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A new case of white-sutton syndrome associated with celiac disease

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Abstract: White-Sutton syndrome (WHSUS) is a neurodevelopmental genetic disorder caused by de novo heterozygous pathogenic variants in POGZ gene. The phenotypic spectrum of the WHSUS is very broad and mainly includes a wide range of neurocognitive and neurobehavioral symptoms, developmental delays, hypotonia, autism spectrum disorder, typical facial features, functional and anatomical gastrointestinal anomalies. We describe a new WHSUS patient harboring a novel, heterozygous, de novo, likely pathogenic variant in the POGZ gene highlighting various components of his neurodevelopment, such as the presence of autistic spectrum disorders, speech and mental delays and the association of WHSUS with celiac disease (CD) that has never been described to our best of knowledge. Knowing that gastrointestinal symptoms are one of the most common WHSUS clinical findings, it becomes critical to carefully analyze these symptoms and, in some cases, to start with a CD screening to see whether they are consistent with celiac disease and if CD could be another WHSUS comorbidity, thus broadening the phenotypic spectrum of WHSUS.

Keywords: POGZ, Intellectual disability, Autism, Developmental delay, Speech delay, Celiac disease

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1 Introduction

White–Sutton syndrome (WHSUS, OMIM: 616364) is an autosomal dominant genetic condition caused by de novo heterozygous pathogenic mutations in the POGZ (pogo transposable element-derived protein with zinc finger domain) gene, which is located on chromosome 1q21.3. (Assia Batzir et al., 2020; Assia Batzir et al., 2021).

This gene encodes a multi-domain nuclear protein that influences chromatin remodeling, chromosome segregation and mitotic progression. Due to dysfunction of POGZ gene, the majority of the cells are unable to form metaphase plates, consequently end prematurely mitosis, causing problems on brain`s development and function (Assia Batzir et al., 2020; Assia Batzir et al., 2021; Donnarumma et al., 2021; Liu et al., 2021; Nozawa et al., 2010; Dentici et al., 2017). More than 90 patients with a pathogenic mutation in POGZ have been reported so far (Assia Batzir et al., 2021).

White–Sutton syndrome is a neurodevelopmental disorder defined by a variety of clinical features such as cognitive dysfunction, developmental delays (particularly in speech and language acquisition), hypotonia and other behavioral problems (Assia Batzir et al., 2021). Up to 0.14% of patients with unexplained autism spectrum disorder ASD or intellectual disability are reported to have de novo gene mutations linked to WHSUS (Liu et al., 2021). Feeding and gastrointestinal problems, sleep disturbance (particularly sleep apnea), mild genital abnormalities in males and urinary tract involvement in both males and females, microcephaly, sensori neural hearing loss refractive errors and strabismus, short stature, tendency towards obesity are among other commonly reported features (Assia Batzir et al., 2021).

We are reporting a case, of a new pediatric patient with a novel, heterozygous pathogenic variant in *POGZ* gene, emphasizing some aspects of his neurodevelopment including the presence of autistic spectrum disorders, speech and mental delays as well as the association of WHSUS with celiac disease (CD), which, to the best of our knowledge has never been described so far.

2 Case Presentation

The patient, a 7-years-old boy, is the only child of two Albanian non consanguineous parents. He was born naturally, at 39-th gestational week after a quite uneventful pregnancy, besides the fact that at 36th gestational week an ultrasound examination noticed small head circumference and low weight of the baby. At birth his weight was 2600 gr and he couldn't suck the breast for the first two weeks. Since the first months of life, the patient presented hypotonia with consequent delay of the developmental milestones as he was able to sit without support only at 12 months and move the first independent steps at 30 months. The child pronounced his first words at 30 months, but he never achieved appropriate language skills. Bowel and bladder continence was gained at 4 years old. At 25 months, he was hospitalized in neuropediatric unit with the presence of focal onset seizures. He was diagnosed with generalized myoclonic Epilepsy and started treatment with Levetiracetam up to 300 mg/day. Sleep EEG showed paroxysmal activity at right parieto-occipital areas. Neurologic examination resulted with

