Association of Autism Spectrum Disorder with Pre-symptomatic Duchenne Muscular Dystrophy: Isolated Elevation of Transaminases as a Diagnostic Clue

To the Editor,

A 3-year-old-boy firstborn to a nonconsanguineous couple presented with isolated language delay. He spoke only one to two meaningful words, demonstrated poor eye contact, poor nonverbal communication, reduced sharing of interest with parents, decreased imaginative play, absence of interest in peers, and considerable deficit in social-emotional reciprocity. He also had simple motor stereotypes, idiosyncratic phrases, and echolalia, along with ritualistic behavior like lining up objects. He also had an excessive preoccupation with inanimate objects like chocolate wrappers, adverse response to loud sounds, excessive smelling of foods before eating, and visual fascination with spinning objects. He satisfied the DSM-V criteria for autism spectrum disorder with a childhood autism rating scale score of 33. He achieved sitting independently at 8 months, standing at 11 months, walking at 1 year of age, and running at around 1½ years of age. Similarly, fine motor milestones including immature and mature pincer grasp were attained at 9 and 12 months, respectively. At the time of presentation, the child was able to pedal a tricycle, catch a large ball, jump with two feet, walk upstairs and downstairs, wash and dry his hands, dress himself with a little assistance, turn pages in a book, one page at a time. His muscle tone, power, muscle stretch reflex, any calf muscle fullness Neuroimaging, and routine laboratory parameters were within normal limits, except elevated liver transaminases (AST-356U/L, ALT-289U/L), without any clinical signs of hepatic involvement. Serum creatine

phosphokinase (CPK) was also elevated (1239U/L). Multiplex ligation-dependent probe amplification detected an out-of-frame hemizygous deletion of exons 49 and 50 of the dystrophin gene, consistent with the diagnosis of Duchenne muscular dystrophy (DMD). Chromosomal microarray and whole exome sequencing detected no additional pathogenic variants. The child was started on applied behavior analysis and close monitoring for motor symptoms.

Dystrophinopathy is the commonest muscular dystrophy in males with X-linked inheritance.[1] Although a minority proportion of affected children have a delay in attainment of motor milestones, most of the cases become symptomatic between 3 and 6 years of age with difficulty in getting up from sitting or squatting position, gait abnormality, and frequent falls during walking.[2] Autism spectrum disorder is also at least four times more common in males and many candidate genes are predisposing toward autistic features on X chromosomes like TRPM3, although autism does not follow a mendelian X-linked inheritance pattern.[3,4] Studies have demonstrated a higher prevalence of difficulties in communication and social behavior, including autistic features in children with DMD, even up to an extent of 19.6%.[1] However, the detection of asymptomatic cases of dystrophinopathy in autistic children like our case was not reported in the existing literature. With the discovery of new effective drugs for DMD including Eteplirsen and Ataluren, it is highly imperative to diagnose presymptomatic/early symptomatic ambulatory DMD cases. Isolated transaminitis without any clinical evidence of hepatic dysfunction should strongly raise suspicion of muscular diseases and in such cases, simple tests like serum creatine phosphokinase may help in suspecting these co-morbidities. Affected cases of dystrophinopathy show highly elevated levels of serum CPK right from birth, thus making it one of the most sensitive, albeit nonspecific screening tests for presymptomatic cases.[2,3] Clinicians should suspect DMD even in the absence of classical clinical features in autistic children with unexplained transaminitis. Children with mutations between exon 31 and 62, as in our case demonstrate more autistic symptoms compared to those with mutations upstream of exon 30. Dystrophin isoforms, especially shorter dystrophin isoforms like Dp140 and Dp71 are widely expressed in the brain and cumulative loss of these isoforms has been postulated to predispose towards intellectual disability and behavioral abnormalities.[5]

This association of autistic spectrum disorder and Duchene muscular dystrophy needs to be kept in mind even in asymptomatic children when there is an isolated elevation of transaminases and serum CPK.

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None

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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