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LETTER TO THE EDITOR

Fampridine improves acute optic neuritis contributing to a long-lasting recovery of nerve function

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Dear Editor,

Inflammatory optic neuropathy, or optic neuritis (ON), is the most common cause of optic nerve injury in young adults and has multiple etiologies, including demyelinating, infectious, and autoimmune causes. The current management of acute ON is mainly focused on expediting visual recovery using high-dose intravenous corticosteroids that have often an insufficient action on vision improvement and cannot prevent retinal loss or optic atrophy [1]. We present two cases of acute ON who achieved a sudden progress of visual function that persisted after 1 month of treatment with PR-fampridine. PR-fampridine, an extended-release formulation of 4-aminopyridine, is a broad-spectrum voltage-dependent potassium channel blocker, currently approved for symptomatic treatment of multiple sclerosis walking disability [2]. Several studies have suggested its possible neuroprotective effects when administered continuously after long-term inflammatory ON, but its use in the acute phase has not previously been described [3].

Case 1

A 50-year-old Caucasian woman was admitted to the Neurological Unit for the subacute onset of fatigue, bilateral orbital pain, and visual disturbances that started 7 days before. The ophthalmological assessment at the onset (O) is reported in Table 1. When hospitalized, her neurological status was normal except for bilateral visual disturbances and a global increase of deep tendon reflexes. The patient underwent contrast-enhanced cerebral MRI showing enlargement and focal contrast enhancement involving the bilateral optic nerve sheath. The medullary MRI visualized multiple T2 hyperintense lesions extending from the 7th cervical to the 3rd thoracic vertebrae, each shorter than three metamers, not fulfilling the criteria for longitudinally extended transverse myelitis (LETM). Lumbar puncture revealed mildly increased protein level (0.5 g/l; normal range: 0.15–0.4 g/l) and white cell count (30 cells/mmc, mostly lymphocytes) with normal glucose. Oligoclonal bands (OB) were not found in the CSF. Cytology at that time was negative for neoplastic cells as well as serum antibodies except for the aquaporin-4 (NMO IgG) ones that were subsequently found to be positive. Based on these findings, inflammatory bilateral ON associated with NMO spectrum disorder was diagnosed. The patient was initially treated with intravenous methylprednisolone 1 g/day for 5 days, without improvement of vision (Snellen Visual Acuity, SVA, of 0.3 in her right and left eyes) (Table 1, PRE).

While waiting to start with alternative standardized rescue treatments such as plasma exchange (PLEX) or intravenous immunoglobulin (IVIg) [1], delayed owing to the ongoing SarsCov2 pandemic, patient continued complaining of persistent and profound fatigue. Thus, we chose to prescribe oral PR-fampridine 20 mg/day for its longstanding use as symptomatic in several neurological diseases and informed consent was obtained from the patient for this unconventional off-label strategy [2, 3]. Immediately, the

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Table 1 Ophthalmological findings of the two cases treated with PR-fampridine

	Case 1 right eye			Case 1 left eye			Case 2 left eye			NV*
	O	PRE	POST	O	PRE	POST	O	PRE	POST	
SVA	*0.3*	*0.3*	1.0	*0.3*	*0.3*	1.0	*0.3*	*0.3*	*0.9*	1.0
CP	*1/22*	*1/22*	*20/22*	*1/22*	*1/22*	*20/22*	*1/22*	*1/22*	*19/22*	22/22
GVF	*GC/CS*	*GC/CS*	*Reduced GC Absence CS*	*GC/CS*	*GC/CS*	*Reduced GC Absence CS*	—-	—-	—-	
HFA MD	—-	—-	—-	—-	—-	—-	*-4.68*	*-5.02*	-0.76	> −2
60′ VEP IT	*173*	*178*	*123*	*170*	*169*	*121*	98	97	100	< 107.25
60′ VEP A	*6.8*	*6.2*	*6.9*	*5.3*	*4.8*	*6.5*	9.38	9.14	9.51	> 8.67
60′ PERG IT	49	50	53	51	52	50	51	49	52	< 53.42
60′ PERG A	2.36	2.52	2.48	2.30	2.48	2.63	2.58	2.76	2.66	> 2.22
15′ VEP IT	*171*	*179*	*122*	*157*	*166*	*124*	*148*	*151*	*114*	< 111.32
15′ VEP A	*6.2*	*6.6*	*10.7*	*5.4*	*4.8*	*8.3*	*7.46*	*7.31*	9.65	> 7.90
15′ PERG IT	51	52	52	51	52	51	52	50	55	< 55.28
15′ PERG A	2.36	2.24	2.56	2.23	2.34	2.43	2.62	2.47	2.40	> 2.18
ONH	No PL No CU	No PL No CU	No PL No CU	No PL No CU	No PL No CU	No PL No CU	No PL No CU	No PL No CU	No PL No CU	No PL No CU