presence of pyramidal syndrome, spasticity and Dexter Hemiparesis. He was treated for 2 years with antiepileptic medication and at 4 yrs. old this treatment was gradually interrupted. During the epilepsy treatment period, a CT scan was performed, which resulted without brain lesions, nasal adenoid hypertrophy and the lack of mastoid cells pneumatisations. When he was about 3 years old, due to lack of communication (expressive language less than 10 words), he was referred for developmental evaluation. Hearing function was unaffected. It was noticed the lack of extra-linguistic elements of communications, poor eye contact, inattentive laughs, individual non-functional playing activity, lack of interactive activities, lack of spontaneous finger pointing, presence of stereotypic hand movements and other stereotypic repetitive activities. Motor skills were deficient in fine movements. He was diagnosed with Autism spectrum disorder and started ABA therapy (the questionnaires such as the Childhood Autism Rating Scale and the Social Responsiveness Scales, and also MSE and ASD diagnostic interview were used). At the age of 6 yrs. and 7 months he was consulted for a psycho-motor evaluation where the lack of speech was the main complaint of his parents. Expressive language was not developed. He turns his head when called by name, gives objects to others under instruction, has learned to use his index finger when asked, points eyes, nose, mouth. He can successfully identify family members or point fingers at them. Had started imitating animals: moo, bee, ham, mau. Short eye contact, poor imitation skills even when just given an example. He had hyperactive behavior, unintentional and uncontrolled movements in the assessment room. He did not play a functional game, he shows a desire to interactive play but just for a few seconds as he fails to concentrate and to understand the task given to him. He often expressed irritation and aggression with others, with children in kindergarten, mostly when there are sudden changes in the rules of the environment. Fine motor skills were improved but still remained shallow (he holds a toy from one hand to the other, grabs and pushes things with his hand, places cubes on top of each other, grabs the pencil well and scribbles). He still couldn't use the spoon or wash his hands without help. He managed to drink water from the glass himself and assisted in the process of dressing-undressing. He could joined points in horizontal and vertical line, managed to close the circle and color them. He failed to mimic the drawing of a square or triangle. Gross motor skills were improved (he walks, goes up and down, runs, climbs the slide and slips without help). Ophthalmologist consultation showed a normal papilla, transparent anterior lens, macula in the limits of its diameter. The presence of strabismus is not noticed in both viewing angles (near and far). Cranial nerves responsible for eye mobility showed normal function. Patient`s mother also referred some mild gastro-intestinal signs, such as sporadic abdominal pain and constipation. Thyroid function and thyroid ultrasound examination were normal too. Blood laboratory tests and ferritin level were normal. There was a low level of Calcium -8.8 mg/dL (8.8-10.8) and magnesium-2.00 mg/dL (2.09-2.84) in the blood. Stool culture and stool examination for G. Lamblia were negative. Assessment of tissue transglutaminase IgA antibodies showed an increased values of an antibody titer (anti IgA-93.8 U/mL (normal range < 20 serum ELISA) and this drew our attention. We performed a second re-evaluation of the antibody titer which also resulted in high values (101 U/ml). Since the titer of antibodies to tissue transglutaminase was approximately 5-fold above the norm, following the ESPGHAN (European Society for Pediatric Gastroenterology, Hepatology and Nutrition) guidelines, we performed the duodenal biopsy through endoscopy of the upper digestive tract.

Macroscopically the duodenal and antral mucosa looked normal. For microscopic evaluation, duodenal mucosa samples has been taken from the duodenal bulb and from distal part of duodenum. To exclude a gastric inflammation and the presence of Helicobacter pylori, biopsy samples have been also taken from antral aria of the stomach. The microscopic examination of antral mucosa was normal, while the histologic picture of the duodenal mucosa was characterized by the presence of the moderate amounts of LIE (intraepithelial lymphocytes) associated with mixed infiltrates in the lamina propria without atrophy of villous. This histological framework strongly suggests the presence of Celiac Disease, grade A type I (Marsh 1) (Figure 1).

