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Short Communication

Acute-onset chronic inflammatory demyelinating polyneuropathy with anti-neurofascin-155 antibodies and bilateral facial nerve enhancement

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ABSTRACT

A 26-year-old female presented with acute onset distal paraparesis, upper limb tremor and bilateral facial palsy. Neurophysiology revealed a sensorimotor demyelinating polyneuropathy and lumbar puncture revealed an albuminocytologic dissociation. Neuroaxis MRI revealed bilateral facial nerve and cauda equina enhancement. Initially diagnosed as Guillain-Barré Syndrome, poor response to intravenous immunoglobulin, persistent deterioration, anti-neurofascin-155 antibodies and clinical response to steroid therapy led to diagnosis of acute-onset chronic inflammatory demyelinating polyneuropathy (CIDP). CIDP patients with anti-neurofascin-155 antibodies are younger, with distal predominant weakness, tremor, and poor response to intravenous immunoglobulin. Up to 16% can present acutely, however bilateral facial weakness is rare.

1. Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is by definition slowly progressive usually during a period of at least 8 weeks (Bunschoten et al., 2019) (Lehmann et al., 2019). Afterwards, there can be a relapsing-remitting, progressive, or monophasic course. However, in certain patients, the early phase can be remarkably acute, with a rapid progressive weakness reminiscent of Guillain-Barré syndrome (GBS), so-called acute-onset CIDP (A-CIDP). It has been reported that as high as 16% of CIDP patients can present as A-CIDP (Dionne et al., 2010). On the other hand, up to 16% of patients with GBS can have treatment related fluctuations (TRFs), which are defined as one or more deteriorations after initial improvement with appropriate therapy (McCombe and Pollard, 1989) (Ruts et al., 2005).

Previous attempts to clarify clinical and electrophysiological features which can accurately differentiate A-CIDP from GBS with TRFs have shown that A-CIDP should be suspected when a patient with GBS deteriorates after 9 weeks from onset or when deterioration occurs at least three times (Ruts et al., 2005) (Kleyweg and Van Der Meche, 1991). Also, A-CIDP patients seem to be more likely to have prominent sensory signs and less likely to have autonomic involvement, facial weakness, preceding infections, or need for mechanical ventilation (Dionne et al., 2010). Facial weakness particularly seems to be more common in GBS when compared to CIDP, although neurophysiological studies have shown that there seems to be a substantial subclinical facial neuropathy in CIDP patients (Kokubun and Hirata, 2007) (Varela and Rubin, 2009).

2. Case report

We present the case of a 26-year-old female patient with no previous relevant history, who presented to the Neurology outpatient clinic with a 3-week history of lower limb distal weakness, with progressive gait disturbance, and no other abnormalities, although she reported upper limb rapid postural tremor since the previous year. She reported a sudden onset of lower limb weakness while walking, and had noted difficulty with some facial expressions. At her first evaluation, her neurological examination was remarkable for a slight bilateral weakness of hip flexion (MRC scale 3/5), foot plantar flexion (MRC scale 3/5) and difficulty with toe walking. There was no sensory or tendon reflex changes nor sphincter disturbances but she had bilateral peripheral facial weakness. Following a normal head CT-scan, and

Abbreviations: A-CIDP, acute-CIDP; AH, adductor hallucis; APB, abductor pollicis brevis; CIDP, Chronic Inflammatory Demyelinating Polyneuropathy; EDB, extensor digitorum brevis; GBS, Guillain-Barré Syndrome; IVIg, intravenous immunoglobulin; MRC, Medical Research Council; MRI, magnetic resonance imaging; NF155, Neurofascin-155; TRF, treatment related fluctuation

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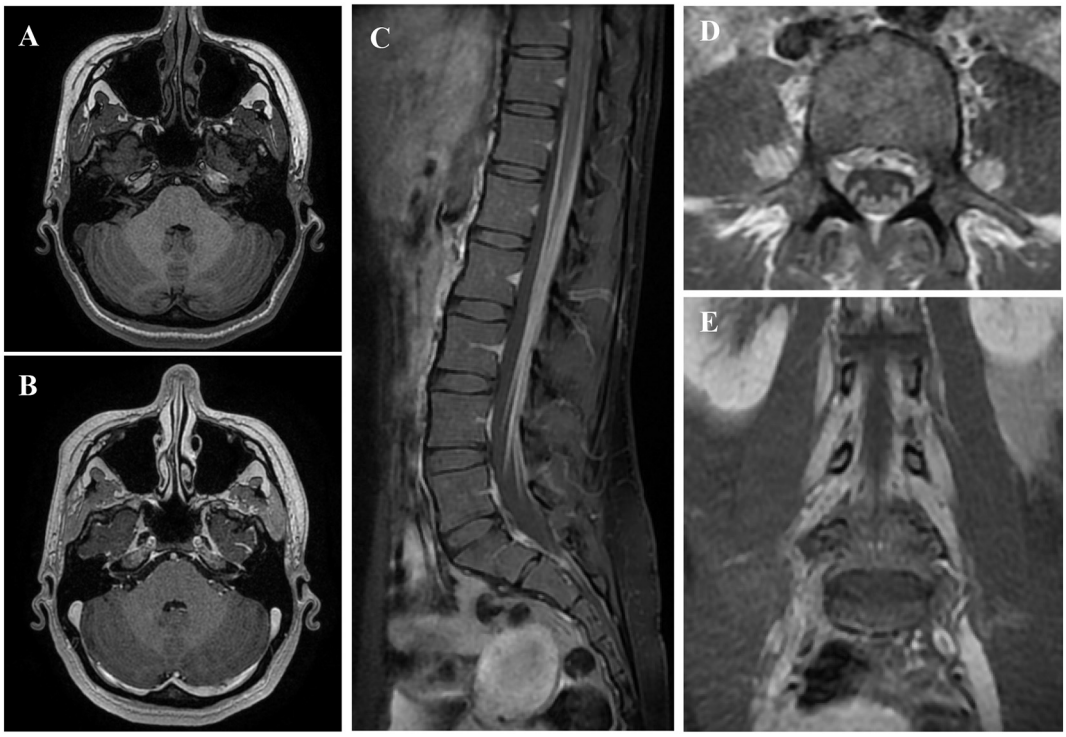

