Psychotic Symptoms as Onset Clinical Presentation in a Case of Pediatric Onset Multiple Sclerosis

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Abstract

Multiple Sclerosis (MS) can have an onset before the age of 16 years in 3-10% of cases. When onset occurs at such a young age, the clinical or neuro-radiological features of MS may be different from MS in adult patients.

We report the case of a 17-year-old girl with an onset of MS characterized by psychotic symptoms. This pattern of clinical presentation has been described in adults with MS, but pediatric cases are anecdotal. With the description of this case, we contribute to reinforce the importance of atypical clinical symptoms in the diagnostic pathway of pediatric onset MS.

Keywords: Multiple sclerosis • Pediatric onset • Psychosis • Children • Adolescents

Abbreviations

ADEM: Acute Demyelinating Encephalomyelitis; **ADS:**Acquires Demyelinating Syndromes; **CNS:** Central Nervous System; **ER:** Emergency Room; **MRI:** Magnetic Resonance Imaging; **MS:** Multiple Sclerosis; **PCR:** Polymerase Chain Reaction; **POMS:** Paediatric-Onset Multiple Sclerosis; **CSF:** Cerebrospinal Fluid.

Introduction

An onset of MS before the age of 18 occurs in 3%-10% of cases [1]. Common presentations of pediatric onset MS (POMS) include poly focal (65%) or brainstem (37%) symptoms, optic neuritis (34%), Acute Demyelinating Encephalomyelitis (ADEM) (15%) and transverse myelitis (7%) [2,3]. MS diagnosis can be challenging due to the heterogeneity of symptom onset [2]. McDonald's criteria, revised in 2017, for adults, and International Pediatric Multiple Sclerosis.

Study Group criteria of 2013, for children, are useful tools for diagnosis [4,5]. Adult-onset MS with psychiatric symptoms occurs rarely, and pediatric cases are anecdotal [6]. We report the case of a girl with POMS and sudden psychiatric symptoms at onset.

Case Presentation

A 17-year-old girl was admitted to our hospital due to behavioral alterations, appeared ten days earlier. No previous infectious symptoms were reported; she had no fever at the time of hospitalization and no previous history of neuropsychiatric disorders. The familiar anamnesis recall was only significant for her grandmother suffering from major depression, while no familiarity for autoimmune or neurological diseases was reported.

She presented acute-onset symptoms and parents referred that a week after she returned from a holiday, she presented the first symptoms of altered body perception. Subsequently, the mother noticed a slowdown in movements and a behavioral disorganization, with a feeling of alienation and perplexity. Two days after the onset, an episode of panic attack was reported, and then she started manifesting paranoid ideas with incongruous fear of the father's health, worry that she was spied on from the windows and that her mobile phone was hacked. Somatic delirium followed, with an inability to recognize her parents whose bodies she perceived as transformed. She had also started to have a sleep disorder, with frequent awakenings and insomnia.

Medical history was also negative for neurodevelopmental disorders, and she had always shown good social functioning, furthermore she had never required access to neuropsychiatric services. It was reported a 20 kg weight loss, because of a low calories diet, during lockdown in 2020, that she regained in the following months. Previous worries about his physical appearance and fear of the judgement of others, but without interfering with daily activities and socialization, were reported.

At the psychiatric observation, the patient presented eloquence if elicited, ideomotor slowdown and fluctuating accessibility to the interview with perplexity towards the examiners. She had increased latency of responses or block of thought, with difficulty in cognitive recovery. She had persecutory thoughts and paranoid ideas. Her vital parameters and the general physical examinations were normal. The neurological exam did not reveal signs in the other functional systems.

The condition appeared suggestive of an acute psychotic onset. During the first twelve hours of her hospitalization the patient's behavior deteriorated, she became more detached from the environment, with rare verbal communications with her parents or the health personnel. She was treated with risperidone (up to 0.03 mg/kg/day) and lorazepam (0.02 mg/kg/day) with minimal benefit on her paranoid ideation and behavior. The acute

onset of symptoms, without a significant psychiatric history and family history of neuropsychiatric pathology, suggested a possible secondary cause of symptoms.