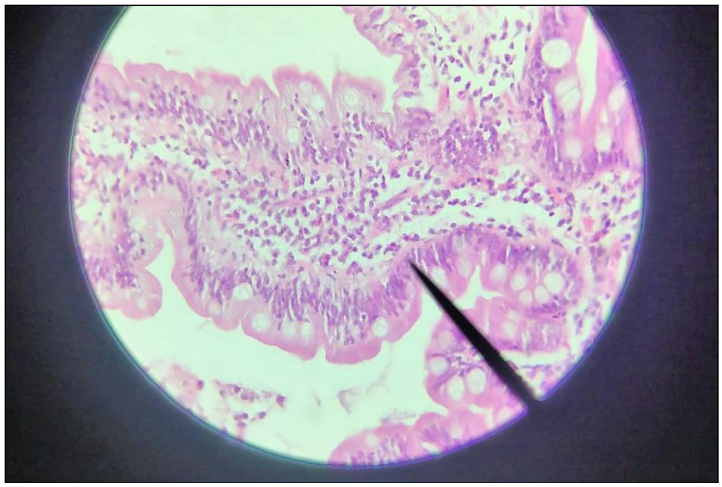

Figure 1: Biopsy image of the duodenal mucosa characterized by the presence of the moderate amounts of intraepithelial lymphocytes associated with mixed infiltrates in the lamina propria without atrophy of villous.

Due to the all above results we performed the HLA typing for the determination of the responsible alleles DQ2/DQ8. HLA typing showed the detection of Dpl2 cis haplotype (hybridization zone DQA1 * 05-DQB1 * 02-DRB1 * 03 genotype-DQA1 * 05-DQB1 * 02-DRB1 * 03 phenotype–DQ2 cis). Taking into consideration all of the above mentioned results and clinical features, we concluded that our patient has potential form of Celiac Disease, which according to the recommendation of ESPGHAN guidelines requires clinical, laboratory and serology analysis as well as further biopsies to monitor possible evolution of villous atrophy (Husby et al., 2020).

We performed the genetic testing because POGZ gene is strongly suspected of being one of the most mutated gene in neurobehavioral and neurocognitive disorders, such as developmental delay, learning difficulties, intellectual disability and autism (Assia Batzir et al., 2020; Assia Batzir et al., 2021; Matsumura et al., 2016). Genomic DNA was extracted from peripheral blood in dried blood spot and the genetic test was developed and its performance was validated by CENTOGENE AG. Molecular genetic testing in our patient identified the presence of a novel, heterozygous, de novo, likely the pathogenic variant in the *POGZ* gene. This result is consistent with the genetic diagnosis of autosomal dominant White-Sutton syndrome. The POGZ variant c.744dup p. (Thr249Aspfs*66) which occurs in exon 6 of the transcript NM_015100.3 (which has a total of 19 exons) creates a shift in the reading frame

starting at codon 249. The new reading frame ends in a stop codon 65 positions downstream. De novo status has been confirmed by parental testing. It is classified as likely pathogenic (class 2) according to the recommendations of CENTOGENE and ACMG.

3 Discussions

A proband is diagnosed with WHSUS in the presence of suggestive clinical features and heterozygous pathogenic variant in POGZ gene found by molecular genetic testing (Assia Batzir et al., 2021). The investigation of the genetic molecular basis of WHSUS in our patient reveals the presence of a novel, heterozygous, de novo, POGZ variant c.744dup p. (Thr249Aspfs*66), that creates a shift in the reading frame starting at codon 249 ending in a stop codon 65 positions, downstream, similar to the majority of pathogenic variants documented heretofore, which cause premature termination codons (Assia Batzir et al., 2021). This variant has never been seen at CENTOGENE in other patients. It is also not listed in the major published available database (HGMD, ClinVar, gnomAD). De novo status has also been confirmed by parental testing. The mutational and clinical and spectrum of WHSUS is very well characterized in our patient.