Fig. 1. Magnetic resonance findings: Brain T1 weighted axial images, before (A) and after (B) contrast injection, showing bilateral enhancement of both facial nerves, in the distal intracanalar portion; Lumbar T1 weighted sagittal (C), axial (D) and coronal (E) images with fat suppression after contrast injection showing diffuse thickening and enhancement of the cauda equina and the lumbar roots.

considering the possibility of an acute inflammatory polyneuropathy she underwent a lumbar puncture which revealed an albuminocytologic dissociation with marked hyperproteinorrachia of 667 mg/dL (normal under 45 mg/dL) and 1 cell/μl. Her nerve conduction studies were remarkable for widespread sensorimotor findings of conduction slowing, with a sural sparing pattern, suggestive of a demyelinating polyneuropathy, whereas needle electromyography showed axonal loss and acute denervation of the lower limbs. Additionally, her MRI revealed bilateral facial nerve enhancement as well as enhancement and nerve root enlargement of the cauda equina (Fig. 1). Given the acute presentation, with bilateral facial palsy, facial nerve enhancement, demyelinating polyneuropathy and albuminocytologic dissociation, she was considered to have an acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome), and started intravenous immunoglobulin (IVIg) 400 mg/Kg/day for 5 days, and she started motor rehabilitation. As there was a positive response to intravenous therapy and motor rehabilitation, she was subsequently discharged to outpatient care and was reevaluated 3 months after discharge. At this time there had been progressive worsening of her distal strength and her neurological examination was remarkable for a bilateral weakness of hip flexion (MRC scale 3/5), knee flexion (4/5), foot dorsiflexion and plantar flexion (MRC scale 2/5). Now there was widespread areflexia and lower limb sensory ataxia, despite no sensory changes. There was still a bilateral peripheral facial palsy with perioral fasciculations. Considering the clinical deterioration following an improvement with IVIg therapy, a treatment related fluctuation was considered and she was re-admitted. A second set of nerve conduction studies (Table 1) confirmed a demyelinating polyneuropathy. She repeated the lumbar puncture which again revealed albuminocytologic dissociation (443 mg/dL of protein content and 3 cells/μl), as well as brain and lumbar MRI which kept showing facial and cauda equina nerve enhancement. She was started on IVIg again (400 mg/Kg/day for another 5 days) as well as motor rehabilitation, however this time without any clinically relevant improvement. Given her progressive worsening, the diagnosis of CIDP was considered and she was started on oral steroid therapy (1 mg/Kg/day) after an initial treatment with intravenous Methylprednisolone 1 g/day for 3 days. There was a significant motor improvement, and she remained clinically stable under oral steroid therapy which was successively weaned down to 2.5 mg every other day. At this time there was a relapse with progressive distal motor weakness and steroids were increased again up to 0.5 mg/Kg/day and she started azathioprine in an increasing dose up to 1.5 mg/Kg/day, again with positive clinical response. Given the clinical presentation with acute-onset, motor predominant involvement, upper limb tremor and limited response to IVIg, we measured her IgG anti-Neurofascin 155 (NF155) antibodies which were positive, using a commercially available cell-based indirect immunofluorescence assay (Mathey et al., 2017). As of now, three years from onset, she has been successfully weaned from steroid therapy and is clinically stable, although with a persistent distal motor weakness of the lower limbs.

3. Discussion

Our case highlights the most distinctive aspects that should lead the clinician to suspect of anti-NF155 related CIDP. Furthermore, we show that anti-NF155 related CIDP might present as GBS, so a high level of suspicion is required. In our patient, the search for anti-NF155 antibodies was delayed due to the initial GBS-like clinical picture, and the treatment with steroids was postponed until the 8th week of deterioration. If found positive earlier in the disease course, the patient might have started therapy with steroids earlier.

