Case Report

Challenge in Identify Acute Psychosis in Autism: An Illustrative Pediatric Case

Alessia Mingarelli1, Francesca Manzoni2, Paola Olgiati2, Maria Paola Canevini1,3, Aglaia Vignoli1,3,6*, and Elena Zambrelli1

1Epilepsy and Sleep Medicine Center, ASST Santi Paolo e Carlo, Italy
2Child Neuropsychiatric Unit, ASST Santi Paolo e Carlo, Italy
3Department of Health Sciences, University of Milan, Italy

Abstract

Autism Spectrum Disorders (ASDs) are neurodevelopmental disorders characterized by persistent impairments in reciprocal social interaction and communication, restricted interests, and stereotypical behaviors. Sleep problems in ASD are a prominent feature, many of which are often unrecognized. Psychiatric and psychotic morbidities can coexist, making differential diagnosis challenging between an exacerbation of pre-existing symptoms and an organic pathology of new onset.

We describe the case of a 6 years old girl with high functioning ASD presenting new onset of subacute psychotic symptoms (vivid terrific visual hallucinations) and sleep disturbance (difficulty at falling asleep, frequent awakenings). Polysomnography (PSG) detected periodic legs movements during sleep (PLMs – Index 11), persisting during REM sleep, with dystonic features. A slight positivity detection of Anti-GAD Antibodies in serum and CSF was detected. Symptoms improved after corticosteroids and intravenous immunoglobulin treatment.

ABBREVIATIONS

ASD: Autism Spectrum Disorders; SD: Sleep Disorders; AE: Autoimmune Encephalitis

INTRODUCTION

Autism spectrum disorders (ASDs) are complex, pervasive, and multifactorial neurodevelopmental conditions characterized by impairments in social communication and interaction, and restricted, repetitive patterns of behavior, interests, or activities [1]. Heterogeneity of presentation is a hallmark with psychiatric and medical comorbidities frequently reported, including social anxiety disorder, oppositional defiant disorder, attention-deficit/hyperactivity disorder, and intellectual disability [2]. Sleep difficulties are the most common concurrent medical comorbidities in children with ASD, with an estimated prevalence of 50% to 80% [3,4].

The spectrum of sleep disturbances includes sleep initiation and maintenance problems, bedtime resistance, night wakings, parasomnias, insomnia, morning arising problems, and daytime sleepiness [5-7].

Polysomnography (PSG) studies of ASD children confirmed the presence of disrupted sleep architecture mainly related to REM sleep (decreased quantity, increased undifferentiated sleep, and immature organization of eye movements into discrete bursts). Decreased time in bed and total sleep time (TST), reduction of REM sleep latency, and increased proportion of stage 1 sleep are also reported [8-11]. Greater number of muscle twitches compared with healthy controls are recorded [12-14].

Furthermore, psychiatric and psychotic morbidities can coexist [2,15], making differential diagnosis challenging between an exacerbation of pre-existing symptoms and an organic pathology of new onset. We present a case of a child with ASD and rapid worsening of psychiatric symptoms associated with the onset of a sleep disorder. We hypothesize that the psychiatric symptoms might be worsened by the sleep disturbance.

CASE PRESENTATION

We present a 6 years-old-female with ASD diagnosed at 3 years of age without accompanying language and intellectual impairment. No important anamnestic/family data were reported. From the age of six months the parents noticed the presence of stereotyped behaviors, characterized by repeated movements of flexion-extension of the lower limbs, followed by the onset of flapping in the upper limbs. From 14 months, at the nursery school, the teachers reported tendency to isolation, lack of interest in peers, and avoidance of group activities.

At 3 years of age, the patient was referred to a neurological...
center for diagnostic evaluation. Investigations were performed, which resulted negative (EEG, brain MRI, metabolic screening, anti GAD-Abs and anti cerebellum-Abs, Array CGH). Psychiatric assessment was also performed, leading to the hypothesis of ASD.

At the age of 4 years and 7 months the patient was referred to our Neuropsychiatric Unit. A comprehensive evaluation was performed, including behavioral assessment, cognitive profile (Wechsler Preschool and Primary Scale of Intelligence WPPSI-III IQ), ADOS test (Autism Diagnostic Observation Schedule). The evaluation detected cognitive skills within the normal range (total IQ=106) with heterogeneous profile between the verbal (verbal IQ=118) and performance components (performance IQ=100). Diagnosis of ASD was confirmed according to DSM-IV criteria and Autism Diagnostic Observation Schedule (ADOS-2, module 2). The results of the test revealed an overall total score of 12 (Autism cut-off score: 10) indicating a likely diagnosis of Moderate ASD (ADOS2 Calibrated severity score: 6). Difficulties were more evident in the “Reciprocal Social Interaction” area and the “Stereotyped Behaviors and Restricted Interests” area.