White-Sutton syndrome is a pleiotropic condition mostly characterized by a wide range of neurocognitive and neurobehavioral symptoms, developmental delays, hypotonia and autism spectrum disorder (Assia Batzir et al., 2020; Assia Batzir et al., 2021). Most of these clinical characteristics are present in our patient, including: moderate to severe developmental delay, intellectual disability and learning difficulties, generalized hypotonia at a very early age, speech and motor delay (especially fine motor skills delay), behavioral problems such as anxiety, attention-deficit/hyperactivity disorder, aggression towards self or others, and sleep disturbance, microcephaly (Assia Batzir et al., 2020; Assia Batzir et al., 2021).

The patient's development assessment fulfilled DSM (Diagnostic and Statistical Manual) criteria of autistic spectrum disorder, which is known as WHSUS comorbidity and found in up to 50% of patients reported so far. De novo mutations in POGZ gene linked to WHSUS have been identified in up to 0.14 percent of patients with unexplained ASD or intellectual disability (Assia Batzir et al., 2020; Assia Batzir et al., 2021; Liu et al., 2021; Stessman et al., 2016). This presented case report demonstrates the importance of evaluating patients with WHSUS for autism, not only to detect mild autistic phenotypes and to better understand the autism prevalence in POGZ-related syndrome, but also to diagnose other probable behavioral disorders (Donnarumma et al., 2021). Our patient had generalized myoclonic epilepsy, even though epilepsy, as well as febrile seizures and EEG abnormalities, were reported only in a few WHSUS patients in the literature (Assia Batzir et al., 2021; Pascolini et al., 2020; Samanta et al., 2020). Our patient has a high and broad forehead, tented or triangular mouth with downturned corners, mid face hypoplasia, a broad nasal root, but this disease cannot be diagnosed clinically solely on the basis of facial or other phenotypic aspects, as it has been suggested (Assia Batzir et al., 2020; Assia Batzir et al., 2021).

We would like to point out that, in addition to the patient's neurocognitive and neurobehavioral symptoms, developmental delays, hypotonia, autism spectrum disorder, and

typical facial features, he also demonstrates some mild gastro-intestinal manifestations, such as sporadic abdominal pain and constipation, as reported by his mother. According to a study of about of 89 % of patients had GI involvement and POGZ might play a role in the etiology of intestinal tract disorders and maybe in gastrointestinal motility (Assia Batzir et al., 2020; Assia Batzir et al., 2021). Even though GI involvement appears to be a key component in WHSUS, it is still under-characterized, possibly due to under-reporting of mild to moderate symptoms, such as constipation and gastroesophageal reflux, which are rather frequent in the general population (Assia Batzir et al., 2020; Assia Batzir et al., 2021; Dentici et al., 2017; Stessman et al., 2016; White et al., 2016). We would like to underline that, based on the findings of the tests, our patient has been diagnosed with CD, which could be another related comorbidity of WHSUS, hence broadening the phenotypic spectrum of WHSUS. CD is a chronic, immuno-mediated systemic disease with a wide range of clinical manifestation varying from typical gastrointestinal (GI) problems to an extra-intestinal involvement (White et al., 2016). Based on the classifications of clinical forms of CD and the test results (a positive CD-serology, as well as a genetic predisposition to CD [positivity of the locus HLA-DQ2 and/or -DQ8], but without the typical alterations of the small bowel mucosa) we concluded that our patient has the "potential" form of Celiac disease (Prosperi et al., 2021; Al-Toma et al., 2019, Nenna et al., 2013, Kurppa et al., 2011). In children, about 20% of patients with potential Celiac Disease more often experience intestinal symptoms, such as malabsorption, chronic diarrhea, and recurrent abdominal pain (Tosco et al., 2011; Lionetti et al., 2012; Auricchio et al., 2014).

4 Conclusion

In conclusion, despite the fact that this is the first report of an association between CD and WHSUS, we can make certain assumptions: Considering that gastrointestinal symptoms are one of the most common WHSUS clinical findings, it appears crucial to carefully analyze these symptoms and, in some cases, to begin with a CD screening to determine whether these are consistent with celiac disease and whether CD could be another comorbidity of WHSUS, consequently broadening the phenotypic spectrum of WHSUS.

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Conflict of interests

The authors declare no conflict of interests.

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