Routine blood work and toxicological investigations, to rule out substance-induced psychosis, resulted normal. To investigate organic causes of acute psychosis, a brain Magnetic Resonance Imaging (MRI) was performed, revealing multiple hyper intense areas on T2-FLAIR sequences in various brain regions, including bilateral periventricular regions, deep white matter of semi oval centers and radiated coronal areas, bilateral frontal subcortical regions, right middle and superior cerebellar peduncles. A focal T2-hyper intense lesion was observed in the cervical spinal cord (C1-C2). Gadolinium injection determined no pathological enhancements (Figure 1).

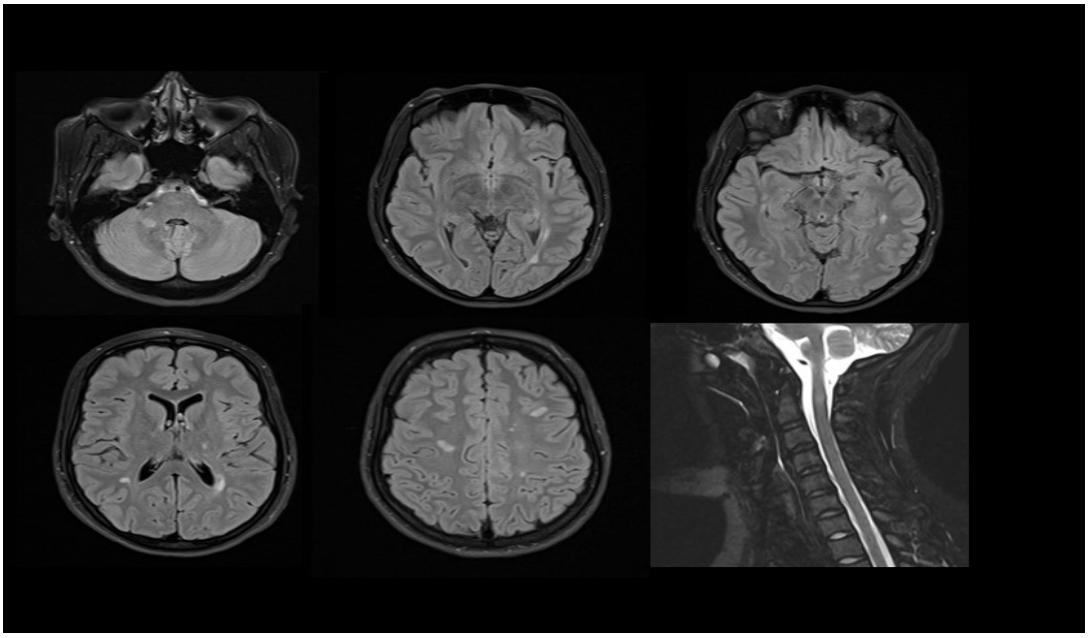

Figure 1. Axial T2-Flair MRI showed multiple brain lesions and cervical spine lesions.

Chemical-physical examination of Cerebrospinal Fluid (CSF) showed a slight increase in proteins (51 mg/dl) and some white blood cells (32 cells/mmc). Virologic tests on blood and CSF resulted negative for ongoing infections. To rule out immune-mediated encephalitis and other autoimmune conditions, antibodies research on CSF and serum was performed, including anti-NMDA-R (N-methyl D-aspartate receptors), antiMOG (myelin oligodendrocyte glycoprotein) and anti-aquaporin-4 antibodies, which resulted negative. CSF immune-electrophoresis showed more than three Oligo Clonal Bands (OCB), without corresponding bands in serum (profile III).

These findings allowed us to conclude for the diagnosis of MS according to 2017 Mc Donald criteria with one clinic episode, more than two lesions at the MRI for dissemination in space and OCB on CSF for dissemination in time [4].

Intravenous (IV) treatment with methyl prednisone 1 gr/day started and continued for five days, resulting in a significant improvement in the patient's clinical condition just after the first dose. She started interacting with medical staff and her parents, her paranoid thoughts decreased; motor, vocal and cognitive skills returned to normal after three days of treatment. She was sent home after five days of treatment, with an oral prednisone prescription of 2 mg/kg/day, risperidone and lorazepam.