At the age of 6 years, she presented a progressive onset and worsening of anxiety symptoms, contact reduction, severe sleep disturbance (difficulty at falling asleep, frequent awakenings), psychomotor agitation, hallucinations, soliloquy, unreasonable laughing, sudden shouts, and regressive behaviors. In few months symptoms worsened with appearance of catatonia, therefore urgent hospitalization was scheduled to perform diagnostic clinical and instrumental tests.

Routine blood and urine tests were normal, including toxicological evaluation, dosage of serum complement factors, anti-nuclear and anti-cardiolipin antibodies, rheumatoid factor, thyroid function and screening for celiac disease. The results of metabolic testing were normal: blood gas analysis, ammonia, lactate, blood and urine amino acids, urine organic acids, carbohydrates, oligosaccharides and glycosaminoglycans. Copper and ceruloplasmin assay, total/esterified carnitine dose, Guthrie test for acylcarnitines, and congenital disorders of glycosylation and neuronal ceroid lipofuscinosis type 1 and type 2.

Genetic analysis for standard karyotype, Rett syndrome (MECP2) and ceroid lipofuscinosis (CLN1 e CLN2) were also normal. Neuro radiological (CT and MRI scan) and neuro physiological evaluations (visual and auditory evoked potentials) were negative.

Cerebrospinal fluid analysis (CSF) for chemical-physical examination, neurotransmitters and oligoclonal bands dosage was normal. The screening assay for infection was also negative in serum and CSF (Mycoplasma, HSV1/2, CMV, EBV, HHV6, HHV8, VZV, JCV). Serum and CSF were negative for anti Ma1, Ma2/Ta, CV2, Yo, Hu, Ri, AmFisina, LG1, Caspr2, AMPA1, AMPA2, NMDA, GABA B1 and VGKC antibodies. Glutamic acid decarboxylase Antibodies (Anti-GAD Abs) showed slight positivity with a serum level of 3,4 UI/ml (v.n. < 1,0 UI/ml) and CSF of 2,3 UI/ml (v.n. < 1,0 UI/ml).

A prolonged Video-EEG-polygraphic monitoring revealed irregular slow theta-delta activity on left temporal lobe during NREM sleep (Figure 1). Polysomnography (PSG) documented the presence of periodic leg movements (PLMs) with dystonic flexor/extensor components and involvement of arms during 1-2 NREM sleep, persisting during REM sleep, which caused awakenings and which persisted during vigilance fluctuations (PLM index: 11 - cut off 5. Sleep efficiency 59%, see Figure 2). Due to increase level of anti-GAD Abs, treatment with intravenous Methylprednisolone (20mg/kg/day for 5 days and progressive decal age according to the following scheme: 15 mg/kg for 3 days, 5 mg/kg for 3 days) replaced with oral therapy with Prednisone (1,5 mg/kg/day for 4 days), in combination with intravenous injection of immunoglobulin (IVIG) at dose of 0,5 g/kg/die, for

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Figure 1 EEG pattern in NREM sleep. The pattern consisted of irregular slow waves predominantly over the left temporal region.
4 days every month for six months, according to the treatment-protocol used in our hospital [16].

After the starting of treatment symptoms improved, with a better interaction with adults, reappearance of movements aim to a purpose, progressive reduction of echolalia and a more restful sleep with fewer nighttime awakenings. Symptomatic antipsychotic treatment was started with low-dose of Risperidone (0,5 mg/die). The patient performed regular follow-up with clinical improvement and stable health conditions in the following months. In particular, the child restarted to interact with parents and environment, recovering purposeful movements (not just stereotypical movements) and she also improved the quality of sleep.

**DISCUSSION**

We report the case of a girl with diagnosis of ASD characterized by regression of social interaction and stereotyped behaviors. The girl experienced a new onset regressive pattern characterized by behavioral disruption with extreme agitation, psychotic symptoms and sleep disorder. These subacute psychotic symptoms (vivid terrific visual hallucinations) could be misdiagnosed as epileptic seizures, especially related to an underlying genetic condition. Terrifying hallucinations associated with focal motor seizures, often sleep-related, or dyscognitive seizures, are prominent features of particular genetic epilepsy associated with Ring chromosome 20 syndromes [17].