Our patient is remarkable not only for the acute onset, motor predominant presentation and tremor, but also for her sustained cranial and lumbar nerve enhancement, a finding rarely reported in CIDP and more often associated with GBS, which actually led to initial misdiagnosis as GBS. The multiple clinical deteriorations following treatment with IVIg prompted us to consider the possibility of A-CIDP, and the coexistence of tremor and poor response to IVIg led us to consider NF-155 antibody associated CIDP (Bunschoten et al., 2019) (Lehmann et al., 2019) (Ogata et al., 2015). The positive response to steroid

Table 1
Nerve conduction study performed at the time of the first relapse[a].

Motor nerves	Onset latency (ms)			Amplitude (mV)			Conduction velocity (m/s)		
	Right	Left	Ref.	Right	Left	Ref.	Right	Left	Ref.
Median (APB)									
Wrist	**5.0**	**5.7**	≤ 3.9	14.5	11.1	≥ 4			
Elbow	9.4	9.4		11.9	12.5		**45.5**	54.8	> 49
Ulnar (ADM)									
Wrist	**5.0**	**3.8**	≤ 3.3	14.6	7.9	≥ 6			
Below-elbow	9.4	7.6		11.9	6.0		**45.5**	**47.4**	> 49
Above-elbow	12.4	10		12.6	5.9		56.7	**32.0**	
Common peroneal (EDB)									
Ankle	**9.9**	NT	≤ 6.5	**0.1**	NT	≥ 2.4			
Fibular head	**19.0**			**0.1**			**30.1**	NT	> 44
Tibial (AH)									
Malleolus	NR	NR	≤ 5.8	NR	NR	≥ 4	NR	NR	> 40
Facial (nasalis)									
Ear	4.2	NT		0.4	NT		NT	NT	> 40
Sensory nerves (Antidromic)	Peak latency (ms)			Amplitude (uV)			Conduction velocity (m/s)		
	Right	Left	Ref.	Right	Left	Ref.	Right	Left	Ref.
Median (digit II)									
Wrist	**5.7**	**4.3**	≤ 4.0	**8.5**	**13**	≥ 20	**24.4**	**32.3**	> 49
Ulnar (digit V)									
Wrist	**4.9**	**4.8**	≤ 4.0	**13.0**	**8.3**	≥ 17	**26.4**	**31.8**	> 49
Sural (lateral malleolus)									
Calf	4.1	4.0	≤ 4.5	15.3	17	≥ 6	**40.0**	54.8	> 39
Superficial peroneal (Dorsum foot)									
Leg	NR	NR	≤ 4.2	NR	NR	≥ 6	NR	NR	> 39
F-waves	Latency (ms) - mean (min-max)								
	Right			Left			Reference		
Median (APB)	38.9 (37–30.1)			38.4 (37.3–40)			≤ 31		
Ulnar (ADM)	36.4 (35.7–38.7)			44.1 (40–46.7)			≤ 32		
Peroneal (EDB)	NR			NR			≤ 56		
Tibial (AH)	NR			NR			≤ 56		

Bold items represent abnormal values.
[a] AH, adductor hallucis; APB, abductor pollicis brevis; EDB, extensor digitorum brevis; NR, no response; NT, not tested; Ref., Reference values.

therapy further reinforced the hypothesis of CIDP as opposed to GBS.

In general, patients with CIDP seldom present with bilateral facial (or other cranial) nerve enhancement, however magnetic resonance imaging (MRI) in CIDP patients can present with hypertrophy and contrast enhancement of cervical roots, brachial and/or lumbar plexus (Duggins et al., 1999) (Inoue et al., 2004) (Ogata et al., 2015). Anti-NF155 antibodies have been reported in a subgroup of CIDP patients who present at younger ages, with predominant distal involvement of the limbs, ataxia and postural and intention tremor, some of them with an acute rapid progressive course which can be mistakenly classified as GBS (Ogata et al., 2015) (Querol et al., 2014) (Devaux et al., 2016) (Garg et al., 2018), which are all features present in this patient. More recently, hypertrophy of cranial nerves has also been highlighted as a further distinctive aspect of CIDP with anti-NF155 antibodies (Franques et al., 2017) and in fact facial palsy has been previously reported as a possible, albeit infrequent (15.4%), feature of NF155-associated CIDP (Ogata et al., 2015), however the bilateral aspect has not been specified. Clinicians should be aware that a subgroup of CIDP patients can present with typical features of GBS, and cranial nerve, and facial nerve in particular, enhancement does not exclude a CIDP diagnosis. Positive IgG anti-NF155 antibodies further strengthen the diagnosis of CIDP and despite a poor response to IVIg these patients can have a good response to steroid therapy (as opposed to GBS) or other more aggressive immunotherapies such as Rituximab (Garg et al., 2018) (Ogata et al., 2015) (Devaux et al., 2016).

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Roles of authors

Dr. Caetano was involved in patient care, literature review, and manuscript preparation. Dr. Ladeira was involved in patient care and manuscript preparation. Dr. Fernandes was involved in patient care and manuscript preparation. Dr. Pires was involved in patient care and manuscript revision. Dr. Medeiros was involved in patient care and manuscript revision.

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