NV, normal values. *O*, observation at onset of visual symptoms; *PRE*, observation before treatment with PR-fampridine; *POST*, observation after treatment with PR-fampridine; *SVA*, Snellen Visual Acuity; *CP*, chromatic perception by Ishihara Tables; *GVF*, kinetic Goldmann visual field; *GC*, generalized constriction; *CS*, central scotoma; *HFA*, Humphrey Field Analyzer 30–2 strategy; *MD*, mean deviation (dB); *VEP*, visual evoked potentials; *IT*, P100 implicit time (msec); *A*, N75-P100 amplitude (microvolt); *PERG*, pattern electroretinogram; *IT*, P50 implicit time (msec); *A*, P50-N95 amplitude (microvolt); 60′ and 15′, visual stimuli checks subtending 60 and 15 min of visual arc; *ONH*, optic nerve head morphology at the ophthalmoscopy; *PL*, sectorial or diffuse pallor; *CU*, disc cupping. Abnormal values are reported in *italics*

patient began to refer a rapid, progressive, and unexpected improvement of her visual symptoms. On day 30 of PR-fampridine treatment, an improvement of SVA, Goldmann visual field (GVF), chromatic perception, visual evoked potentials (VEP), and pattern electroretinogram (PERG) responses were detected (Table 1, POST). The recovery of each parameter of visual function was then maintained over time up to the subsequent evaluation 1 month after the end of PR-fampridine treatment.

Case 2

A 30-year-old migraineur woman was admitted to the Headache Center for a 1-week history of referred reduction of color vision and blurred vision in her left eye. Besides, she reported mild retro-orbital pain and floaters on the same side in association with chronic fatigue. The ophthalmological findings at the onset (O) are reported in Table 1. At the neurological admission, brain and spine MRI showed only one lesion in the left optical radiation with contrast enhancement. Biochemistry, coagulation results, and autoimmune screening were unremarkable. Oligoclonal bands were found on CSF analysis but not in serum suggesting intrathecal immune response. A diagnosis of single unilateral ON/clinically isolated syndrome was done, but not of MS according to the 2017 McDonald Criteria. Similarly to case 1, no changes of visual deficit were noted after intravenous methylprednisolone at the dose of 1 g/day for 5 days (Table 1, PRE; Fig. 1A). Since the patient complained of weakness and visual fatigue, we proposed oral PR-fampridine 20 mg/day as symptomatic off-label therapy before deciding to administer more standardized rescue treatment of acute steroid-refractory ON [1–3]. Informed consent was obtained from the patient, and surprisingly, she experienced visual benefits already after 2 days of PR-fampridine intake. On day 30, a significant improvement of all parameters of visual function was observed at the ophthalmological evaluation (Table 1, POST; Fig. 1B) and this recovery was maintained 1 month after the end of PR-fampridine treatment.

Discussion

In these two cases of acute ONs, we reported that PR-fampridine may be a potential add-on therapeutic option with an early improvement of the neural conduction along the visual pathways (amelioration of VEP parameters), leading to a recovery of SVA, visual field, and to a concomitant absence of retinal ganglion cell (RGC) dysfunction due to post-neuritis retrograde degeneration (see normal PERG responses). High-dose intravenous corticosteroids, with or without oral tapering, are the gold standard treatment for acute ON at present, according to the Cochrane Database

