Journal of Neurology (2023) 270:1224–1228
https://doi.org/10.1007/s00415-022-11548-3

LETTER TO THE EDITORS

A rare case of a wall-eyed bilateral internuclear ophthalmoplegia (WEBINO) syndrome in a patient with cutaneous lupus erythematosus after COVID-19 infection

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Received: 19 November 2022 / Revised: 22 December 2022 / Accepted: 23 December 2022 / Published online: 28 December 2022

Abbreviations

cMRI	Cerebral magnetic resonance tomography
CNS	Central nervous system
COI	Cut of Index
DWI	Diffusion weighted imaging
FLAIR	Fluid-attenuated inversion recovery
INO	Internuclear ophthalmoplegia
isoDWI	Isotopic diffusion weighted imaging
MLF	Medial longitudinal fasciculus
MS	Multiple sclerosis
PPRF	Pontine paramedian reticular formation
PSP	Progressive supranuclear palsy
sCLE	Subacute cutaneous lupus erythematosus
SLE	Systemic lupus erythematosus
SWI	Susceptibility weighted imaging
WEBINO	Wall-eyed bilateral internuclear ophthalmoplegia

Dear Sirs,

The wall-eyed bilateral internuclear ophthalmoplegia (WEBINO) syndrome describes a relatively rare clinical condition, in which patients present a bilateral adduction deficiency, centripetal nystagmus of the abducting eye and a gaze exotropia [1]. On the basis of different case reports and smaller reviews ischemic [2, 3], haemorrhagic [4, 5], autoimmune [6, 7], infectious [8–10], toxic [11], neoplastic [12], degenerative [13, 14] aetiology and in one article, an association with idiopathic intracranial hypertonia [15] has been described. The prevalence among patients with Multiple Sclerosis (MS) has been estimated between 17 and 41% [6]. Depending on the underlying aetiology and consecutive therapy, different clinical outcomes were observed [16]. Fast clinical diagnosis, identification of aetiology and initiation of a targeted therapy is crucial for attaining the best possible clinical outcome. To illustrate the benefit of an early detection and treatment, we present a patient with an autoimmune WEBINO syndrome, who showed an excellent clinical response on a high dose steroid course.

A 55-year-old teacher, married with two children, presented at the emergency unit of the ophthalmology department with blurred vision that suddenly occurred two hours before self-referral. She reported that her eyes suddenly "failed to follow her orders" after having consumed two glasses of wine. The double vision and associated vertigo occurred in all gaze position. The vertigo was visually induced, as it disappeared with closed eyes. Medical history was positive for subacute cutaneous lupus erythematosus (sCLE) with positive Anti-Neutrophil Cytoplasmic Antibodies (ANCA) (Titer of 1:80) and Anti-SS-A (27 E/ml) levels, which previously was treated with hydroxychloroquine and steroids (Prednisone© 10 mg). In addition, the patient suffered from a COVID-19 infection 2 months before onset of ocular symptoms (at time of incubation, the patient had her first COVID-vaccination with Spikevax© (Moderna) administered) and an adequately substituted hypothyroidism. The ocular examination showed bilateral adduction ocular paralysis with absent convergence reaction and bilateral abducting nystagmus (Videos 1&2). The remaining neurological and general examination were inconspicuous. The patient was normotensive (130/75 mmHg), in sinus rhythm (93 bpm) and afebrile (36.6 °C).

On follow-up history tacking, the patient reported on minor cognitive impairments with increased forgetfulness and difficulties concentrating, which started after infection with SARS-CoV-2 8 weeks before. The family history was positive for sclerodermia (father) and insignificant for neurological diseases.

