Abstract

Distal acquired demyelinating symmetric (DADS) neuropathy is clinically characterised by distal motor and sensory disturbances. Typically DADS does not respond or responds poorly to intravenous immunoglobulins (IV Ig). We report the case of a 58-year-old patient who developed distal paraparesis. Serum electrophoresis demonstrated monoclonal IgM paraproteinemia having an anti-GM1 but no anti-MAG activity. Conduction velocities showed demyelinating pattern. Work-up excluded a lymphoproliferative disorder. After IV Ig treatment we observed a clinical and neurophysiological improvement.

Regarding these peculiar findings, we suggest that DADS needs to be splitted in several forms determined among others by clinical, neurophysiological and anti-ganglioside profile and therapeutic response. We advocate to perform systematic antiganglioside antibodies assay additionnaly to anti-MAG when DADS is suspected in order to improve dysimmune neuropathies classification.

Key words: Distal acquired demyelinating symmetric neuropathy; anti-GM1 antibodies; dysimmune neuropathy; paraproteinemia; chronic inflammatory demyelinating polynueuropathy.

Introduction

Distal acquired demyelinating symmetric (DADS) neuropathy is clinically characterized by distal sensory and motor disturbances Sensory predominance and restriction of muscle weakness to distal muscles differentiate DADS from chronic inflammatory demyelinating polyneuropathy (CIDP) (Katz et al., 2000).

Electrophysiological measurements indicate demyelination but conduction blocks are rare. IgM (kappa chain) with anti-myelin associated glycoprotein (anti-MAG) activity is present in 50 to 70% (Saperstein et al., 2001).

Typically DADS does not respond to steroids, occasionally to plasma exchange (PE) and incompletely to intravenous immunoglobulins (IVIg) or to agents like chemotherapeutic drugs that lower IgM titers (Katz et al., 2000; Saperstein et al., 2001).

DADS without IgM monoclonal protein (M-protein) readily respond to treatment (steroids, PE, or IVIg) (Katz et al., 2000).

We report an atypical DADS case disclosing an anti-GM1 antigenicity, unusual neurophysiological findings and good response to IVIg.

Case history

A 58 year-old-male patient without past medical history developed over years distal paraparesis and cramps. Neurological examination showed distal amyotrophy, hammertoes and pes cavus (Fig. 1A).
Before IV Ig treatment, based on American Academy of Neurology criteria, we observe demyelination, including focal signs, on several nerves. Sensory responses are also abnormal. After IV Ig treatment, distal CMAP amplitudes and areas on right peroneal, ulnar and median and on left ulnar nerves are improved. Partial decrease of temporal dispersion on right median nerve is demonstrated.

Table 1: Nerve conduction study findings

<table>
<thead>
<tr>
<th>Nerve (Site of recording)</th>
<th>Site of stimulation</th>
<th>Nerve conduction velocity (m/s)</th>
<th>Distal latency (ms)</th>
<th>Amplitude (% of LLN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median R (ABR)</td>
<td>WR</td>
<td>4.0 (158.8%)</td>
<td>3.1 (66.7%)</td>
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Abbreviations:
- NCV: nerve conduction velocity
- LLN: lower limit of normal
- ULN: upper limit of normal
- ADL: abductor digiti minimi
- AAB: abductor hallucis
- AFB: above fibular head
- ABE: above elbow
- ABH: abductor hallucis
- AEB: above elbow
- AHR: above humeral head
- AEP: above elbow
- ARH: above radial head
- AFA: above fibular head
- AFE: above elbow
- ALR: above lateral head
- AFH: above fibular head
- AFB: below fibular head
- ABE: below elbow
- AEB: below elbow
- ARH: below radial head
- ALR: below lateral head
- LLN: lower limit of normal
- ULN: upper limit of normal
- NP: not performed
- NR: no response

Demyelinating values are shown in red underlined.

Improved parameters (>25%) after IV Ig are shown in grey.

Table 1: Nerve conduction study findings
Distal strength, pallesthesia and ankle reflexes were decreased. No proximal weakness was found. Nerve conduction studies are summarized in table 1.

Type 1 a Charcot-Marie-Tooth was excluded. Blood tests (renal function, glycaemia, thyroid tests, antinuclear antibody, antineutrophil cytoplasmic antibody, B and C hepatitis, HIV and Borrelia Burgdorferi,...) were unremarkable. Serum immunoelectrophoresis disclosed a monoclonal IgM kappa paraproteimemia (titer of 383 mg/100 ml; N: 40-250).

