they will not become wheelchair dependent. Repeated examinations in typical cases are not necessary, as a hidden cause for the neuropathy will not emerge.

The clinical signs and symptoms of CIDP are quite different from CIAP (Hughes 2002). In CIDP the signs are rarely confined to the feet and lower legs and there is usually impairment both distally and proximally in the legs and arms. Tendon reflexes are usually absent in the arms, which is rare in CIAP. Why then were patients with CIAP referred to me with the diagnosis CIDP? The answer is because more emphasis had been placed on the neurophysiological investigations than on the history and physical examination. Also we had no neurophysiological criteria for demyelination. Most patients with CIAP who were referred with the diagnosis of CIDP had small compound muscle action potentials (CMAPs) after stimulation of the peroneal nerves. These small CMAPs are explained by axonal loss. If fast conducting fibres are lost, nerve conduction velocities will decrease. Considerable decreases in conduction velocities can be seen when the CMAPs are less than 1 mV if measured from peak to peak, or less than 0.5 mV if measured from peak to baseline. These conduction velocities can easily be within the range seen in demyelinating neuropathies. So when the reports of the neurophysiological studies mentioned slow conduction velocities consistent with demyelination, the jump to CIDP was easily made – the patient must have an acquired neuropathy, without a cause, which was chronic and demyelinating.

Over the years several neurophysiological criteria for demyelination have been described. These cannot be used to *diagnose* CIDP but what these criteria do is increase or decrease the probability of the diagnosis.

The way in which a diagnostic test changes the probability of the diagnosis depends on the characteristics of the test. To determine these

characteristics, first the sensitivity and specificity of the test have to be calculated, followed by likelihood ratios after either a positive or a negative test result. The positive likelihood ratio refers to the odds of a positive diagnostic test in patients with CIDP compared with patients without CIDP. The negative likelihood ratio reflects the odds of a negative test result. Of all the neurophysiological criteria, those of the ad hoc subcommittee appear to be the most helpful in the diagnosis of CIDP (Molenaar *et al.* 2002). Table 2 shows how the probability of the diagnosis of CIDP changes according to the neurophysiological test results. If, on the basis of the history and physical examination the probability of the diagnosis of CIDP seems to be low, but the neurophysiological criteria for demyelination are fulfilled, the diagnosis CIDP becomes very likely. In Table 2, I have set the pretest probability at 8% as this was the percentage of patients with a demyelinating neuropathy in a group of patients presenting with signs and symptoms suggesting a chronic polyneuropathy. If, however, the clinical features indicate a high probability of the diagnosis of CIDP, but the neurophysiological results are not consistent with demyelination, the diagnosis CIDP should not be changed as the probability of CIDP is still considerable.

In medicine, biopsy results have a special status, probably because they show pathology and we are accustomed to pathologists having the last word. But what I have learned is that sural nerve biopsy should be considered as a diagnostic test just like any other diagnostic test. Biopsies have to be taken at the right place, the right stains have to be used and intra- and interobserver variability may be substantial. The diagnostic value of sural nerve biopsy in the diagnosis CIDP has been investigated and appears to be very disappointing (Molenaar *et al.* 1998). The strongest predictors of CIDP are neurophysiological tests and a very raised CSF protein concentration (> 1 g/L) (Table 3). Sural nerve biopsy is the most invasive test of all the tests for a peripheral neuropathy and should therefore be considered only after the results of the other tests are known. Because the other tests have much better characteristics than sural nerve biopsy it is unlikely that this test provides any additional diagnostic value. Indeed, in a logistic regression model sural nerve biopsy had no independent predictive value. Moreover, when all the data from a group of 64 patients were presented to me, I could distinguish between patients with and without CIDP, irre-

Table 2 The probability of a correct diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) in patients fulfilling or not fulfilling the neurophysiological criteria for demyelination of the ad hoc subcommittee

A PRIORI	AFTER POSITIVE TEST RESULT	AFTER NEGATIVE TEST RESULT
8% ($P = 0.08$)	71%	4%
80% ($P = 0.8$)	99%	64%

Probability of CIDP is calculated after a positive and negative test result. The a priori probability (P) is converted to the a priori odds (a priori odds = $P/1-P$). The a priori odds are multiplied by the odds of a positive or negative test result in patients with CIDP compared to those without. The post test odds is converted back to a post test probability by dividing it by itself plus 1.

Table 3 The diagnostic value of tests in chronic inflammatory demyelinating polyneuropathy (CIDP)

CLINICAL FEATURE	ODDS RATIO	P-VALUE
Neurophysiological studies consistent with CIDP	62	0.002
Raised CSF protein concentration (> 1 g/L)	58	0.01
Raised CSF protein concentration (0.5–1.0 g/L)	9	0.11
Sural nerve biopsy consistent with CIDP	2	0.42

The features were entered into a logistic model to identify all significant features. These significant features were entered into a second model. The effect sizes of both were expressed as odds ratios. The odds ratio approximates to how much more likely CIDP is among patients with the characteristic of interest than among patients without.

spective of the biopsy result. Therefore, sural nerve biopsy has no value in clinical practice in confirming the diagnosis CIDP before embarking on immunosuppressive treatment.

When patients with CIDP respond to treatment with IVIg, it still impresses me as much as when I saw it for the first time in 1982. Equally impressive has been to learn that biopsy to demonstrate the histopathology of the disease is the weakest of all the tests in CIDP, while I was taught that we should see the pathology before starting immunosuppressive treatment.

The picture was supplied by the patient.

REFERENCES

- Imbach P, Barandun S, d'Appuzzo U *et al.* (1981) High dose intravenous gamma-globulin for idiopathic thrombocytopenic purpura in childhood. *Lancet*, 1228–31.
- Molenaar DSM, Vermeulen M & de Haan RJ (1998) Diagnostic value of sural nerve biopsy in chronic inflammatory demyelinating polyneuropathy. *Journal of Neurology, Neurosurgery and Psychiatry*, **64**, 84–9.
- Molenaar DSM, Vermeulen M & de Haan RJ (2002) Comparison of electrodiagnostic criteria for demyelination in patients with chronic inflammatory demyelinating polyneuropathy (CIDP). *Journal of Neurology*, **249**, 400–3.
- Hughes R (2002) Article title. *Practical Neurology*, **2**, 000–000.