Blood examination showed normal inflammatory parameters (C-reactive Proteine (CRP) < 0.6 mg/l,

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interleukine-6 < 1.5 ng/l, leucocytes 5.37 G/l) and electrolytes concentrations (natrium 137 mmol/l, potassium 4.2 mmol/l) and blood alcohol level was at 0.6‰. Initial cerebral magnetic resonance tomography (cMRI) with a posterior fossa protocol and increased resolution of the brain stem, (Fig. 1A, B) showed bilateral symmetric diffusion restriction in the area of the mesencephalic tegmentum, corresponding to the Pontine Paramedian Reticular Formation (PPRF) without signal alteration in the FLAIR (Fig. 2) and SWI sequences and without contrast enhancement suspicious for inflammatory lesions. To rule out an association

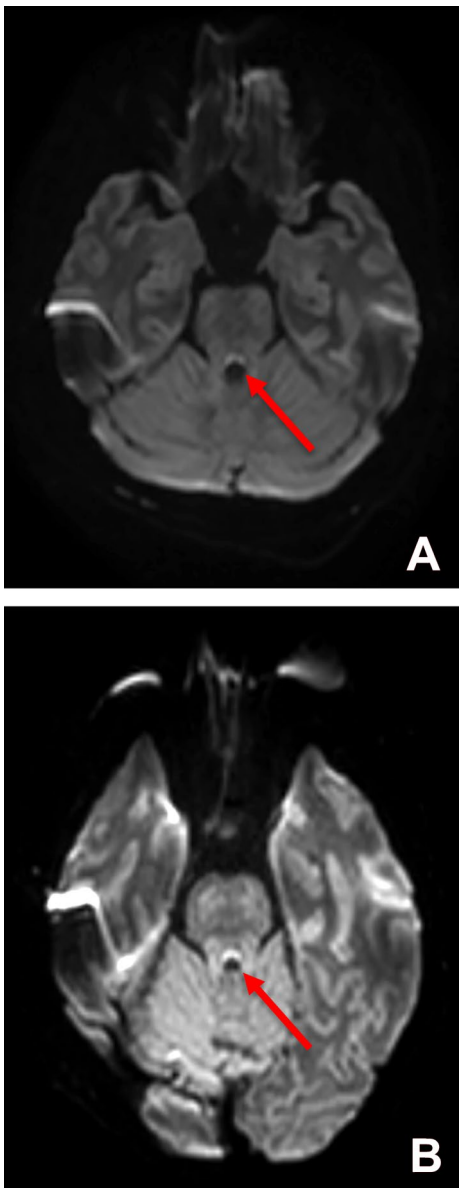

Fig. 1 **A** Diffusion weighted imaging (DWI) **B** isotopic diffusion weighted imaging (isoDWI) indicating a bilateral diffusion restriction in the area of the paramedian pontine formatio reticularis (medial longitudinal fasciculus (MLF), see arrows)

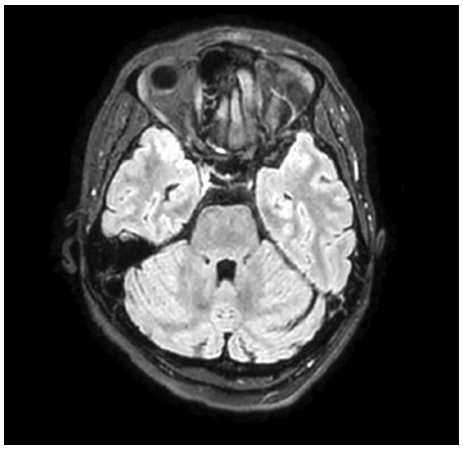

Fig. 2 Fluid-attenuated inversion recovery (FLAIR) sequence at the level of brainstem. No corresponding signal alteration in FLAIR sequence

with a disseminated autoimmune disease, a spinal cord MRI showed normal findings. Examination of cerebrospinal fluid (CSF) showed a slightly increased cell count (11 cells per microliter), normal glucose- (3.4 mmol/l) and protein-levels (0.45 g/l) and no sings for intrathecal immunoglobulin synthesis (IgG index 0.47). In addition, CSF was positive for SARS-CoV-2 nucleoprotein (NP) immunoglobulin (40.08 cut of index (COI) > 1.0), SARS-CoV-2 S immunoglobulin (627.1 Unit/ml) but unconspicuous Reiber-Scheme of 1.21. Anti-CNS Antibody Panel (Hu, Ri, Yo, Amphiphysin, CV2, Ta/Ma2, Mal, SOX1, GAD65, ZIC4, Tr) as well as Anti-NMO and Anti-MOG Antibodies were negative.

