



Case report: Look at my eyes

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Abstract

The comorbidity of migraine and Autism Spectrum Disorder (ASD) still remain unclear. In spite of plausible evidences of such comorbidity, there is a scarcity of populational studies focusing this hypothesis. The diagnosis of migraine in children with ASD is very challenge due to the large clinical heterogeneity and limited communication skills, particularly verbal abilities in young children and those with intellectual disability. ASD and migraine are chronic prevalent disorders sharing some pathophysiological changes (neurotransmission dysregulation, altered immune response, abnormal findings in the cortical minicolumn organization, and dysfunctions in the gut–brain axis), susceptibility genes (including calcium channel mutations and polymorphisms), and atypical sensory processing. Herein, we take advantage of a prototypical case of an adolescent with episodic migraine transformed to chronic, not responsive to preventive treatment, to explore the diagnostic workup and successful personalized clinical and therapeutical management.

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Introduction

The sizable burden caused by migraine in children and adolescents is better expressed by the evidences of poor quality of life^{1,2}, lower school functioning^{3,4}, and high psychiatric comorbidity^{5,6}, particularly in those with high frequency of headache attacks^{7,8}. The psychiatric comorbidity of migraine in childhood is reported by clinical and population-based studies showing a higher prevalence of somatic, depressive and anxiety symptoms^{5,9}, suicide risk¹⁰, psychosocial adjustment problems⁷, and diagnosis of Attention Deficit Hyperactivity Disorder (ADHD)^{11,12}, also with a higher risk in those children with high frequency of attacks.

The comorbidity of migraine with other neurodevelopmental disorders (NDDs) still remain unclear^{13,14}. According to the DSM-5, NDDs are defined as a group of conditions with onset in the developmental period, inducing deficits that produce impairments of functioning¹⁵. NDDs comprise: 1) Intellectual disability (Intellectual Developmental Disorder and Global Developmental Delay); 2) Communication Disorders (language disorder, speech sound disorder, childhood-onset fluency disorder [stuttering], social [pragmatic] communication disorder); 3) Autism Spectrum Disorder (ASD); 4) ADHD; 5) Neurodevelopmental Motor Disorders (Developmental Coordination Disorder, Stereotypic Movement Disorder, and Tic Disorders); and 6) Specific Learning Disorders (Dyslexia, Dysgraphia, Dyscalculia)¹⁵.

Herein, we take advantage of a prototypical clinical case to explore the plausibility of such comorbidities between migraine and NDDs based on their phenotypical overlaps.

Case report

A 14-years-old boy presented to the Glia Institute Headache Clinic complaining episodic headaches for 5 years with an evident worsening in the last 4 months when turned into a daily basis frequency. The location was frontal, affecting both sides of the head but sometimes unilaterally, non-side-locked, with no time preference and no sleep disruption. The pain quality was described as pulsating, with variable intensity, and aggravated by routine physical activity. Before transforming in a daily headache, the attacks were mostly accompanied by nausea, vomiting, photo, phono, and osmophobia. Some reported triggers of the attacks were stressful situations, fasting, prolonged sun exposure, and certain foods. Analgesic and other substance abuse were not disclosed. His early development was unremarkable, and no relevant morbid antecedents was

reported. Magnetic resonance imaging (MRI) performed three months before his first appointment was normal. Previous treatment with flunarizine, propranolol, topiramate, divalproate, and amitriptyline in adequate posology and duration of use was unsuccessful. Clinical and neurological examination was unremarkable, excepting for a short eye contact, a mild generalized hypotonia, and motor clumsiness.

Exploring the possibility of psychiatric comorbidity as a cause of headache chronification in this boy, we expanded the clinical history that revealed important psychosocial adjustment problems dated since his 10 years with reports of poor mixer with other children, teasing and bullying, school phobia, and current symptoms of social phobia with panic attacks, "air hunger", feeling of "suffocation", dysautonomia, and "dread" (sic). In spite of a history of hyperlexia and impeccable school performance, a recent decline in his grades had been observed. The boy reported in his own words the feeling of "melancholy" (sic). The Child Behavior Checklist (CBCL)¹⁶ revealed many internalizing symptoms with abnormal scores in the following domains: withdrawn, somatic complaints, anxious-depressed, social and thought problems. The Executive Function Inventory for Children and Adolescents (EFICA)¹⁷ showed marked difficulties in emotional regulation, self-monitoring, and cognitive flexibility. Back to the clinical setting looking for more information we could verify a poor eye contact, a speech over-precise and pedantic, mannered vocabulary, excessive literal interpretation, maliciousness, failure to use non-verbal social skills (i.e. eye contact, gestures, body posture, facial expressions), invasive and unpleasant behaviors, and unusual specific interests (i.e. Astronomy, the beginning of the universe, engines). He is of average intelligence but listening to him talk about his favorite topics appears to be extremely bright. The anamnesis also revealed subtle symptoms of unusual distress due to light touch on skin or scalp, unexpected noises, noisy and crowded places (e.g. supermarket, shopping centers), and food selectivity.

