A novel variant of DeSanto-Shinawi Syndrome with joint manifestations

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ARTICLE INFO

Keywords:
DeSanto-Shinawi syndrome
Juvenile Idiopathic Arthritis
Limited range of motion
Autophagy
Autoimmunity

ABSTRACT

The clinical features associated with WAC haploinsufficiency include recognizable dysmorphic facial features, variable degrees of developmental delay and intellectual disability that were recently delineated as DeSanto-Shinawi syndrome (OMIM 616708). We describe a patient with DeSanto-Shinawi syndrome caused by a novel frameshift variant in WAC gene (NM_016628.4(WAC):c.1689del (p.Phe563Leufs*6)). As noted in cases previously reported, our patient phenotype included facial dysmorphism, intellectual disability, behavioral problems, feeding difficulties, hirsutism, constipation and astigmatism. She also had limited range of motion of joints since birth and Juvenile Idiopathic Arthritis diagnosed at eleven years old. Although in the last years some additional features were reported in DeSanto-Shinawi syndrome, joint manifestations have not been previously described. As limited range of motion of joints was reported since birth with no correlation with arthritis onset, it could be a new clinical feature. Polyarthritis in this patient can be only a coincidence, since there is a first degree relative with psoriasis, or might be related to WAC mutation. Indeed, WAC encodes a protein that plays a vital role in autophagy. It has already been demonstrated that WAC haploinsufficiency leads to increased autophagy and, according to different authors, increased autophagy may display a pathogenic role in several autoimmune disorders such as Rheumatoid Arthritis and Juvenile Idiopathic Arthritis. Thus, WAC haploinsufficiency may have contributed to autoimmune disorder in this patient.

1. Background

Intellectual disability (ID) is a heterogeneous disorder, both clinically and genetically (Lugtenberg et al., 2016). WAC-related ID is an uncommon autosomal dominant genetic condition caused by loss-of-function mutations in WAC gene (Varvagiannis et al., 2017). The clinical features associated with WAC haploinsufficiency include recognizable dysmorphic facial features that were recently delineated as DeSanto-Shinawi syndrome (DESSH, OMIM 616708) (Vanegas et al., 2018). Until 2020, only twenty patients have been described with DESSH and all have been identified to have a de novo mutation in the WAC gene (Alashlawi et al., 2020).

Facial features are nonspecific but mildly dysmorphic: square-shaped face with a broad or prominent forehead, deeply set eyes with long palpebral fissures, broad or depressed nasal bridge and wide mouth with a broad chin. Others features that may be observed include synophrys, hypertelorism, epicanthus, and bulbous nose or broad nasal tip (Varvagiannis et al., 2017).

It is typically characterized by variable degrees of developmental delay and intellectual disability. In the majority of patients behavioral abnormalities are observed including anxiety, attention deficit hyperactivity disorder or autism spectrum disorder. Most affected infants have significant but nonspecific features at birth such as neonatal hypotonia and feeding problems. Some patients previously described had abnormal vision including cortical visual impairment, strabismus and refractive errors. Other less specific features of this diagnosis include: seizures, brachydactyly, presence of fetal finger pads, planovalgus deformity of the feet and inverted nipples (Varvagiannis et al., 2017).

In the last years some cases displayed additional problems: two patients were reported to have recurrent infections by Vanegas et al. (2018) and Alashlawi et al. (2020), one associated with hypogammaglobulinemia (Varvagiannis et al., 2017)(3). Even so there is no description of joint involvement. We describe a patient with DESSH with limited range of motion (ROM) of joints reported since birth and Juvenile Idiopathic Arthritis (JIA) diagnosed at 11 years old. Additionally, our patient also had Von Willebrand Disease.