Oral prednisone was progressively suspended one month after release from hospital. She continued treatment with risperidone and lorazepam until the neuropsychiatric assessment, two months after her discharge, when psychiatric symptoms were no longer present. She started intravenous Ocrelizumab 600 mg iv every 6 months.

Four months after initiation of clinical treatment and two months after initiation of Ocrelizumab treatment, follow-up MRI showed a stable neuro-radiological profile, without gadolinium enhancing lesions.

Discussion

This unusual presentation of POMS suggests that psychiatric symptoms should be regarded as potential initial manifestations of MS also in POMS. Although the psychiatric onset of MS appears unusual [6], psychiatric symptoms are more common as the disease progresses. Depression occurs most often (79%), followed by agitation (40%), anxiety (37%), irritability (35%), apathy (20%), euphoria or disinhibition (13%), hallucinations (10%) [7].

In literature, only one case described POMS with psychiatric features at onset. Treadwell-Deering et al. reported a 14-year-old boy with acute psychiatric symptoms (paranoid ideas, impaired thoughts, and hallucinations), sleep and eating disorders, speech disorders, and aggressive behavior [8]. The patient did not respond to psychiatric treatment with paroxetine, risperidone and quetiapine; the brain MRI showed two hyper intense lesions without contrast enhancement and CSF analysis revealed the presence of intrathecal oligo clonal bands. The patient initiated five days of intravenous treatment with methyl prednisone (500 mg/day), but exhibited agitation not responsive to benzodiazepines and valproic acid. He was non-adherent to immunomodulation therapy, and further MRI scans showed new lesions. The immunomodulatory treatment after discharge was not specified by authors [8].

There are more reports of onset psychiatric symptoms in adult MS (Table1). Camara-Lemarroy et al. described 91 adults with MS and psychotic symptoms: 28.6% of them showed immediate improvement with corticosteroid treatment during the acute psychotic phase, although specific schemes and dosages were not specified [9]. In addition, anti-psychotics are unlikely to control these symptoms of multiple sclerosis [10]. In our patient, antipsychotic therapy was ineffective, but there was a progressive improvement following the introduction of corticosteroids. This data reinforces the importance of investigating organic causes

through neuroimaging and biochemical tests in case of unresponsive psychiatric symptoms.

Table 1. Previous reported cases of MS with psychiatric symptoms at onset.

Year	Authors	Sex	Age	Symptoms at onset	Exams	Treatment	Outcome
2006	Peter J.H. Jongen	F	26	Behavioural changes: hiding from people, religious phrases, confusion, depersonalisation, derealisation, auditive and visual hallucinations, incoherent thinking. Neurological examination: right-sided ptosis, asymmetric sternocleidoid muscle, torticollis, apraxia, tingling sensations in right arm and leg, and difficulties in walking.	EEG: diffuse hypofunction, irritative activity, and paroxysms. Cranial CT: normal. Brain MRI: multiple T2 hyper intense lesions located in the brain stem, in the periventricular and subcortical white matter of both cerebral hemispheres. CSF: oligo clonal bands, intrathecal IgG production.	Not specified	Not specified
2007	Treadwell-Deering D et al.	M	14	Impairments in word-finding, bilateral fine motor skills, and attention	Brain MRI: Multiple lesions CSF: Presence of oligo clonal bands	5-day course of intravenous methylprednisone, 500 mg b.i.d., and psychotropic medications	Improvement of symptoms
2010	Lo Fermo et al.	- 5 M - 11 F	31 +/- 8.7	9 patients (56%) presented with a mood disorder (major depressive-like Episode) 5 patients (32%) had psychotic symptoms, 1 patient (6%) was diagnosed with a manic episode 1 patient had panic attacks associated with a generalized anxiety disorder.	Brain MRI: psychotic patients showed a higher number of T2 hyper intense lesions in the left temporal area than patients with depression; no additional differences were observed in the other areas.	High-dose intravenous methylprednisolone Combination of anti-depressants and anxiolytic drugs for patients with affective symptoms Combination of antipsychotic agents and antidepressants for patients with mixed depression symptoms. Antipsychotic and/or mood stabilizing drugs for patients with psychotic symptoms. Disease modifying drug therapy or immunosuppressant drugs for all the patients.	All patients experienced neurological relapses. 14 of the 16 patients experienced psychiatric relapses.
2014	Adrenoulakis et al.	M	46	Dizziness, nausea, walking instability, headache, anxiety, irritability, depression, fear of being abandoned, outbursts of anger toward his wife, accusing her of being unfaithful to him. Neurological examination: right hemianopsia, right paresis of VII and right pyramidal symptomatology.	Brain MRI: multiple hyperintensities in the subcortical white matter, the semioval centers, the periventricular white matter, and the left hippocam-pus. CSF: 10 cells, 20% proteins and 60% sugar, and oligoclonic band of IgG in the cerebrospinal fluid.	Haloperidol, Paliperidone, Lorazepam, Viperiden, Carbamazepine, Glatiramer acetate, Calcium folinate.	Complete recovery from psychotic symptoms, although the patient did not achieve full insight.
2017	Aadil et al.	F	27	Crying, laughing without any reason, aggressive behavior. Neurological examination: bilaterally positive	Brain MRI: abnormal signal intensity areas involving multiple bilateral subcortical superficial white matter of frontal, parietal and temporal regions and deep white matter of		