The Australian Scale for Asperger's Syndrome¹⁸ unlocked aberrant skills in the following domains: social and emotional, communication, cognitive, movement, and specific interests, fulfilling the DSM-515 diagnostic criteria for Autism Spectrum Disorder Level 1 (requiring minimal supports, formerly known as Asperger's Syndrome) and Adjustment Disorder with Mixed Anxiety and Depressed Mood.



A polypharmacotherapy with venlafaxine, aripiprazol, and topiramate was introduced in association with cognitive behavior therapy (with focus on psychosocial adjustment, executive functions, theory of mind, and socioemotional skills), and psychoeducational interventions with the patient, his parents and school staff. After two weeks of treatment a significant relief of headache (frequency, duration, and intensity) and anxious-depressive symptoms was reported. Two months later, the patient reported a >80% reduction in the monthly migraine days, as well as a total remission of depressive symptoms and panic attacks. No side effects were reported. During the 12 months follow-up, a sustained satisfactory effect was observed in migraine control and the boy showed much better social functioning, the grades raised again, and the bullying events finally ceased.

Discussion

ASD is a multifactorial and dimensional NDD characterized by difficulties in social interaction and communication, restricted and repetitive patterns of behavior, interests and activities and altered sensory processing¹⁵. The prevalence of autism has increased dramatically during the last two decades from 1/167 in 2000 to 1/44 children in 2018, with a four times greater frequency in males than females¹⁹. The clinical heterogeneity of the ASD is well represented in the case herein reported which the diagnosis was lately defined in adolescence due to headache, panic attacks, anxious-depressive symptoms, and recent declining in school achievement, not because the core manifestations of the ASD. Formerly known as Asperger's Syndrome, the DSM-5 classification and diagnosis criteria has currently defines these "subtle" cases as ASD level 1, which require minimal supports and sometimes are associated with high cognitive abilities and even savant skills²⁰.

The heterogeneity and complexity of ASD hinder the better understanding and diagnosis of co-occurring/comorbid conditions such as headache/migraine due to the limited communication skills, particularly verbal abilities in young children and those with intellectual disability.

Comorbidity in ASD is the rule rather than the exception and may explain the higher risk of premature mortality in autistic individuals, compared to the general population²¹⁻²³. The most commonly reported ASD comorbidities are NDDs, epilepsy, cerebral palsy, sleep disorders, psychiatric disorders (anxiety, depression, obsessive-compulsive disorder, psychotic disorders, substance use disorders, oppositional defiant disorder, eating disorders, personality

disorders), and general medical conditions (gastrointestinal problems, immune dysregulation, genetic syndromes)^{24,25}.

The plausibility of ASD and migraine comorbidity may be grounded in important common features, as follows: both are chronic prevalent disorders, affecting 2 and 10% of children and adolescents worldwide, respectively^{19, 26,27}; they share some pathophysiological changes (neurotransmission dysregulation, especially of the serotonergic system²⁸; altered immune response causing neurogenic neuroinflammation²⁹; abnormal findings especially in the cortical minicolumn organization³⁰; and dysfunctions in the gut-brain axis^{31,32}); susceptibility genes (including calcium channel mutations and polymorphisms^{34,35}); and atypical sensory processing³⁶. However, there is a scarcity of populational studies focusing in this apparently unusual comorbidity³³.

A recent systematic review and meta-analysis study based on 6 studies (5 case-control studies and 1 prevalence study totalizing 5240 participants) found that children with ASD have a higher risk of having headaches or migraines than controls without ASD (pooled odds ratio = 1.86, 95% CI = 1.42-2.40) and a lower risk compared to children with ADHD (pooled odds ratio = 0.63, 95% CI = 0.47-0.84)²⁵. However, substantial heterogeneity was found across studies due to their methodological diversity.

More relevant findings come from a large cohort study performed in Taiwan comparing 18,035 children and adolescents with ASD and 18,035 age- and sex matched controls. The participants were monitored from 2001 until the end of 2011. After adjustment for medical and psychiatric comorbidities, children and adolescents with ASD showed a significantly higher risk of developing migraine than controls without ASD (hazard ratio = 2.71, 95% CI = 1.63-4.51)³⁶.

Accordingly, the present case clearly demonstrates the importance of a comprehensive investigation of NDDs, including ASD, in children with migraine, especially in those with a high frequency of attacks and not responsive to prophylactic treatment. The diagnostic approach and personalized clinical and therapeutical management have made a difference in this case of utmost importance for clinicians who care children with headache.

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Authors contribution

MAA, acquisition, analysis, and interpretation of case report data, drafting and revising the manuscript; RA, acquisition, analysis, and interpretation of case report data, drafting and revising the manuscript.

Conflict of interest

The authors testify no conflict of interest.

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