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LETTER TO THE EDITORS

Chronic vertigo and central oculomotor dysfunction with evidence of anti-ITPR1 antibodies

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Dear Sirs,

Inositol 1,4,5-trisphosphate receptor type 1 (ITPR1) is expressed in the central nervous system, particularly in Purkinje cells of the cerebellum, but also in the hippocampus and cortical regions [1].

ITPR1 is involved in the release of calcium from the endoplasmic reticulum and therefore also has an effect on synaptic plasticity. Spinal ITPR1 plays a role in the regulation of pain perception [2]. In 2014, the first description of autoantibodies against ITPR1 in association with autoimmune-mediated cerebellar ataxias was published [3]. A number of clinical manifestations have been observed in patients with anti-ITPR1 antibodies, including cerebellar symptoms, neuropsychiatric symptoms, and involvement of the peripheral nervous system. A frequent association with malignancies suggests a paraneoplastic genesis of the antibodies. The response to immunotherapies, including steroids, intravenous immunoglobulins (IVIG), and plasmapheresis, is described as moderate to low. Due to the rarity of the disease, only individual or grouped case descriptions can be consulted. The literature indicates that neurological symptoms frequently persist and that tumor-associated death is typically observed in patients [4]. In this case, we present a novel symptomatology consisting of chronic vertigo symptoms in combination with a complex central oculomotor disorder, with evidence of antibodies against ITPR1 and discrete improvement of symptoms and clinical stabilization under steroids, plasmapheresis, and rituximab as well as psychosomatic and antidepressant co-treatment.

A 44-year-old male patient reported that he had been experiencing dizziness for several months. One year before the current presentation, he had already noticed a restriction of gaze fixation to the right. Several inpatient and outpatient examinations revealed an unspecified central oculomotor disorder and left vestibular neuritis. He also complained generalized sensitivity to noise and tinnitus; however, hearing loss could not be objectified. Several days of prednisolone treatment according to the Stennert scheme did not change the symptoms [5].

The patient had a history of renal cell carcinoma which had been curatively removed 10 years ago. Additionally, he exhibited a paternal history of urogenital neoplasia.

A detailed oculomotor examination, including videooculography, performed several months earlier in another hospital showed spontaneous nystagmus on the right side with visual block and hypofunction on the left side during head impulse test. A horizontal and vertical saccadic gaze sequence suggested a central oculomotor disorder. There was no evidence of positional vertigo.

Clinical neurological findings at the time of admission to our clinic included rotatory nystagmus on both left and right gaze and bilateral upward nystagmus. Furthermore, no focal deficits were detected. A cranial MRI showed normal brain parenchyma, no contrast enhancement, and focused examination of the internal auditory canal bilaterally revealed no

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pathology. Acoustically evoked potentials were unremarkable. The CSF examination showed a borderline elevated cell count of 5 cells/µl, the total protein was also marginally increased (580 mg/l), and no isolated oligoclonal bands were found in the CSF (type IV). Serum testing revealed the presence of low-titer antibodies to CASPR2 (1:100). Due to a suspicious binding pattern of patients CSF in the brain section (Fig. 1), the patient's serum was further tested in an external laboratory (Klinisch-Immunologisches Labor Stoecker), where anti-ITPR1 antibodies (1:10 000) were detected using an immunofluorescence test (IFT).

Due to the described paraneoplastic occurrence of the anti-ITPR1 antibody, a PET–CT with statistical parametrical mapping (SPM) analysis was performed. It showed no signs of a malignancy; however, hypometabolism in the supplementary motor area and in the cerebellum was found. We initiated immunomodulatory therapy with five days of high-dose steroids (1g per day), followed by four cycles of immunoadsorption. Due to insufficient clinical effects another five cycles of plasmapheresis were performed. One month after the diagnosis, the first cycle of rituximab was administered (1000 mg at 14-day intervals).

The patient described a new dynamic of symptoms during therapy. Previously there had been a consistent persistence of vertigo and oculomotor dysfunction. However, these now seemed to fluctuate, sometimes being absent and sometimes increasing. A clear improvement was denied, but no deterioration was reported either.