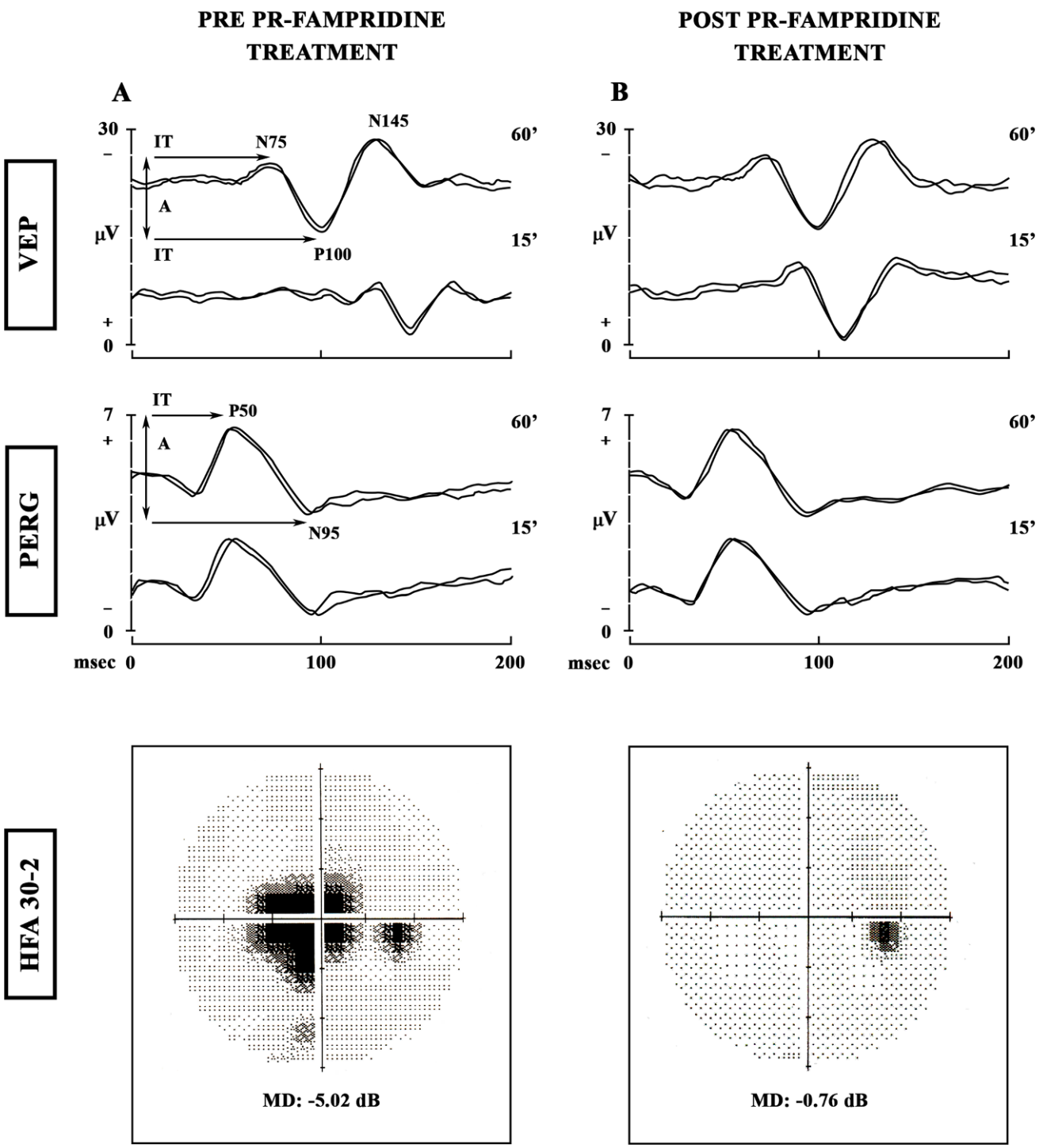

Fig. 1 *Case 2:* Visual evoked potentials (VEP) and pattern electroretinogram (PERG) simultaneous recordings (in response to 60′ and 15′ checks), and Humphrey Field Analyzer (HFA 30–2 strategy) in a 30-year-old patient affected by unilateral (left eye) visual acuity reduction (0.3 Snellen), blurred vision, mild retro-orbital pain, and fatigue. Patient was treated with prolonged release-fampridine (PR-fampridine) for 1 month. **A** Pre PR-fampridine treatment instrumental evaluation shows severe delay of the neural conduction along the visual pathways, selectively involving the small axons forming the papillo-macular bundle with delayed VEP P100 implicit time (IT→) and normal N75-P100 amplitude (A↕) at the 15′ stimulation. The neural conduction of the large axons was normal (normal 60′ VEP P100 IT and N75-P100 A). Normal retinal ganglion cell (RGC) function was detected by 15′ and 60′ PERG P50 IT and P50-N95 A. HFA 30–2 shows marked reduced mean deviation with a large central scotoma. **B** Post PR-fampridine treatment shows an improvement of the neural conduction along the small axons forming the papillo-macular bundle (shortening of the 15′ VEP P100 IT) with unmodified neural conduction of the large axons of the visual pathways (normal 60′ VEP P100 IT and N75-P100 A) and the absence of post-neuritis retrograde neurodegeneration involving the RGCs, as suggested by normal 15′ and 60′ PERG P50 IT and P50-N95 A. HFA 30–2 shows mean deviation within normal limits and the disappearance of the central scotoma.

and the more recently systematic review of the literature [1, 4]. However, several retrospective studies have demonstrated that this approach is often insufficient for preserving the functional and structural components of the optic nerve because it does not induce a complete visual remission and does not prevent the subsequent development of optic nerve atrophy [1]. Therefore, it remains unclear whether other novel treatment regimens, substituted or combined with steroids in acute inflammatory ON, may be more efficacious for improving visual parameters and determining long-term stabilization of functional outcomes. In this context, 4-aminopyridine (4-AP) and its prolonged-release formulation called PR-fampridine have been recently rediscovered as neuroprotective compounds. They are broad-spectrum voltage-dependent potassium channel blockers, currently used for the treatment of walking disability in multiple sclerosis (MS) [2]. Growing evidence supports the hypothesis that aminopyridines are not just a symptomatic therapy, but they may preserve visual function, inner retina morphology, and myelin status [3]. This is particularly relevant in the setting of patients with ON and autoimmune disorders, who complain of visual disturbances