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Surgical Research

A Storm in a Small Body: Johanson – Blizzard Syndrome Unveiled

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ABSTRACT

Background: *Johanson–Blizzard syndrome (JBS) is a rare autosomal recessive disorder caused by mutations in the Ubiquitin Protein Ligase E3 Component N-Recognin 1 (UBR1) gene, characterised by exocrine pancreatic insufficiency, craniofacial anomalies, endocrine dysfunction, hearing loss, and genitourinary abnormalities*

Case Report: *We report the case of a young girl diagnosed in infancy with JBS following recognition by characteristic craniofacial features, cutis aplasia, ambiguous genitalia, and failure to thrive. Genetic testing confirmed a homozygous UBR1 mutation. Multisystem evaluation revealed growth hormone deficiency, hypothyroidism, profound sensorineural hearing loss, anorectal malformation and genitourinary abnormalities. Management included pancreatic enzyme replacement, nutritional supplementation, cochlear implantation, thyroid and growth hormone therapy, and staged genitourinary reconstructive surgeries. She remains on a close developmental, renal, and endocrine follow-up*

Conclusion: *This case highlights few rare associations in JBS, the importance of comprehensive multidisciplinary care and long-term follow-up in these children to optimise functional outcomes and mitigate complications*

Keywords

Johanson – Blizzard Syndrome, Comprehensive, Multidisciplinary treatment.

Introduction

Johanson Blizzard syndrome (JBS) is a rare genetic disorder with multisystem involvement. It is caused by biallelic mutations in UBR1 gene, with an incidence of 1/250000 live births [1]. It presents with distinctive craniofacial and dental abnormalities. Its diagnosis is rather prompt if one recognises the striking phenotype, however, treatment of various system abnormalities is complex and remains challenging. Rarity of a few associations, highlight on multidisciplinary treatment, complications during the course and a long follow up makes our case unique.

Case Report

The child first presented at 3months of age with a typical facies, failure to thrive and urinary tract infection. She was born preterm (32 weeks gestational age) by normal vaginal delivery with birth weight of 1.6 kgs, to young couple with consanguinity. Baby was breast fed, however, weight and height for age were both below the 3rd percentile, hence was on supplemental formula feeds as

advised by the primary Paediatrician. Presence of microcephaly, frontal upsweep of hair making the forehead prominent, sparse eyebrows, hypoplastic alae nasi, and thin upper lip contributed to the typical facies nearly confirming the diagnosis. Other clinical features are collated in Table 1 (Figures 1 & 2). Examination of the perineum revealed clitoromegaly, two orifices in the perineum (UGS and anteriorly placed anus), hypoplastic labia majora and absent labia minora (Figure 3). The array of specific investigations and the multidisciplinary management are depicted in sequence. Though the diagnosis was by and large established by the typical presentation, other probable differentials like Galactosemia, Cystic Fibrosis, and Schwachman Diamond syndrome were ruled out by detailed investigation.

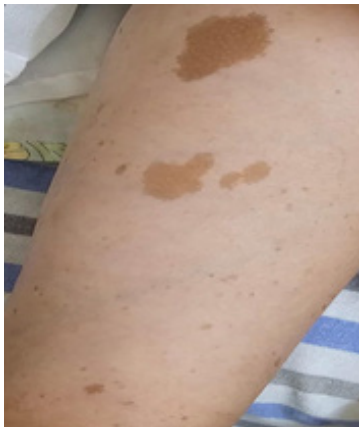

Figure 1: Café-au-lait macules on the thigh.

Figure 2: Cutis aplasia – scalp.

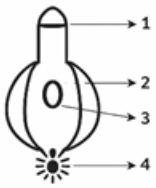

Figure 3: Perineal examination 1- clitoromegaly, 2- hypoplastic labia majora, 3- urogenital sinus opening, 4 – anteriorly placed anus.

Investigations

Genetic analysis

Whole exome sequencing identified a homozygous nonsense variation in exon 39 of the UBR1 gene, leading to a premature stop codon and truncation of the UBR1 protein. Both parents were found to be heterozygous carriers. Karyotype -46XX.

Growth hormone evaluation

Growth hormone stimulation test demonstrated growth hormone deficiency.

Developmental assessment

A Bayley Scales of Infant and Toddler Development (BSID) assessment performed at 2 years of age revealed global developmental delay. Motor and language domains were more severely affected than cognitive function, likely impacted by profound hearing loss.

Audiological assessment and imaging

Audiological screening confirmed profound bilateral sensorineural hearing loss with audiological brainstem response (ABR) testing demonstrating absent responses to high-intensity stimuli.