				Babinski sign, increased tone in the lower extremity, exaggerated knee reflex, diminished ankle reflex, decreased sensation. In upper limbs, normal tone with inverted biceps reflex and absent brachioradialis reflex, intact sensations.	right parietal and left temporal regions. Lesions were hypointense on T1 weight image (T1W1) and hyper intense on T2W1 and fluid-attenuated inversion recovery (FLAIR) sequence. CSF: positive oligo clonal bands.	Not specified	Not specified
2018	Enderami et el.	M	27	Feeling of being followed by others, irritability, anger outbursts, bad tempering, antisocial behavior. He thought his colleagues at work are likely to harm him due to his good skills at his job. Depression, severe fatigue and loss of energy, loss of appetite, and weight loss, joint stiffness and loss of movement control at upper and lower limbs.	Brain MRI: The T2-weighted MRI demonstrated periventricular and white matter multiple sclerotic plugs with lesions.	Methylprednisolone (5 mg three times a day/until remission) and interferon therapy,	Improvements in sensory and motor neuron involvement and socio-occupational behavior; disappearance of hallucination
2020	Nandy et al.	M	23	Confusion, extreme restlessness, diffuse cognitive deficits, aggressive self-harming behavior, paranoia, suicidal thoughts, motor restlessness, confusion, agnosia, not able to recognize either his mother or girlfriend.	Cranial CT: multiple low-density lesions without intracranial hemorrhages, ischemia or space-occupying lesions. Brain MRI: fulminant contrast enhancing ovoid lesions involving both cerebral hemispheres, callososeptal interface, medulla. CSF: positive oligo clonal bands.	High-dose intravenous methylprednisolone and 6 cycles of plasmapheresis Immunomodulatory treatment with Cladribine	Complete recovery
2021	Ozbudak et al.	M	14	Auditory hallucinations	Brain MRI: demyelinating lesions in the mesencephalon and periventricular regions CSF: Presence of oligo clonal bands	Pulses of intravenous corticosteroids	Improvement of symptoms

Conclusions

POMS can appear with psychotic symptoms, however rare. In the diagnostic process of patients with atypical psychosis, it is useful to continue instrumental and laboratory investigations, including MS in differential diagnosis. Psychosis during the onset or relapse of multiple sclerosis can greatly benefit from treatment with intravenous corticosteroids.

Data Availability Statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethic Statements

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author Contribution

EC, CCT and GT drafted the manuscript for intellectual content. MANF, GM revised the figures and critically reviewed the manuscript. AM, MPC and ST revised the psychological and neuropsychiatric description of the case. EC, CCT and GT prepared the MRI scans as figures and critically reviewed the manuscript. MV and LP critically reviewed the manuscript. LM and SV contributed to review the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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