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CASE REPORT

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Ocular Flutter-Myoclonus-Ataxia Syndrome After mRNA BNT162b2 COVID-19 Vaccine: A Case Report

Turan Poyraz[1], Armağan Varol[2], Hasan Armağan Uysal[3]

[1]İzmir University of Economics, Vocational Schools of Health Services, Department of Elderly Care, İzmir, Turkey
[2]İzmir Medifema Hospital, Department of Neurology, Neurologist, İzmir, Turkey
[3]İzmir University of Economics, Faculty of Medicine, Department of Neurology, İzmir, Turkey

ABSTRACT

Ocular flutter (OF) is a rare oculomotor syndrome. The most common etiologies are paraneoplastic, postinfectious and toxic-metabolic. However post-vaccinal etiology was rarely reported in OF. Here, we reported a post-vaccinal clinical syndrome characterized by OF-myoclonus and ataxia associated with oligoclonal bands (OCBs).

A 60-year-old male who presented with dizziness, unsteady gait, involuntary movements, involuntary conjugate eye oscillations and extremity jerks that started 3 days after the second dose of mRNA BNT162b2 Covid-19 vaccine. Routine biochemical and serological analysis were within normal limits. No pathological finding was detected in brain MRI. Paraneoplastic and autoimmune encephalitis tests were unremarkable in cerebrospinal fluid (CSF). Oligoclonal bands were positive in CSF. This is the first description of the relationship between vaccines against SARS-CoV-2 and the clinical syndrome of OF, Myoclonus and Ataxia (OFMAS). Humoral immune mechanisms seem to play an important role in OFMAS. Presence of OCBs in CSF may also be associated with this condition.

Keywords: Ataxia, myoclonus, ocular flutter, oligoclonal bands, SARS-CoV-2, vaccine

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INTRODUCTION

Severe acute respiratory syndrome –coronavirus 2 (SARS-CoV2) associated coronavirus disease - 2019 (COVID-19)– was first documented in December 2019 at Wuhan, China (1). COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. Since the outbreak of the COVID-19 pandemic, many neurological symptoms, syndromes and complications have been reported. Data on neurological involvement is increasing day by day. The most common neurological complaints in patients with COVID-19 are anosmia, ageusia, and headache. However, more serious adverse events such as stroke, impaired consciousness, seizures and encephalopathy have also been reported. (2) In addition to the neurological manifestations of COVID-19, neurological involvement due to vaccines developed against COVID-19 has also been reported (3). We report a case of ocular flutter-myoclonus and ataxia syndrome associated with mRNA BNT162b2 Covid-19 vaccine and discuss their phenomenology and possible pathophysiology.

Highlights

- **A post-vaccinal Ocular Flutter-myoclonus-Ataxia (OFMAS) case is presented.**
- **A high number of oligoclonal bands (OCBs) were detected in the Cerebrospinal Fluid.**
- **OCBs positivity can be related to humoral immunity and molecular mimicry.**
- **Our case is the first case of OFMAS reported after mRNA vaccines.**
- **Intravenous immunoglobulin (IVIG) and pulse corticotherapy can be used for treatment.**

CASE

The patient was a 60-year-old male who presented with dizziness, unsteady gait, anxiety, insomnia, rapid and shallow breathing, involuntary tremors and extremity jerks that started 3 days after the second dose of mRNA BNT162b2 Covid-19 vaccine. He only had type 2 Diabetes Mellitus and obesity in his history. His vital signs were normal. He was awake, alert and oriented. His pupils were equal size in both eyes. The direct and indirect light reflexes were normal. In the neuroophthalmological evaluation; saccadic rapid conjugated horizontal eye movements were present in the primary position. He had intermittent bursts of involuntary conjugate eye oscillations with a strict preponderance for the horizontal plane and without intersaccadic interval. This condition, called ocular flutter (OF), was not accompanied by gaze paresis or visual field loss (video1). Myoclonus was present with high amplitude movement in the face and 4 extremities. Continued myoclonic jerking of the head, and a bilateral kinetic tremor was present in his upper extremities. Strength of