Considering the acute onset of the symptoms and the diffusion restriction in the cMRI, an ischemic aetiology appeared initially very probable. However, the medical history did not include any relevant cardiovascular risk factors besides the SLE. Furthermore, the location of the lesion did not correspond to a single vascular territory, so that an arterio-arterial or cardioembolic genesis seemed less probable. In addition, there was no ADC correlation of the lesion. Since the patient was not suffering from arterial hypertension, lacunar stroke or microvascular malfunction did not likely reflect the neurological deficits. As the patient presented acute symmetric signs without the presence of fever or elevated inflammation parameters in the blood tests and the CSF, an infectious aetiology was also unlikely. Finally, since the patient reported a moderate alcohol consumption and the blood alcohol level was low, an acute alcohol intoxication could also be excluded. Cerebral imaging did not reflect findings of a possible idiopathic intracranial hypertension which was associated with WEBINO in a case report.

Considering the positive medical history for SLE, an inflammatory aetiology appeared probable. Neither the cerebral or spinal MRI, nor the CSF results indicated

Multiple Sclerosis (MS) specific findings CSF findings. An association with COVID-19 infection and/or vaccination is possible due to a temporal correlation and the CSF findings of an involvement of the central nervous system (CNS), but no intrathecal antibody-synthesis was apparent applying the Reiber-scheme [17, 18]. In this regard, a systematic review reported on a low prevalence of intrathecal antibody synthesis in patients with an acute COVID-19 infection and neurological symptoms. Thus, clinical symptoms associated with a COVID-19 infection might result from a post-viral or vaccine-associated aetiology rather direct viral neuroinvasion [19]. The patient showed promptly an improvement of the symptoms under high-dose steroid therapy, which favours the aetiology of an inflammatory process. However, despite the above-mentioned findings and the timely coincidence between the manifestation of the WEBINO syndrome and the COVID-19 infection and vaccination, a casual links can neither be proved nor ruled out and the exact nature of pathophysiological mechanism correlating sCLE and COVID-19 as well as the COVID-19 vaccine and the brainstem neurons remains to be understood.

Due to inability to walk and to complete the diagnostic work-up, the patient was admitted to the department of neurology. We suspected an autoimmune disorder and initiated an immunomodulating therapy with high-dose steroids (1000 mg methylprednisolone daily for 5 days along with physiotherapy and occupational therapy). In the third day of hospitalization, we observed an improvement of the eye motility with restored convergence reaction, but adducting saccades were still slowed and a slight abduction nystagmus visible. The clinical correlated with the patient's subjective recovery. Three days after disease onset, the patient was able to walk again and to perform all tasks of daily life. Nevertheless, she still reported on a difficulties reading, as she had to focus more on single letters and words. To accelerate ocular motor recovery, the patient got a temporary ocular occlusion foil and was discharged on the 7th hospitalization day.

One month after hospitalization, no ocular motor deficit could be detected. In the clinical follow-up, 3 months after hospitalisation still was inconspicuous. However, the patient still reported on "ocular fatigue", while reading with occasional blurred vision.

Next to heterogeneous literature in regard of the aetiology of the WEBINO syndrome, there is ambiguity regarding the responsible pathology. Initially, pontine lesions among the level of the PPRF and at the area of the medial longitudinal fasciculus (MLF) were described [16], especially involving the medial rectus subnucleus, which caused the exotropia [20, 21]. Some articles describe lesions at different levels of the brainstem and the midbrain [22], which might reflect heterogenous lesion patterns leading to the very same syndrome (Fig. 3).