A lymphoproliferative disorder was excluded. Anti-MAG antibodies were negative. IgM anti-GM1 and anti-GM2 antibodies were positive: up to 1/12500 (N < 1/500) (no Ig G antigenicity) (negative assay for anti-GM3, GA1, GD1a, GD1b, GT1b, GQ1b, GD3, sulphatides and globosides IgM and IgG except anti-sulphatide IgM: 1/3000: N < 1/10000). CSF cell count and glucose level was normal with moderate protein level elevation (79 mg/dL – N < 45). Over two and a half years, walking condition worsened. Initially he was treated with methylprednisolone (1 mg/kg/day followed by 0.5 mg/kg/day: for three months). We observed a recovery of ankle reflexes but no functional improvement. He developed side effects due to steroids which led us to stop the treatment. Initial IV Ig treatment (2 g/kg given in five days followed by maintenance cures of 0.4 g/kg per day every four weeks) provided a satisfactory response after ten months: recovery of hallux extension, ankle reflexes and improvement of feet extension. New neurophysiological examination 10 months after first infusion showed significant improvement (Table 1).

Discussion

Antiganglioside antibodies are associated with chronic demyelinating neuropathies and IgM monoclonal gammopathy (Pestronk et al., 2005). Anti-GM1 antibodies are frequently associated with multifocal motor neuropathy (MMN) and may be associated with CIDP (Saperstein et al., 2001; Willison, 2002; Kyle et al., 2005; Pestronk et al., 2005).

Anti-GM1 activity was never reported in DADS. In contrast to CIDP, DADS is characterized by a predominantly sensory symmetric distal involvement.

The role of anti-GM2 antibodies mainly described in Guillaum-Barré syndrome related to Cytomegalovirus is unclear in chronic neuropathies (Willison et al., 2002; Pestronk et al., 2005). Cross-reactivity with anti-GM1 is known (Willison et al., 2002).

Saperstein et al distinguish CIDP associated with MGUS and DADS. One of the distinctive features is the presence of IgG or IgA in MGUS-CIDP and IgM in DADS (Katz et al., 2000; Saperstein et al., 2001). They consider these entities as different CIDP variants. In most DADS cases, IgM kappa paraproteimemia is found (Saperstein et al., 2001). Presence of monoclonal IgM kappa defines “DADS-M” which represents roughly two-thirds of DADS (Katz et al., 2000; Saperstein et al., 2001). DADS-M is described with predominant sensory symptoms (Saperstein et al., 2001). “DADS-I” (idiopathic, without paraproteimemia) is characterized by a purely sensory neuropathy (Saperstein et al., 2001). The latter has a better response to treatment. Formal distinction between DADS-I and CIDP remains to be determined and has practically minimal implications on clinical management (Katz et al., 2000; Saperstein et al., 2001). We considered the diagnosis of DADS because of exclusive distal and symmetric involvement (Katz et al., 2000) and presence of IgM paraproteimemia (Saperstein et al., 2001; Koski et al., 2009). To the best of our knowledge, this is the first case of DADS with anti-GM1 antigenicity. Predominant motor symptoms, presence of focal demyelinating features, anti-GM1 antibodies and favourable therapeutic response to IV Ig characterize the unusual presentation of DADS in this patient.

We advocate that an anti-GM1 antibody assay may be useful in demyelinating neuropathies with a clinical pattern of DADS. It could provide helpful information about pathophysiology, therapeutic response, prognosis and improve our current classifications. Our observation may suggest that DADS-M should be subdivided into two variants: the “classical sensory variant” (predominantly sensory, without focal demyelinating features and with anti-MAG antibodies); the “atypical motor variant” (predominantly motor, with focal demyelinating features, anti-GM1 antibodies and better response to treatment). It is generally agreed that DADS and IgM MGUS associated neuropathies poorly respond to IV Ig (Finsterer, 2005). Our observation suggests that this assertion has to be taken with caution and warrants future research.

Conclusions

This case illustrates the difficulty to clearly differentiate CIDP and DADS and underlines the need for an improvement of the current classification of demyelinating neuropathies. Systematic research for anti-GM1 and anti-GM2 anti-ganglioside antibodies may lead to a better classification of DADS entity and help to identify patients susceptible to respond to IV Ig treatment.
REFERENCES


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