Correspondence Address: Turan Poyraz, İzmir Ekonomi Üniversitesi, Sağlık Hizmetleri Meslek Yüksekokulları, Yaşlı Bakımı Anabilim Dalı, 35000, İzmir, Turkey • **E-mail:** turanpoyraz@gmail.com
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the muscles was normal in all extremities. There was no sensorial deficit. Plantar responses were flexor. He had severe truncal ataxia and therefore he couldn't walk or sit. He was anxious and distracted.

Cardiac examination was normal, but he had hypoventilation in pulmonary examination.

Routine biochemical and hemogram analyses were within normal limits. Ocular movements were recorded by Electro-Oculography (EOG) (Nihon Kohden, Neuropack-2). Electro-Oculography shows the OF: bursts of rapid, back-to-back and symmetrical saccadic oscillations in the horizontal plane without intersaccadic interval (Figure 1). Brain MRI (also Diffusion weighted sequences) and brainstem thin section MRI were repeated 2 times. No pathological finding was detected in either of the MRIs which were performed 1 week apart (video 2). COVID-19 PCR test was negative (repeated 2 times). Results of electroencephalogram (EEG) were normal. Electroneuromyography (ENMG) was found to be consistent with (predominantly sensory) sensorimotor polyneuropathy (Nihon-kohden, Neurpack-2).

The patient was hospitalized with a diagnosis of Ocular Flutter-Myoclonus-Ataxia Syndrome (OFMAS). Lumbar puncture was performed. Cerebrospinal Fluid (CSF) pressure was found to be normal. There was a mild protein elevation in CSF examination but no cells. Cerebrospinal fluid lactate and glucose levels were within the normal range. No growth was detected in the CSF culture. Paraneoplastic and autoimmune encephalitis tests were requested in CSF. Oligoclonal band and IgG index levels were requested. Oligoclonal bands were positive and quantitative cerebrospinal fluid IgG and IgM indexes were normal. Serological tests, cultures, and polymerase chain reactions performed on blood and cerebrospinal fluid samples were negative for viral, bacterial, and fungal infections. Serological tests of blood and CSF for paraneoplastic antibodies were negative. Ganglioside antibodies were negative (Table 1). Results of screening examinations for neoplasms, including abdominal ultrasonography, computed tomography of the abdomen and chest were all unremarkable.

Symptomatic treatment with clonazepam and valproic acid was ineffective. For OFMAS, 5 days of intravenous immunoglobulin treatment at a dose of 0.4 g/d was started.