despite relative preservation of axons, likely due to inflammation-triggered demyelination [5]. The exact mechanisms by which aminopyridines could improve visual function are not yet fully understood. Acting as a potassium channel antagonist, PR-fampridine may increase action potential amplitude and duration, thus ameliorating the neural conduction along the visual pathways and amplifying neurotransmitter release in the synaptic clefts. This is supported by experimental studies in which the 4-AP enhances axonal conduction of demyelinated fibers. In addition, it increases astrocyte markers and brain-derived neurotrophic factor (BDNF) expression preserving ON axons from inflammatory damage [3]. Another mechanism might be represented by a possible immunomodulatory action, inhibiting the T-cell and microglial activation and, in turn, limiting inflammation, demyelination, and axonal degeneration [3]. The lack of RGC post-neuritis dysfunction may be related to the recent data that 4-AP treatment reduces retinal degeneration and increases myelin density in the optic nerve in mice with EAE-ON compared to sham-treated ones, which remain over time despite the withdrawal of medication [6]. Similarly, Horton et al. found an improved visual acuity and a larger amelioration of VEP latency in MS patients treated with 4-AP compared to those with placebo [5]. This drug had a greater effect only in patients with a retinal nerve fiber layer thickness of more than 60 mm (a measure of neurodegeneration), probably due to the mostly demyelinating underlying damage. Unfortunately, that study considered patients who presented their last ON at least 6 months before the treatment. Therefore, because of the established structural axonal damage, the 4-AP neuroprotection on ganglion cells and remyelination could not be optimal [5]. To date, although the panel of immunomodulatory therapies is continuously increasing, efficacious treatment strategies for preventing neuroaxonal degeneration earlier during inflammatory ONs are missing.

In our two cases, we do not exclude that a delayed response to intravenous corticosteroids might have partly contributed to the therapeutic efficacy, but we want to suggest a novel possible combined approach for acute treatment of newly diagnosed ON, minimizing injury and preventing long-term functional outcomes. This produces prompt and sustained visual recovery that lasted 1 month after treatment with PR-fampridine. In line with these observations, double-blind and larger studies are necessary to definitely establish if a precocious treatment with PR-fampridine has an early and late therapeutic advantage in ON.

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Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval None.

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