Radio-imaging

a. CT imaging revealed overcrowding at the foramen magnum with a posteriorly angulated C1 vertebra compressing the anterior brainstem.

Head & Neck	Skin & neuromuscular	Genitourinary	Gastrointestinal	Growth & development	Endocrinology
Microcephaly	Multiple Café-au-lait spots (Figure 1)	Recurrent urinary tract infection	Anterior ectopic anus	Anaemia	Hypothyroidism
Frontal upsweep of hair	Cutis aplasia (Figure 2)	clitoromegaly	Malabsorption	Hypocalcemia	Pancreatic exocrine insufficiency
Sparse eyebrows	Sensorineural hearing loss with cochlear dilatation	Urogenital sinus		Vitamin D deficiency	Steatorrhea
Aplasia of lacrimal punctum	hypotonia	Double vagina, uterus didelphys		Failure to thrive	Growth hormone deficiency
Hypoplastic ala nasi, beaked nose		CKD stage III		Stunting, short stature	
Thin upper lip				Delayed physical milestones	
Hypoplastic deciduous teeth				No speech (deaf mutism)	

b. MRI identified bilateral cystic cochlear dilatation (incomplete partition anomaly), hypoplastic or absent modiolus, left cochlear nerve hypoplasia, and enlarged bilateral vestibules.
c. Renal imaging and function
i. Ultrasound demonstrated normal-sized kidneys with preserved corticomedullary differentiation.
ii. Dimercapto-succinic acid (DMSA) scan showed a well-perfused, normally functioning right kidney (differential function 76%), and a left kidney with reduced perfusion and function (24%), with focal photopenic defects in the bipolar region.
iii. Serum creatinine was 0.6 mg/dL (eGFR 58 mL/min/1.73m^2 consistent with chronic kidney disease stage III) along with metabolic acidosis.

Endoscopic evaluation

Cysto-genitoscopy performed at 1.5 years of age revealed a urogenital sinus with a 1 cm common channel, draining into the urethra and two well-formed vaginas, with two distinct cervical impressions consistent with uterus didelphys (Figure 4). The bladder was normal.

Figure 4: Cystogenitoscopy finding.

A multidisciplinary treatment approach aimed to optimise growth and development, and prevent long-term complications.

Nutritional support

Initiation of pancreatic enzyme replacement therapy, titrated based on meal size, weight, and severity of steatorrhea. Supplementation with fat-soluble vitamins (A, D, E, and K), calcium, and iron to address malabsorption and micronutrient deficiencies along with high-protein, energy-dense diet.

Endocrine management

Growth hormone and Thyroxine supplementation.

Hearing Rehabilitation

Early fitting of binaural hearing aids at infancy was tried but adherence was suboptimal. She subsequently had a successful right-sided cochlear implantation. Post-implantation, she received regular speech and language therapy, initially biweekly, progressing to 38 sessions to date, with documented improvements in auditory awareness, speech production, and communication skills.

Anorectal malformation and genitourinary abnormalities

Management extended from 1.5 yrs - 8 years of age - An initial cysto-genitoscopy aided in the confirmation of the genitourinary anatomy. Thereafter she underwent urogenital sinus mobilisation, anterior sagittal anorectoplasty (ASARP), clitoral reduction and feminising genitoplasty. An interim postoperative wound dehiscence following ASARP necessitated a diverting sigmoid colostomy. A future colostomy closure was complicated by anastomotic leak rectified by sigmoid abdominoperineal pull through. She requires bowel washes occasionally but has bowel, bladder continence and has had no urinary tract infections thus far.

Renal management

Oral bicarbonate supplementation and regular chronic kidney disease (CKD) follow up for stage III with the paediatric nephrologists.

Developmental support

Speech therapy and preparation for individualised educational planning with behavioural and psychological interventions to support overall development are ongoing.

Current status - She is 9 years old and well till date. She is undergoing speech therapy with mapping showing 40 – 50 % hearing. She continues to be on growth hormone injections, Vitamin A, D, E, K, pancreatic enzymes, sodium bicarbonate, iron and calcium supplements. However, she remains stunted (below the 5th centile), can comprehend, communicates with sign language and is trainable with appreciable learning abilities. Has social continence for both bowel and bladder with good renal health.

Discussion

Dr. Ann Johanson and Dr. Robert Blizzard in 1958, encountered a 7-year-old child with developmental delay and characteristic phenotype. Subsequently they went on to see two other children with similar features, not falling into any of the categorized syndromes. Hence in 1971, they established a new syndrome, eponymously called Johanson-Blizzard Syndrome [2,3].

