CASE REPORT

Autism spectrum disorder in Say-Barber-Biesecker-Young-Simpson syndrome

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SUMMARY

Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS), also known as Ohdo syndrome SBBYS type, is a rare genetic disorder characterised by dysmorphic facial features and severe intellectual disability, as well as cardiac, dental and hearing abnormalities. There has been little psychiatric or psychological description of children with SBBYSS, although previous reports noted repetitive self-injurious behaviours, sensitivity to light and noise and severe deficits in communication. In this report, a 4-year-old male with SBBYSS is described with a focus on psychiatric and psychological assessment, including formal testing for autism spectrum disorder (ASD). Results of multiple behavioural assessment scales are reported. Testing revealed characteristic ASD features, and the patient met criteria for ASD diagnosis in the context of SBBYSS. His behaviours improved with Applied Behavioural Analysis therapy and communication skills training. This is the first documented case of ASD reported alongside SBBYSS. These results suggest ASD may be a clinical feature of SBBYSS.

BACKGROUND

Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS) *KAT6B* gene on chromosome 10, which encodes a histone acetyltransferase enzyme and is thought to be involved in early development of the nervous and skeletal systems.¹ Clinical features include characteristic dysmorphic facies, severe intellectual disability, hypotonia, hypoplastic teeth, hearing impairments and cardiac defects among other findings as described in figure 1.

While cognitive disability and severe developmental delays are well documented within literature, only one publication to date has recorded the behavioural features of those affected. Day *et al* described patients as affectionate and sociable, and enjoying activities appropriate for younger age groups such as playing with balls and simple books rather than age appropriate toys.² Additionally, many children exhibited stereotypies such as self-injurious behaviour (ie, hitting or biting oneself). These behaviours were more pronounced during periods of frustration or difficulty with communication. Interestingly, severe communication difficulties have also been implicated as a common feature of the syndrome by several case reports.^{2,3}

This profile of behavioural symptoms shares many similarities with autism spectrum disorder (ASD). For this reason, it may be important to screen patients with SBBYSS for ASD as well, as

these patients may benefit from therapies that target ASD. Perhaps just as important, an ASD diagnosis, if appropriate, can help parents and other caregivers (such as school personnel) to better understand and accommodate them.

CASE PRESENTATION

A 4-year old Caucasian male with SBBYSS was seen in the hospital by the psychiatry consultation liaison service for aggressive and self-injurious behaviour. The patient was receiving inpatient wound care of a non-healing ulcer, which had developed as a complication to G-tube removal 7 days prior. Significant ulceration surrounding the G tube site was noted on admission, as well as dehydration. In addition to wound care, he received intravenous hydration and pain management via morphine, Toradol and Ativan. During the hospitalisation course, violent head butting behaviours were noted by the patient's parents as well as staff. These behaviours had been seen in the past, but were rare and minimal in scope compared with those seen during the hospitalisation course. Dilaudid was substituted for morphine due to concerns that pain was contributing to the self-injurious behaviour. Physical examination in the hospital demonstrated facial and musculoskeletal features typical of SBBYSS, which are detailed in figures 1 and 2. During the initial examination, the patient was asleep and did not arouse during the interview.

The patient's mother provided his medical history. He was the first child born to a 25-year-old primigravid mother at 38 weeks via emergency caesarean. At birth, he weighed 6 lb 8 oz and necessitated a 3-month neonatal intensive care unit course secondary to respiratory and feeding difficulties. His SBBYSS diagnosis was confirmed at age 4 via PCR and targeted gene sequencing of the *KAT6B* gene (10q22.2), identifying a c.5118T>G (p. Y1706) variation using the reference sequence (NM_12330.3). Of note, the patient had undergone multiple procedures prior to the time of presentation including repair of cryptorchidism, ptosis, cleft palate, clubfoot, stenotic tear duct, persistent left superior vena cava and hypospadias. Additional procedures prior to presentation included supraglottoplasty, tympanostomy tube placement and G-tube insertion and removal procedures. Before admission, he carried diagnoses of chronic lung disease, sleep apnoea, sensory processing disorder, tethered spinal cord, neurogenic bladder, chronic constipation, atrial septal defect, ventricular septal defect and hypothyroidism. The patient's home