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https://doi.org/10.1016/j.ejmg.2022.104534
Received 2 February 2022; Received in revised form 9 May 2022; Accepted 26 May 2022
Available online 28 May 2022
1769-7212/ © 2022 Published by Elsevier Masson SAS.
2. Case report

Eleven-years-old female, first child of non-consanguineous Caucasian parents. Her father had psoriasis but was otherwise healthy. Both pregnancy and delivery were uncomplicated with Apgar scores of 9 and 10 at first and fifth minute, respectively. Her birth weight was 3250g (0 Z-score), length was 51 cm (+0.5 Z-score) and head circumference was 35.8 cm (+0.5 Z-score). During the first year of life, she presented larngomalacia associated with feeding difficulties that resolved spontaneously. A development delay was first noticed at six months of age when she started exhibiting motor delay; sitting independently at ten months and walking at two years. Language development was also delayed, at four years old she continued to use only non-verbal communication for which she started speech therapy. She also needed early education intervention at school. Some behavioral problems were noticed, including anxiety and attention deficit hyperactivity disorder (ADHD). Thereby she was placed on methylphenidate by the age of 9 years, with learning improvement. No social problems were identified.

Her physical growth gradually declined and by the age of 12 years she was diagnosed with short stature (stature $-2$ Z-score). Growth hormone deficiency and secondary causes of short stature were excluded and Synacthen test was normal. Functional constipation was documented.

Physical examination revealed dysmorphic features, including square-shaped face with a prominent forehead, deeply set eyes, hirsutism, synophrys, bilateral hypoplasia of the thanar eminence and alterations in tooth structure.

By the same age that she started to cross growth percentiles (eleven years old), she was referenced to pediatric rheumatological evaluation due to joint complaints. An additive symmetric polyarthralgia was reported, involved wrists, slowly progressed to involve the neck, shoulders, knees, ankles and interphalangeal joints over a period of one year along with morning stiffness and limited range of motion. She presented bilateral subcutaneous nodules over the wrists. Fever, weight loss, rash, gastrointestinal symptoms and aphthous were absent. No previous gastrointestinal or respiratory infection was reported. At first consultation she had fourteen active joints (which are defined as non-bony swelling or limitation of motion with either pain on motion or tenderness to palpation). She had six swollen joints (wrists, tibiotarsal joints and second and third metacarpophalangeal joints of left hand) and limitation of motion with pain of shoulders, elbows, ankles and knees.

Laboratory findings showed a mild increase in C-reactive protein (12.7 mg/L) level and erythrocyte sedimentation rate (34 mm/h); ANA titer was 1:80; rheumatoid factor, HLA-B27 and anti-dsDNA were negative. An ultrasound confirmed intra-articular effusion at metacarpophalangeal joints of left hand and chronic polyarthritis ten years after, which to the best of our knowledge has not been previously described.

3. Genetics analysis

An array-CGH was first performed which revealed no alterations. Subsequently clinical exome was performed. The coding and flanking intronic regions were enriched using Agilent solution (Agilent Technologies) and sequenced using the NExtSeq system (Illumina). Clinical exome sequencing revealed a heterozygous frameshift variant in WAC gene (NM_016628.4(WAC):c.1689del (p.Phe563Leufs*6)), resulting in a premature stop codon and a truncated protein, a novel likely pathogenic genetic variant. The variant was not present in both parents (confirmed by Sanger sequencing).

4. Discussion

Our patient phenotype included facial dysmorphism, ID, behavioral problems, feeding difficulties, hirsutism, constipation and astigmatism as noted in patients previously described. No formal clinical diagnostic criteria exist for WAC-related intellectual disability (Varvagiannis et al., 2017).

Additionally, our patient displayed limited ROM of some joints since birth and chronic polyarthritis ten years after, which to the best of our knowledge has not been previously described.