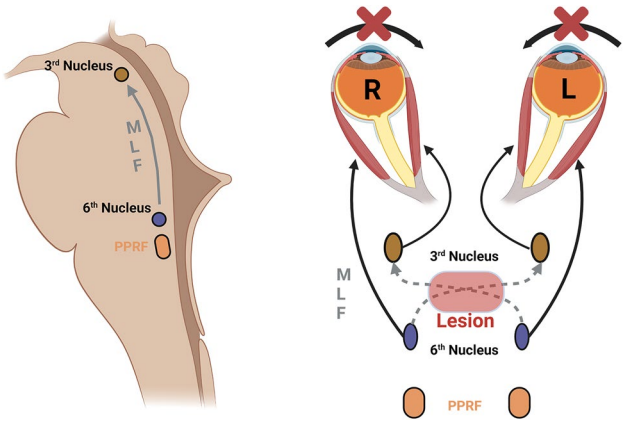

Fig. 3 Location of the lesion in our patient in the area of the medial longitudinal fasciculus based on "Brainstem pathways for horizontal eye movement: pathologic correlation with MR Imaging" of Bae et al. (created with BioRender.com)

In regard of the diagnostics, the literature does not provide a standard work-up. In our opinion, timely cerebral imaging is needed to detect an ischemic or haemorrhagic aetiology and initiate consecutive treatment. To provide most detailed information about the posterior fossa, we recommend cMRI as initial imaging modality. For the remaining differential diagnosis, we recommend to complete the diagnostic with blood test including inflammatory parameters, electrolytes and screening for autoimmune diseases, drug screening and examination of CSF including screening for oligoclonal bands and myelin oligodendendrocyte glycoprotein (MOG) immunoglobulin and neuromyelitis optica (NMO) antibody [23].

The therapy of WEBINO syndrome will depend on the aetiology and focus on improving the diplopia [16]. Therefore, two different approaches are established with, on one hand, surgical correction in case of stable exotropia (at least for 1 year) by extraocular muscle surgery [24]. On the other hand, a conservative approach with prism and injections of botulinum toxin [25, 26]. In regards to our patient, initially, an occlusion foil was administered, at 1-month follow-up since hospitalization, there was no evidence of any gaze deficits.

As described by Wu et al., the literature provides limited data regarding the prognosis since higher number of patients and long-term follow-ups are missing. Importantly, the prognosis depends on the underlying aetiology. Regarding the associated internuclear ophthalmoplegia (INO), 38–78% with ischemic origin of the lesion experienced spontaneous resolution of the symptoms [12, 27]. In contrast, INO related to MS, which in 85% of the cases is associated with the relapsing–remitting form of MS, a spontaneous resolution can be expected in 60% of the cases [12]. While patients with infectious origin tended to show complete clinical

remission after adequate therapy, patients with neoplastic aetiology did not recover [12]. Finally, in the case of systemic lupus erythematosus (SLE), 75% of patients showed after high-dose corticosteroid therapy with prednisone (one to two mg/kg/day for 3 days followed by maintenance dose) complete resolution of signs and symptoms [28]. An association with COVID-19 and Spikevax (Moderna) vaccine and relapse of autoimmune diseases has been described [29, 30]. It is possible that the former triggered a CNS manifestation of previously cuteaneuos lupus erythematodes. This would be a first reported case of WEBINO in a sCLE patient after COVID-19.

- WEBINO is a clinical syndrome with a wide differential diagnosis/aetiologies
- The syndrome frequently localises to bilateral medial longitudinal fasciculus (MLF).
- Prompt brain MRI imaging preferably with posterior fossa focus is crucial and further CSF analysis may be required.
- A specific diagnostic work-up is mandatory to adapt specific treatment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-022-11548-3.

Funding No funding was received towards this work.

Declarations

Conflict of interest The authors report no competing interests.

Ethical standard This Case Report is in line with the CARE criteria.

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