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	Case Patient	Clinical Features of 8 patients with SBBYSS [2]
Blepharophimosis	Present	8/8
Ptosis	Present	8/8
Broad/Flat Nasal Bridge	Present	8/8
Bulb Tipped Nose	Present	8/8
Auricular Abnormalities	Present	8/8
Mask Like Face	Present	8/8
Small Mouth	Present	8/8
Severe Developmental Delay	Present	8/8
Hypotonia	Present	8/8
Communication & Speech Difficulties	Present	8/8
Feeding/ Swallowing Difficulties	Present	8/8
Dental Abnormalities	Present	8/8
Long thumbs & toes	Present	8/8
Patellar/ Lower Limb abnormalities	Present	4/8
Hearing impairments	Present	6/8
Eye Abnormalities	Present	8/8
Congenital Cardiac Defects	Present	4/8
Thyroid abnormalities	Present	3/8

Figure 1 SBBYSS features present in case patient. SBBYSS, Say-Barber-Biesecker-Young-Simpson syndrome.

medications included stool softeners for constipation and levothyroxine 50 µg daily for hypothyroidism.

Growing up, he exhibited intellectual disability and developmental delay, with his language ability more severely impaired relative to other developmental milestones. This is consistent with the developmental progress reported by other authors.³ He was first evaluated by our practice at 4 years of age. At that time he was non-verbal, showing expressive language at a 3–6 month level and receptive language at a 6–7 month level. He could grab and manipulate toys he liked, and point to an animal that made a given sound. His communication skills included reaching for things he wanted and shaking his head ‘no’. The patient began crawling around 17 months, and by age 4 he could walk using a walker and move around in a wheelchair independently. Socially, he demonstrated only minor delays, attending preschool by age 4 and enjoying it. He showed awareness of toileting but no interest in training. Additionally, he had difficulties with sensory processing, refusing to eat food on his own without his mother feeding him and avoiding certain textures such as cotton balls or rubber therapy balls.

INVESTIGATIONS

A diagnosis of ASD was suspected, and the patient was subsequently followed by outpatient psychiatry and psychology for evaluation and therapy 2 months later. By the time he was seen in the outpatient setting, his gastrocutaneous fistula had healed without complication after surgical repair. The self-injurious behaviours improved somewhat by this time although he still had not returned

to his baseline frequency or ‘gentle’ nature of head-butting present prior to the hospitalisation. (Prior to hospitalisation, the head butting was of a mild degree that would not cause injury to the patient or others.) His mother reported that for the past few months, the patient had been very anxious and would suffer daily emotional meltdowns triggered by transitions from a car to their house or not getting his way. When anxious he would cry, hide his face, shut down and show aggressive behaviours. These behaviours included hitting people, throwing things and head banging.

Psychological testing was performed, focusing on assessing for possible ASD. Testing included the Autism Diagnostic Observation Schedule Module 1, which indicated a diagnosis of ASD was appropriate due to impairments in communication and social interaction and restricted interest. Furthermore, the Gilliam Autism Rating Scale 3 classified the patient into a ‘very likely’ category in terms of an ASD diagnoses based on these core criteria. The Vineland Adaptive Behaviour Scale II questionnaire was completed by the patient’s mother and showed delay in all core areas. The Bayley Scales of Infant Development, which aimed to measure current cognitive development, was of questionable validity due to difficulties in patient engagement. Clinical and formal psychological examination revealed multiple stereotypies such as rocking and head banging, restricted interests, limited ability to initiate socialisation, difficulty in sharing enjoyment, limited make believe play and difficulties in sensory processing. Test results noted particularly low scores in social communication in comparison to other aspects of his development. Based on these results, the child was found to meet criteria for ASD. The results of his psychological evaluations are included in [figure 3](#).