WAC encodes a protein-regulating transcription-couple histone H2B ubiquitination. According to DeSanto et al. (2015), the severity of phenotype and clinical features could vary depending on the position of the mutation (DeSanto et al., 2015). Furthermore, the more severe phenotype may also be caused by others yet unknown potential genetic modifier(s) or reflects the severe end of the clinical spectrum caused by WAC haploinsufficiency (Lugtenberg et al., 2016). These, along with the fact that is a novel mutation, could explain not only why our patient didn’t present some clinical features related to DESSH, but also the new manifestations not previously described.

In this patient the limited ROM of joints was present since birth many years before the arthritis onset, with no improvement after control of disease activity. Delayed diagnosis and late remission are the main causes of sequelae in JIA patients. However, in our patient JIA was timely diagnosed and the control of disease was rapidly achieved. Since the authors didn’t find any other explanation for it and there are no previous reports of this manifestation in patients with DESSH, this could be a new clinical feature.

Polyarthritis in this patient can be only a coincidence, since there is a first degree relative with psoriasis, or might be related to WAC mutation. Indeed, WAC encodes a protein that plays a vital role as a transcription regulator in several biological processes, including autophagy (Alsablawi et al., 2020). According to Joachim J. et al. (2012), WAC regulates autophagy because is required for autophagosome formation and, considering WAC nuclear localization and function, it may also control the transcription of autophagy-related genes (Joachim et al., 2012).
Nowadays, it is widely accepted that autophagy is involved in several pathophysiological processes and complex diseases, such as autoimmune disorders, because it is an essential process for immune system regulation, activating innate and adaptive immunities (Vanegas et al., 2018). Concerning WAC haploinsufficiency, David-Morrison et al. (2016) have demonstrated that loss of WAC leads to neuronal dysfunction, defective mTOR activity and increased autophagy (David-Morrison et al., 2016). Therefore, the de novo WAC mutation may have contributed for this inflammatory manifestation in our patient.

In fact, increased autophagy may display a pathogenic role in several autoimmune disorders such as Rheumatoid Arthritis (RA) and JIA (Wu and Adamopoulos, 2017; Yin et al., 2018). Autophagy influences RA pathology in two major ways: synovial inflammation and bone destruction (Wu and Adamopoulos, 2017). Increased levels of autophagy have been observed in the synovial tissues from patients with active RA and are correlated with disease activity. Additionally, increased autophagy has been observed in RA CD4+ T cells, resulting in T-cell hyperactivation and resistance to apoptosis (Yin et al., 2018). Autophagy also modulates osteoclast-mediated bone destruction and inhibition of autophagy using ATG5/lysMCre+ transgenic mice show reduced bone destruction in TNF-mediated arthritis (Wu and Adamopoulos, 2017).

In JIA, inflammation in the joint synovial fluid is characterized by an increase in autoreactive, highly activated effector T cells and impaired control by Treg, but the exact disease mechanism remains unclear (Peeters et al., 2017). Peeters et al. (2017) studied autophagy in T cells of JIA patients and observed that autophagy is increased in T cells obtained from inflamed joints (Peeters et al., 2017). However, the same study couldn’t conclude if increased autophagy is a cause or a consequence of disease pathology.

We cannot establish a link between Von Willebrand disease (VWD) and WAC mutations. Although one patient of DESSH has been described to developed leukopenia and thrombocytopenia, no other types of hematological abnormalities were described (Uehara et al., 2018). Furthermore, no genetic causality seems to exist between DESSH and VWD.

5. Conclusion

In conclusion, we describe a patient with a novel mutation in WAC gene with recognizable clinical and craniofacial dysmorphic features plus a new manifestation since birth – limited ROM of joints. The patient also presented chronic polyarthritis diagnosed as JIA. Considering the role of this gene in autophagy, WAC haploinsufficiency may have contributed to this autoimmune disorder. However, further reports and experimental studies are required to confirm this observation.

CRediT authorship contribution statement

Joana Branco: Writing – original draft, wrote the manuscript. Marta Amorim: reviewed the manuscript. Marta Conde: reviewed the manuscript. All authors have read and approved the final manuscript.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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