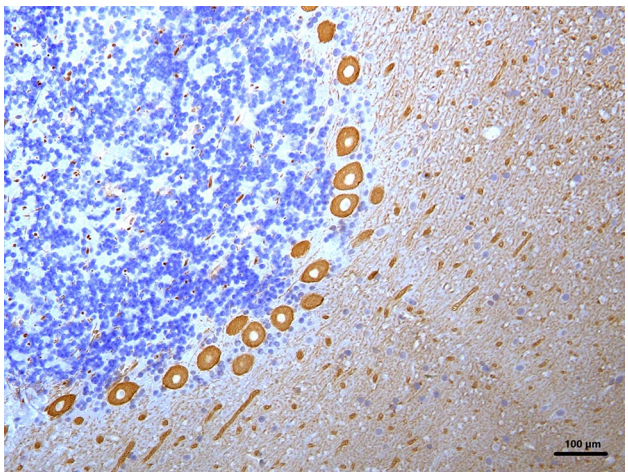

Fig. 1 Detection of antibodies in cerebellar tissue using immunohistochemistry. A cerebellar tissue section was incubated with the patient's cerebrospinal fluid (CSF) to allow the binding of antibodies to target antigens. Subsequently, the section was treated with anti-human IgG conjugated to a dye. If antibodies against structures in the cerebellar tissue are present, they are visualized through a colorimetric signal. The histological section of the monkey cerebellum was visualized at 20×magnification with a 1:1 CSF dilution. An unusual staining pattern was observed, which highlighted the Purkinje cells intensely, as well as the matrix of the molecular layer (Stratum moleculare). Additionally, scattered nuclei within the granular layer (Stratum granulosum) were also distinctly stained. The pattern can be explained by the strong expression of ITPR-1 in Purkinje cells of the cerebellum and has already been demonstrated immunohistochemically after the binding of antibodies against ITPR1 (1)

Three months later, the patient was admitted to our clinic on an emergency basis due to subjective worsening in dizziness, increased headaches, and anxiety, especially in relation to physical performance. Due to the persistence of serological antibodies against ITPR1 without a change in titer, we decided to repeat the immunoadsorption for five cycles.

Due to persistent sleep disturbances and an accompanying depressive disorder, antidepressant medication with mirtazapine was started as part of the co-management of the psychosomatic department. During further treatment, at a follow-up examination five months after the initial diagnosis, a further deterioration was denied, subjectively there were still episodes of dizziness, but also phases of symptom freedom, and the severity of the symptoms was persistently stable. The patient had also noticed an improvement in his emotional imbalance. He stated that, despite the persistence of symptoms, he was able to cope with them much better. The serum antibody titer against ITPR1 decreased to a titer of 1:3200.

The clinical manifestations of anti-ITPR1-associated autoimmune encephalitis documented in reviews and case reports are autoimmune cerebellar ataxias, polyneuropathies, autonomic neuropathies, encephalopathies, or myelitis. Additional dizziness or visual disturbances in the sense of double vision have also been reported [3, 4, 6]. With this case presentation, we aim to expand the clinical manifestations of anti-ITPR1-associated neurological symptoms presented in the literature to include a complex oculomotor disorder. This is the fourth case in the literature in which central nervous system (CNS) inflammation with the detection of ITPR1 antibodies has been described, and in which rituximab was used for treatment. In contrast to our case, myelitis was described in all previously reported cases. Additionally, two of the three previously described cases demonstrated the presence of antibodies against surface proteins in addition to antibodies against ITPR1 (2×anti-GFAP, 1×anti-NMDAR), as observed in our case (anti-CASPR2). A malignant neoplasm was identified in only one case at the time of diagnosis [7, 8]. In our case, a neoplasm was present only years before, with no evidence of recurrence. Only one case demonstrated a transient improvement following therapy, which was short-lived [7]. In our case, the patient showed clinical stability of the symptoms after treatment and was able to come to terms with the persistent symptom complex with the additional help of psychosomatic treatment and antidepressant medication. Therefore, our case is the first of an anti-ITPR1-mediated CNS inflammation with a favorable outcome. It should be noted, however, that the previously described patients were significantly more severely affected

Table 1 Patients with inflammation of the central nervous system with detection of antibodies against ITPR1 and therapy with Rituximab

Sex/age at diagnosis	Prodromal signs and clinical neurological presentation	MRI findings (brain/spine)	CSF findings	Anti-ITPR1 titer	Additional antibodies/titer detected	Malignancy screening/detection?	Immunotherapy	Clinical and neurological outcome
M/21 [7]	Symptoms of a previous viral illness Seizures, opsoclonus myoclonus syndrome Tetraplegia	Brain: T2 hyperintense signal in the right mesial temporal lobe and right middle cerebellar peduncle. Spine: extensive myelitis, contrast uptake in the nerve roots	WBC: 188/µl; Total protein: 1270 mg/l	Serum: – CSF: 1:8	Serum: – CSF: anti-NMDAR, anti-GFAP titer: N/A	Yes (PET–CT, testicular ultrasound, bone marrow aspiration)/No	Steroids, unspecified IVIG, unspecified Rituximab, unspecified PLEX, unspecified	Persistent tetraplegic state ICU treatment > 4 months
F/13 [7]	Gradual onset, rapidly progressive spastic paraparesis	Brain: CNS calcification since birth, possibly progressive. Evidence of three large lesions, unspecified, during the course of the disease, located supratentorial, cerebellar, spinal, and meningeal	N/A	Serum: 1:240 CSF: 1:8	No	Known Fanconi anemia, bone marrow transplant 5 years previously; underlying disease associated with increased risk of leukemia. No evidence of malignancy	IVIG, unspecified PLEX, unspecified Rituximab, unspecified	Brief, albeit modest, improvement

