Jejunal atresia, periodic fevers and psoriatic arthropathy in Baraitser Winter malformation syndrome

Avi Saskin[1], DDD Study[2], Marc Tischkowitz[3]

1. Department of Medical Genetics, McGill University, Montreal, Quebec, Canada
2. Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK
3. Department of Medical Genetics, University of Cambridge, Cambridge, UK

Corresponding author:
Dr. Marc Tischkowitz
University Reader and Honorary Consultant in the Department of Medical Genetics at Cambridge
Department of Medical Genetics, Box 134, Level 6, Addenbrooke's Treatment Centre, Addenbrooke's Hospital, Hills Rd., Cambridge CB2 0QQ, United Kingdom
mdt33@cam.ac.uk.

Running head: Jejunal atresia in Baraister Winter syndrome

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Key features

Baraitser Winter malformation syndrome
ACTB
Jejunal atresia
Recurrent fevers
Psoriatic arthropathy

Introduction

Baraitser Winter malformation syndrome (BWMS, OMIM 243310) is an autosomal dominant multi system disorder characterized by typical craniofacial features, intellectual disability, brain malformation, iris or retinal coloboma, sensorineural deafness, and muscle wasting resulting in a typical stance with kyphosis, anteverted shoulders, and flexed flexion deformities of elbows and knees(Verloes et al., 2015). BWMS is caused by mutations in the cytoplasmic actin genes *ACTB* and *ACTG1* (Rivière et al., 2012). To date, the association of BWMS with jejunal atresia, recurrent fevers or psoriatic arthritis has not been reported. Here, we describe a 22 year old male presenting at birth with jejunal atresia, recurrent fevers, and psoriatic arthritis with typical dysmorphic, intellectual, joint and auditory features of BWMS found to have a novel heterozygous pathogenic *ACTB* missense variant on whole exome sequencing (WES).

Clinical Summary

Our patient, now 22 years old, initially presented at birth with multiple jejunal atresias requiring a significant small bowel resection with subsequent short bowel syndrome and failure to thrive requiring on-going gastrostomy and enteral feeding, further complicated by recurrent bouts of gastrointestinal bleeding. He was the result of a natural conception with the pregnancy significant for maternal abdominal pain, followed closely with nine normal prenatal ultrasounds. It was otherwise unremarkable. The parents were of English, Swedish and German descent with his mother and father having two and one unaffected offspring with different partners respectively. Review of family history was non-contributory.

At 3 years of age, he was noted to have sensorineural hearing loss, requiring bilateral hearing aids, thought at the time to be related to aminoglycoside exposure. The following year, he experienced an isolated seizure attributed to an electrolyte imbalance secondary to his short bowel syndrome treated with steroids. After weaning off steroids, he began to develop recurrent fevers with variable frequency and duration. These fevers occurred without an identifiable trigger, could last up to 5 days, can be associated with erythematous macules, and are still ongoing. Around the age of 17, he then developed psoriatic arthritis treated with immunotherapy and weekly methotrexate. Recently, beginning at the age of 21 years, he developed a predominantly upper, left sided peripheral neuropathy confirmed on electromyogram, with significant muscle wasting. The degree of muscle wasting has begun to impact his ability to perform his activities of daily living (ADL).

In terms of intellectual development, our patient had a global developmental delay requiring a specialized school, physio and occupational therapy. He is currently regarded as having the mental abilities in the range of a 6-7 year old. He is described as naive and innocent, requiring assistance with all instrumental activities of daily living (IADL) as well as some ADLs.

On physical examination, his growth parameters were under the 3rd percentile for height and weight with a head circumference at the 90th percentile. His facial appearance displayed typical features of BWMS with a prominent brow, arched eyebrows, hypertelorism, ptosis, long downslanting palpebral fissures, broad nose with large tip and prominent root, and low set ears (Figure 1a). His posture, characteristic of BWMS, was defined by fixed flexion deformities of the elbows and knees, and anteverted shoulders (1b). Additionally, on musculoskeletal examination, significant muscular atrophy was evident in his right hand, with limited strength and atrophic posturing. Skin examination revealed global follicular keratinous plugging sparing the facial region.

Investigations

Prior to WES he had a number of genetic investigations including karyotype, microarray, a recurrent fevers panel consisting of *MEFV, MVK, NLRP3, NLRP12* and *TNFRSF1A*, alpha-galactosidase enzymatic activity, GJB2 sequencing, and *GJB6* deletions analysis. Research-based WES through the Deciphering Developmental Disorders study (DECIPHER id 273880) subsequently identified a heterozygous pathogenic *ACTB* variant, namely c.434C>G (p.Ser145Cys) which was confirmed on clinical sequencing. Testing of parental samples revealed this change to be *de novo.*

Discussion

Although rare, BWMS has been well characterized in the medical literature. The largest case study by Verloes et al included 42 molecularly confirmed BWMS cases with the majority of these patients (33/42) having pathogenic *ACTB* pathogenic missense variants (Verloes et al., 2015). However, to date there have been no reported BWMS patients affected with jejunal atresia, recurrent fevers or psoriatic arthritis.