Deficiency of UBR1, a ubiquitin ligase, involved in the N-end rule pathway, which is crucial for protein degradation and cellular homeostasis is the underlying genetic defect. Mutations lead to a loss of function of this enzyme, resulting in the accumulation of defective proteins and subsequent cellular dysfunction across multiple organ systems. Pancreatic dysfunction, specifically results from massive acinar cell loss and lack of apoptotic cells leading to necrotic destruction of the pancreas [4], which is a ubiquitous occurrence in these children. UBR1 deficiency was established in our child by whole exome sequencing.

JBS presents with distinctive craniofacial and dental abnormalities. Affected infants have a beak-shaped nose due to nasal alae aplasia or hypoplasia, maxillary hypoplasia, a small, pointed chin, a long narrow upper lip, and microcephaly. Some may lack lacrimal puncta or develop a nasolacrimal-cutaneous fistula. Various facial abnormalities like cleft lip, cleft palate, and lateral facial

clefts are reported [5]. Dental abnormalities are common, with microdontia, most permanent teeth are absent, and those that develop are often small and malformed with misshapen roots [6]. Infants have low birth weight, hypotonia, and failure to thrive, developmental delays and intellectual disability of varying degrees are common, though some individuals have normal intelligence [7,8]. Hearing loss or deafness may be present at birth or develop later. Hypothyroidism with growth retardation and psychomotor delays are again universal. Most symptoms manifest in childhood [9,10]. Our child had characteristic facies, abnormal dentition and significant developmental retardation making the diagnosis quite obvious.

Clitoromegaly, vulvar fistulas, septate vagina, bifid uterus in females, undescended testes, micropenis, hypospadias in males and cloaca in either are the common genitourinary abnormalities [11,12]. Sood A et al. reported successful management of a child with clitoromegaly, duplicate urethra, persistent urogenital sinus (UGS), bifid uterus and vesicoureteral reflux [13]. She was managed with feminising genitoplasty, excision of duplicate urethra, posterior sagittal anorectoplasty and remained on vesicostomy at follow up. Genitourinary anomaly in our child was more complex with clitoromegaly, UGS, anorectal malformation with diminutive labia majora and absent labia minora (Figure 3). Cysto-genitoscopy showed a UGS with a common channel length of 1cm, leading to urethra, normal bladder and another leading to 2 well-formed vagina and two cervical impressions (uterus didelphys with 2 vagina) which is not reported so far (Figure 4). Developmental disarray of the genitourinary anatomy contributed to recurrent urinary tract infections (UTIs) in the child since the age of 3 months requiring multiple hospital admissions and intravenous antibiotics adding to the morbidity. Like-wise UGS mobilisation, feminising genitoplasty and ASARP were sought with complications secondary to poor development and fragile tissues along with suboptimal nutrition necessitating multiple surgeries. The variations and the spectrum of genitourinary anomalies probably point towards a wider field defect which is not directly related to UBR1 gene mutation involved primarily in causing exocrine pancreatic insufficiency. Similarly, hypoplastic sclerotic mastoid, low lying dura, incomplete patency of the cochlear duct needed certain modifications in the cochlear implant technique so as to minimise complications and ensure better results leading to significantly improved response to auditory stimulus and awareness of sound. Assessment of a 7-year-old girl with JBS who received a cochlear implant at 4years of age showed that she could recognize the environmental sounds; but her connected speech was unintelligible, and her primary mode of communication was manual by gestures [14]. It was concluded that multisystem involvement, global developmental delay and intellectual disability hinder development of spoken language in spite of a successful implant as was seen in our child, though she is only a year into her implant. Another notable feature in our case is the growth hormone deficiency, with a marginal response to hormonal replacement not commonly reported in JBS except for one boy who showed poor growth in spite of early pancreatic and thyroid replacement therapy and subsequently responded well to growth hormone supplementation [15]. Growth development in our child has been slow even with all the necessary supplements.

Conclusion

JBS is a rare genetic disorder with multisystem involvement and a constellation of clinical features. Sensori-neural deafness and genitourinary anomalies can be effectively addressed by surgery. Significant failure to thrive persists in-spite of adequate hormone and enzyme supplementation. Collaboration across various specialities ensures comprehensive evaluation and management along with motivation and dedication by the parents/care givers which plays a vital role in the wellbeing of these children.

Atypical genitourinary anomalies, complications associated with its reconstruction, partial response to successful cochlear implant in spite of a difficult anatomy and an additional growth hormone deficiency are unique to our case

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