Acute psychiatric manifestations are also described as a distinctive electro-clinical pattern of a female-related epilepsy of variable severity, with or without mental retardation and autistic features, characterized by focal seizures with prominent affective symptoms (ictal fearful screaming or prominent hypomotor semiology), suggesting an epileptogenic dysfunction involving the fronto-temporal limbic system [18].

Furthermore, a number of productive symptoms concerning emotions such as “catastrophic” and “depressive” reactions, or deficits in emotion recognition, are described in individuals with temporal lobe epilepsies (TLE) with a predominant involvement of the right hemisphere [19]. To rule out the possibility of an epileptic condition with predominant hallucinatory/affective symptoms, prolonged Video-EEG recording is mandatory. However, in our patient no abnormality was recorded on EEG during the episodes.

On the basis of clinical symptoms and the type of antibodies detected, clinical exclusion of autoimmune encephalitis should be considered. Autoimmune encephalitis is a rare disease characterized by inflammation of brain and the presence of auto antibodies in the bloodstream, directed mostly against synaptic and neuronal cell antigens. Owing to the variety of antigens targeted by auto antibodies, autoimmune encephalitis are clinically heterogeneous; common symptoms include a wide range of psychiatric and neurological symptoms that can affect any age [20], characterized by acute or subacute development of seizures, short-term memory loss, irritability, hallucinations and psychiatric symptoms with a pathogenesis related to inflammation of the mesial temporal lobe [21].

In our patient, the increase of anti-GAD-Abson both serum and CSF, although at low titer, could be seen as an element in favor of the dysimmune nature of psychiatric worsening. In addition, the positive response to immunosuppressive therapy could support this diagnostic hypothesis. Normal findings of MRI scan cannot exclude this diagnosis. Brain MRI is unremarkable in 50% of patients with autoimmune encephalitis and follow-up MRIs either remain normal or show minimum change despite the severity and duration of symptoms [22]. However, because of the low antibody positivity and the presence of a psychiatric condition also previously, the diagnostic hypothesis cannot be confirmed.

A range of psychiatric disorders can present with psychoses as a main feature. Very early onset schizophrenia with onset prior to 13 years of age is extremely rare, but exist [23]. Awareness of childhood-onset schizophrenia is rapidly increasing, with a more precise definition now available of the clinical picture and early signs. The main diagnostic challenges are with differentiating childhood-onset schizophrenia from affective disorders (both depression and bipolar disorder) with psychotic symptoms, pervasive developmental disorders and severe personality disorders [23].

According to the DSM-V definitions, the presence of catatonia can be used as a specifier in psychiatric conditions other than schizophrenia, specifically in the context of autism and other neurodevelopmental disorders, although in our patient other complex psychiatric and neurological features were present.

There is a high prevalence of sleep disturbances among children with ASDs, with an estimated prevalence of 50% to 80% [3,4], many of which are unrecognized [11]. Our patient present a new onset sleep-related movement disorder (PLMs disorder), persisting during REM sleep, with dystonic features.

Thirumalai et al., described REM sleep behavioral disorders in 5/11 patient in children with ASD: symptoms of disrupted sleep and nocturnal awakenings, one of them having PSG-documented PLMs disorder (PLMS disorder index 17/h), have been reported. Sleep abnormalities are also recognized as an accompaniment to autoimmune encephalitis [24-26]. Recent studies have...
described a peculiar movement disorder persisting during sleep characterized by stereotyped limb movements similar to those seen in "Status Dissociates" or RBD in patient with autoimmune encephalitis [27,28].

Sleep disturbances are associated to autoimmune encephalitis and consist of severe insomnia/hypersomnia, dream enactment behavior and nocturnal spells. However, details of the sleep disturbances have not been delineated and the frequency and spectrum of sleep disorders in autoimmunity is largely unknown [25].

The occurrence of a new onset sleep disorder in a patient with a pre-existing neurodevelopmental disorder needs a clear documentation of the sleep pattern throughout a PSG recording. Our patient showed PLMs with dystonic flexor/extensor components and involvement of arms during 1-2 NREM sleep, persisting during REM sleep, which caused awakenings and reduced sleep efficacy.

In conclusion, sleep disorders associated with acute psychosis and ASD are challenging for differential diagnosis in different neuropsychiatric condition. PSG-lab should be considered a diagnostic test for early detection and characterization of sleep disorders, and a useful tool for follow up. Video-EEG recording is mandatory to rule out the presence of epileptic condition with neuropsychiatric condition. PSG-lab should be considered a multidimensional approach. Sleep. 2006; 29: 1563-1571.

REFERENCES