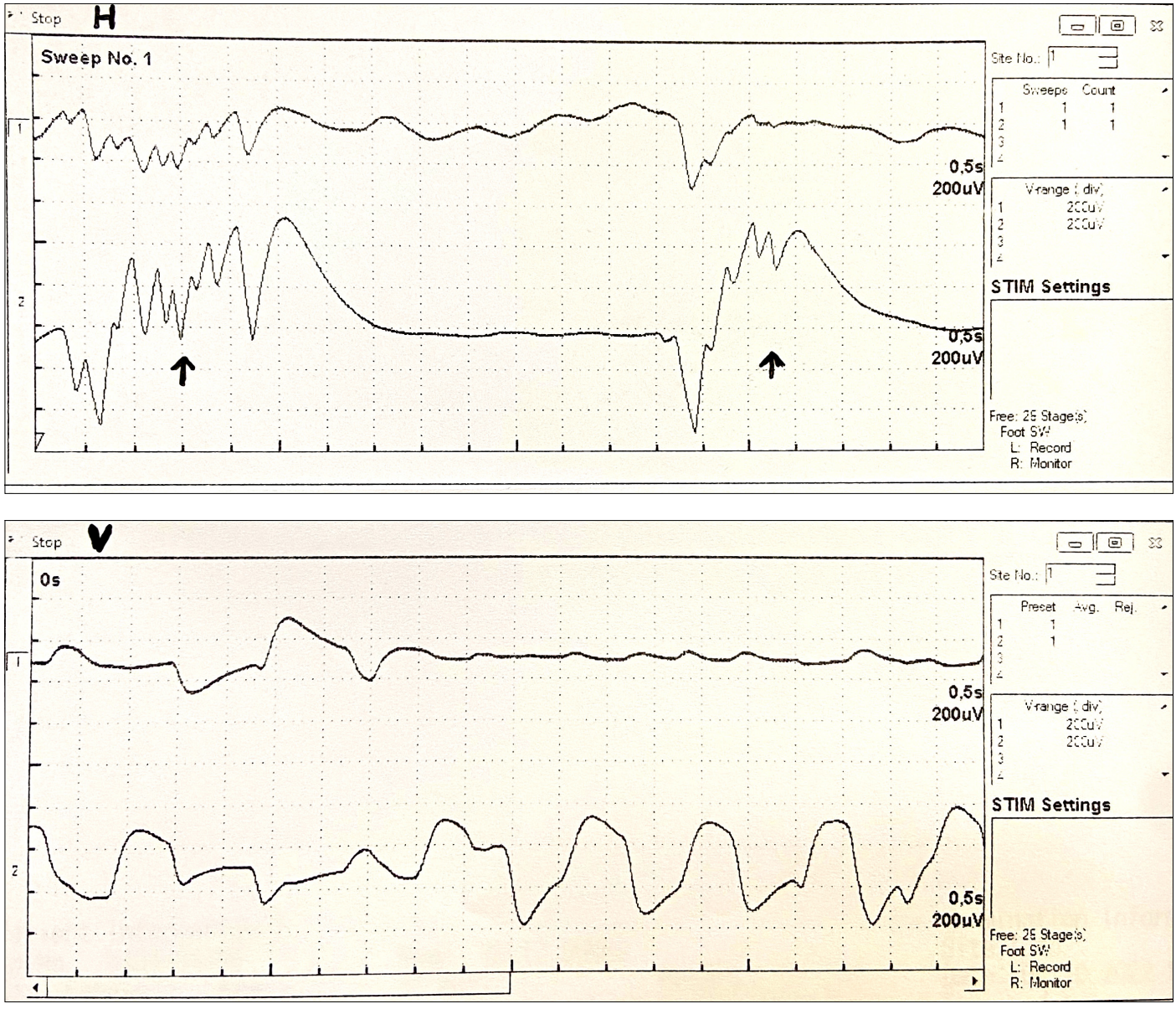

Figure 1. Electro-oculography (EOG) (H: Horizontal; V: Vertical; (up arrow ↑), saccadic oscillations in the horizontal plane without intersaccadic interval).