Jejunal atresia, a complex surgical condition, has been found in retrospective studies to have a high rate of associated anomalies in the range of 19-52% (Best et al., 2012; Burjonrappa et al., 2011), the majority being structural cardiac defects. However, these studies have no postnatal data available and full dysmorphology work-ups were not completed. Therefore, this value is likely an underestimate of the true incidence of associated problems, including intellectual deficiency. Moreover, subtle dysmorphic features that may not have been evident at birth, such as in our case, may only come to light over time. It is therefore possible that a higher proportion of atresia cases have multisystem involvement and likely a genetic aetiology. In our case, WES did not identify other genetic causes that may explain the jejunal atresia. *ACTB* is widely expressed in jejunal tissue, with some studies of the jejunum using *ACTB* expression levels for normalisation of other mRNA levels or as a control (Fernández-Blanco et al., 2015). It is therefore plausible that pathogenic *ACTB* variants could have an effect on intestinal development.

With a prevalence of 0.7 per 10,000 births, jejunal atresia is a much rarer anomaly than recurrent fevers or psoriatic arthritis. These two conditions, are not uncommon, and typically result from immunological dysfunction and activation. Data from Riviere et al. indicated that mutations associated with BWMS resulted in increased F-actin content and altered F-actin dynamics in lymphoblastoid cell lines (Riviere et al. 2012). These effects were predicted to impact cell morphology, motility, and other actin-related functions in these lymphoblast cells. Additionally, multiple cell lines were investigated from a patient with immunological and intellectual dysfunction found to harbour a pathogenic *ACTB* variant (Nunoi et al,. 1999). These cell lines had altered immunological functions such as chemotaxis that was directly linked to actin function, and also disruption of non-actin related function such as superoxide generating ability. In view of the abundance of β-actin in leukocytes, it is plausible that immunological function could be disrupted in BWMS and may have led to or contributed to our patient's psoriatic arthritis and recurrent fevers.

Conclusion

We report the first case of jejunal atresia in BWMS. Further case reports will be required to confirm the association of BWMS with jejunal atresia and immunological dysfunction. However, based on the pathophysiology cited above, the negative genetic testing prior to WES and the lack of additional pathogenic variants found on WES, it is a reasonable possibility that the *ACTB* variant was causal or at least contributory to our patient's phenotype.

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Conflicts of interest

There are no conflicts of interest.

Consent

Consent for publication of clinical photos was given.

References

Best KE, Tennant PW, Addor MC, Bianchi F, Boyd P, Calzolari E, et al (2012). Epidemiology of small intestinal atresia in Europe: a register-based study. Arch Dis Child Fetal Neonatal Ed, pp.fetalneonatal-2011.

Burjonrappa S, Crete E, Bouchard S (2011). Comparative outcomes in intestinal atresia: a clinical outcome and pathophysiology analysis. Pediatr Surg Int *27*(4), pp.437-442.

Fernández-Blanco JA, Estévez J, Shea-Donohue T, Martínez V, Vergara P (2015). Changes in epithelial barrier function in response to parasitic infection: implications for IBD pathogenesis. J Crohns Colitis, *9*(6), pp.463-476.

Nunoi H, Yamazaki T, Tsuchiya H, Kato S, Malech HL, Matsuda I, Kanegasaki S (1999). A heterozygous mutation of β-actin associated with neutrophil dysfunction and recurrent infection. *PNAS 96*(15), pp.8693-8698.

Rivière JB, Van Bon BW, Hoischen A, Kholmanskikh SS, O'Roak BJ, Gilissen C, et al (2012). De novo mutations in the actin genes ACTB and ACTG1 cause Baraitser-Winter syndrome. Nat Genet *44*(4), pp.440-444.

Verloes A, Di Donato N, Masliah-Planchon J, Jongmans M, Abdul-Raman OA, Albrecht B, et al (2015). Baraitser–Winter cerebrofrontofacial syndrome: delineation of the spectrum in 42 cases. Eur J Hum Genet, *23*(3), pp.292-301.

Figures:

1a

1b

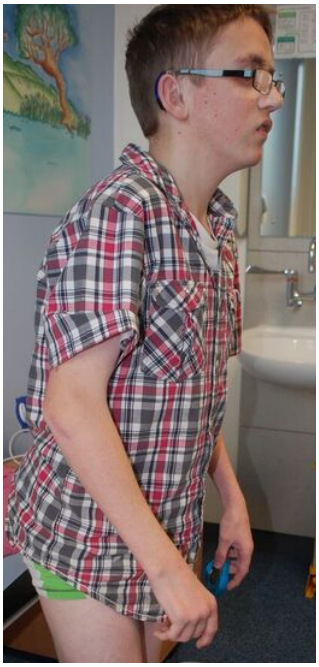

Figure 1. Features of BWMS include (a) prominent brow, arched eyebrows, hypertelorism, ptosis, long downslanting palpebral fissures, broad nose with large tip and prominent root, low set ears (b) fixed flexion deformities of the elbows and knees, and anteverted shoulders