Table 1 (continued)

Sex/age at diagnosis	Prodromal signs and clinical neurological presentation	MRI findings (brain/spine)	CSF findings	Anti-ITPR1 titer	Additional antibodies/titer detected	Malignancy screening/detection?	Immunotherapy	Clinical and neurological outcome
F/44 [8]	Symptoms of flu-like infection for four weeks and a vaginal herpes infection Temporary confusion, psychomotor retardation with progressive impairment of consciousness up to sopor. Paraplegia of the legs, moderate paresis of both arms. Finger–nose test ataxic, gaze nystagmus, urinary retention. Respiratory insufficiency led to intubation	Brain: Diffusion-restricted T2w-hyperintense cortical and subcortical lesions, bilaterally, with parieto-occipital predominance T2w-hyperintense signal alterations mesial temporal and along the upper brainstem and medulla oblongata Corresponding DWI restriction observed Spine: edema from the medulla oblongata along the entire myelon	WBC: 58/µl Total Protein: 1336 mg/l OCB: neg	Initial: Serum/CSF: negative Day 77: Serum: neg CSF: 1:100	Initial: Anti-GFAP Serum: neg CSF 1:10 Anti-MOG Serum: 1:80 CSF: 1:2 Day 77: Anti-GFAP Serum: neg. CSF: 1:10 Anti-MOG Serum 1:40 CSF: neg	CT thorax/abdomen: tumor in the left ovary Histopathology: borderline tumor (pTis (BT) pR1 V0 L0 Pn0) of micro papillary type	Ampicillin (3×5 g/d) Ceftriaxone (2 g/d) Acyclovir 3×750 mg/d) Levetiracetam (2×1 g/d) Valproate (3×1.5 g/d) Lacosamide (2×100 mg/d) Methylprednisolone 500 mg/d IVIG (total dose: 90 g) Rituximab 1000 mg twice within 14 days PLEX (5 cycles)	Persistent tetraplegia. Tracheostoma, but can breathe independently. Implantation of a pacemaker due to damage of autonomic system
M/44	Dizziness for months, restriction of gaze fixation to the right. Unspecified central oculomotor disorder and left vestibular neuritis. Generalized sensitivity to noise and tinnitus Depressive mood during the course	Brain: unremarkable Spine: –	WBC: 5/µl Total Protein: 580 mg/l OCB: neg	Serum: 1:10 000 CSF: 1:100	CASPR2 Serum: 1:100 CSF: neg	Curative removal of a renal cell carcinoma 10 years prior to onset of symptoms. Currently no evidence of neoplasia	Methylprednisolone 1 g/d for five days Immunoadsorption (4 cycles) Plasmapheresis (5 cycles) Rituximab 1000 mg twice within 14 days	Clinical stability and improvement in emotional imbalance

Summary of previously documented cases of CNS inflammation with detection of anti-ITPR1 antibodies and treatment with rituximab

CNS central nervous system, *CSF* cerebrospinal fluid, *DWI* diffusion-weighted imaging, *GFAP* glial fibrillary acidic protein, *ICU* intensive care unit, *ITPR1* Inositol 1,4,5-trisphosphate receptor type 1, *IVIG* intravenous immunoglobulins, *MOG* Myelin oligodendrocyte glycoprotein, *MRI* magnetic resonance imaging, *NMDAR* N-Methyl-D-Aspartate-Receptor, *OCB* oligoclonal bands, *PET–CT* positron emission tomography–computed tomography, *PLEX* plasma exchange, *WBC* white blood cell count

at the initial presentation. Table 1 provides an overview of the clinical, radiological, liquor chemical, and therapeutic aspects of the present patients [7, 8]. It should also be emphasized that the intensity of symptoms was subjectively reported by the patient and that psychosomatic and psychopharmacological co-treatment was an important stabilizing and coping factor. Another notable limitation of the present study is the lack of evidence of a clear pathophysiological link between the presence of anti-ITPR1 antibodies and clinical manifestation. This is primarily due to the lack of conducted passive transfer experiments [4]. Consequently, the potential for incidental findings in the context of concurrent neurological symptoms should be acknowledged. However, previous studies investigating the relevance of this antibody detection have not identified any patients or healthy controls with antibodies against ITPR1 without a corresponding clinical presentation [3, 7, 9]. Furthermore, the observed, albeit transient, improvement under immunosuppressive therapy supports an antibody-mediated origin of the symptoms, as mentioned in previous investigations [4]. It is not possible to derive the path mechanism from a case study or make specific recommendations on diagnosis and treatment, but we consider it important to present the diversity of the clinical picture with a detailed review.

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Data availability Data supporting the findings can be found in the table and figure. Additional data extracted may be shared upon request.

Declarations

Conflicts of interest The authors declare that they have no competing interests.

Ethical approval and consent to participate Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements.

Consent for publication The patient provided written informed consent to participate in this study.

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