Table 1. Cerebrospinal fluid (CSF) study result

Parameters	Results
Opening pressure (10–18 cm of H_2O)	12 cm of H_2O
Color	Clear
Cells	o/mm^3
Gram stain and culture	Negative
Glucose (40–70 mg/dL)	72 mg/dL
Protein (15–45 mg/dL)	60 mg/dL
VDRL test	Non-reactive
HSV 1–2 by PCR	Negative
CMV IgM	Negative
B. burgdorferi IgGM and IgG	Negative
VZV by PCR	Negative
EBV by PCR	Negative
Paraneoplastic Autoantibodies Panel	
ANNA-1/anti-Hu	Negative at <1:2
ANNA-2/anti-Ri	Negative at <1:2
ANNA-3	Negative at <1:2
AGNA-1	Negative at <1:2
PCA-1/anti-Yo	Negative at <1:2
Amphiphysin Ab	Negative at <1:2
CRMP-5-IgG/anti-CV2	Negative at <1:2
PNMA-2/Ma2/Ta	Negative at <1:2
Recoverin	Negative at <1:2
SOX-1	Negative at <1:2
Titin	Negative at <1:2
Zic4	Negative at <1:2
Tr (DNER)	Negative at <1:2
GAD65	Negative at <1:2
Autoimmune Encephalitis Panel	
NMDAR	Negative
AMPA-1	Negative
AMPA-2	Negative
CASPR-2	Negative
GABAR-B1/B2	Negative
LGI-1	Negative
SARS-CoV-2 (2019-nCoV RNA) PCR	Negative
Oligoclonal bands (OCBs)	**Tip 2 (21 bands positive)**
IgG Index (<0.77)	0.4668
IgG (0–34 mg/L)	47
Anti-ganglioside Panel	
GM1, GM2, GM3	Negative
GD1a, GD1b	Negative
GT1b	Negative
GQ1b	Negative

AMPA: Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANNA: Antineuronal nuclear antibody; CASPR2: Contactin-associated protein-like 2; CMV: Cytomegalovirus; CRMP: Collapsin response mediator protein; DNER: Delta/notch-like epidermal growth factor-related receptor; EBV: Epstein Barr Virus; GABAR: Gamma aminobutyric acid receptor; GAD65: Glutamic Acid Decarboxylase; GM: Ganglioside-monosialic acid; HSV: Herpes Simplex Virus; LGI-1: Leucine rich glioma inactivated-1; NMDAR: N-methyl D-aspartate receptor; PCA: Purkinje cell cytoplasmic antibody; PNMA: Paraneoplastic Ma antigen; VZV: Varicella Zoster Virus.

From the 2nd day of IVIG, an increase in communication, a decrease in anxiety and a moderate regression in ataxia began. Since there was no significant improvement in her general condition starting from the 5th day, 1 g/d intravenous Methylprednisolone treatment was started. After steroid treatment, her complaints subsided.

DISCUSSION

Ocular Flutter (OF) is a rare oculomotor syndrome and has been considered to be a sub-form of opsoclonus, probably caused by a loss of tonic stimulation of omnipause neurons. These abnormal ocular oscillations are believed to be caused by dysfunction of 'pause/burst' cells in the pons, particularly in the paramedian pontine reticular formation, which arrest or fire the development of saccadic movements. (4). OFMAS is a new clinical entity and characterized by a combination of OF (intermittent bursts of involuntary conjugate eye oscillations with a strict preponderance for the horizontal plane and without intersaccadic interval), myoclonus (refers to sudden, brief involuntary twitching or jerking of a muscle or group of muscles) and ataxia (abnormal, uncoordinated movements specially to stand or ambulate). Neuropsychiatric symptoms such as changes in mental status, disruption in sleep cycle, mood changes and hypoventilation can be seen in most patients. Rhombencephalitis/Rhombencephalopathy (RE) refers to combined brainstem and cerebellum (hindbrain) dysfunction due to infectious diseases, primary central nervous system (CNS) demyelinating disorders, systemic inflammatory conditions with CNS involvement, and autoantibody-mediated autoimmune disorders (5). The most important feature that distinguishes the clinical picture from OMAS is the observation of OF instead of Opsoclonus. Opsoclonus and OF are rare but well-defined disorders of the saccadic system. OF is a burst of back-to-back horizontal saccades without an intersaccadic interval. If these saccades occur in all directions, the involuntary eye movements are called opsoclonus (6). According to Büttner et al; OF is an ocular motor disorder consisting of involuntary back-to-back saccades in the horizontal plane without a saccadic interval. In opsoclonus, these pathological eye movements occur not only in the horizontal but also in the vertical plane. Spontaneous OF has been associated with brainstem and cerebellar lesions and is presumed to reflect an intrinsic membrane receptor malfunction of the pontine saccadic burst neurons (SBN), omnipause neurons, and/or cerebellar vermis/fastigial nucleus complex leading to SBN increased firing (7). There are also cases reported to be associated with autoimmunity. A 37-year-old female case of OFMAS associated with anti-GQ1b antibodies was reported in 2008 (8). OFMAS associated with anti-GM1, GD1a and GD1b antibodies in a 6 year-old-child has been reported (9).

Since the emergence of pandemic, many data and cases associated with CNS involvement of SARS-CoV-2 have been reported. The possible mechanisms of SARS-Cov-2 neurotropism are mainly thought to be due to direct viral invasion (olfactory nerve route and blood brain barrier defect) or indirect pathways (hypoxia and autoimmunity) (10). Several cases of OMAS following SARS-CoV-2 infection has been recently reported. Foucard et al. reported a total of seven patients (11), three of whom demonstrated signs and symptoms consistent with OMAS. The other patients manifested myoclonus and ataxia without opsoclonus. Cases with OMAS secondary to COVID-19 continue to be reported (12).

The immunopathogenesis of OFMAS/OMAS is unclear. Humoral and cell-mediated immune mechanisms are thought to be involved in both paraneoplastic and idiopathic syndromes. In many cases, the symptoms are reversible after treatment with immunotherapy (13). In idiopathic OMAS cases, most patients are seronegative for antineuronal antibodies, as in this case. Our patient received the mRNA BioNTech 3 days prior to the onset of neurological symptoms. Given that humoral immune mechanisms seem to

play a role in OMAS, it could be possible that the vaccine or a combination of vaccine generated an immune response that led to antibodies causing neuronal dysfunction. In our patient, OCBs were detected as a type 2 pattern with a high number of bands. In general, 5 different patterns are emphasized in CSF and Type 2 pattern refers to oligoclonal bands detected only in CSF. The presence of oligoclonal bands in CSF, which is seen as evidence of B-cell mediated humoral immunity, may be associated with the presence of a humoral immune response to the vaccine. In a case series of 7 diseases related to COVID-19 mRNA vaccination leading to CNS inflammation, OCBs have been detected in CSF in only one of 3 cases in which CSF could be analyzed (14). There are a few case reports in the literature that may be associated with post vaccinal OMAS. The last of these developed after influenza vaccine in 2012 (15).

Despite all these data, no cases of OFMAS/OMAS related to vaccines developed against SARS-CoV-2 have been reported. Infections, including with SARS-CoV-2, may induce autoimmunity through an aberrant immune response triggered by molecular mimicry and bystander activation, especially in predisposed individuals (16). Vaccination against SARS-CoV-2 could, through similar mechanisms, also trigger autoimmunity, as it has been described with other vaccines. Recently a new case of autoimmune hepatitis after mRNA-1273 SARS-CoV-2 vaccine has been reported (17).

On the other hand, our case report and review of literature had some limitations. The first of these is that the meta-analyses of the studies conducted during the ongoing pandemic process do not provide sufficient evidence for causality. Another limitation is the lack of a precise measurement to detect causality between vaccines and disease. Recognition and understanding of the range of neurological disorders associated with COVID-19 and or vaccines may lead to improved clinical outcomes and better treatment algorithms.

Neuropathology-based longitudinal studies are needed to evaluate the effects of COVID-19 and vaccines on the nervous system.

This is the first description of the relationship between vaccines against SARS-CoV-2 and the clinical syndrome of OFMAS. In this case, OFMAS has been presented as a separate clinical entity. Humoral immune mechanisms seem to play an important role in OFMAS. Presence of OCBs in CSF may also be associated with this condition. The link between SARS-CoV-2 vaccination and the development of autoimmune diseases needs to be further investigated. Although a causality relationship cannot be proven, caution may be warranted when vaccinating individuals with known autoimmune diseases. To overcome this pandemic, vaccination is still the most effective and safest way to help build protection and reduce disease spread.

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