TREATMENT

After ASD diagnosis was made, Applied Behaviour Analysis therapy was begun for 3 hours per week with notable improvement, and the head banging episodes decreased from a daily occurrence to twice weekly. Additional therapy focused on improving communication ability, including oral and sign language and the Picture Exchange Communication System. The family and care team jointly decided to allow time for the

Figure 2 Photographic documentation of the patient’s facial features. Published with permission from the patient’s family.

Test Administered	Testing Purpose	Results	Notes
Bayley Scales of Infant Development 2nd Edition	Measure current cognitive development & assessment of memory, problem solving, number concepts, generalizations, classifications, & social skills	Calculation of Mental Development score was inappropriate due to difficulties engaging in examination and resulting questionable validity of this test	Patient would not imitate, showed no interest in scribbling, would not engage with puzzles or cubes. Patient was able to push a toy car and display object permanence
Autism Diagnostic Observation Schedule	Semi- structured interview to evaluate concern of ASD or PDD focused on areas of communication, socialization, and play	ASD criteria met	
Gilliam Autism Rating Scale 3rd Edition	Used to identify and rate the severity of ASD	Very Likely ASD with greatest difficulty in initiation of interaction, sharing enjoyment, and make believe play	Full results included in Table 1.2
Vineland Adaptive Behavioral Scale- II Survey Interview Form	Scale completed by patient's mother	Persistent pattern of delay in all areas with slightly better results in socialization	Full results included in Table 1.3
Clinical Evaluation	Describe the patient's behaviors during clinical interview based on professional opinion	Explored room independently and frequently mouthed objects. Happy appearing and at times would smile at his mother.	Difficult to engage and showed distaste by crying at loud laughter, clapping, and a balloon.

	Standard Score	Percentile Rank
Restricted/Repetitive Behaviors (RB)	12	75
Social Interaction(SI)	13	84
Social Communication(SC)	5	3
Emotional Responses(ER)	9	37
Cognitive Style(CS)	NA	NA
Maladaptive Speech (CS)	NA	NA
Autism Index (4 scores)	99	47

Figure 3.3: Vineland Adaptive Behavior Scale Results

Subdomain /Domain	V-Scale/ Standard Score	Confidence Interval 90%	Adaptive Level
Receptive	7	+/-3	Low
Expressive	5	+/-2	Low
Written	9	+/-2	Low
Communication	49	+/- 8	Low
Personal	6	+/-3	Low
Domestic	8	+/-3	Low
Community	6	+/-2	Low
Daily Living Skills	46	+/-9	Low
Interpersonal Relationships	6	+/-2	Low
Play & Leisure Time	7	+/-3	Low
Coping Skills	9	+/-2	Low
Socialization	57	+/- 8	Low
Gross	7	+/-2	Low
Fine	5	+/-2	Low
Motor Skills	49	+/-10	Low

Figure 3 Psychological testing results for case patient.

behavioural therapy to show benefits before initiating pharmacotherapy.

OUTCOME AND FOLLOW-UP

The patient continued to follow with outpatient psychiatry and psychology for 2.5 years since his initial presentation. He responded well to the Applied

Behaviour Analysis and communication skills training, and his family did not feel medication was necessary beyond 3 mg melatonin at night for sleep.

At age 5, he began school and enjoyed it greatly. Aggressive behaviours such as hitting, throwing things and head banging continued, but were rare and were only brought on by frustration. He was able to walk without support but often used a walker and crawled 50% of the time. When he was 6 years old, temper tantrums became more frequent, and twice-daily guanfacine 1 mg was begun for behaviours. The medication appeared to worsen his aggression, so guanfacine was discontinued and risperidone 0.25 mg was begun morning and evening. The patient improved with this medication and continued taking it on a morning and afternoon schedule. He still follows with the clinic at the time of writing.

DISCUSSION

There is significant overlap in behavioural symptomatology between SBBYSS and ASD. SBBYSS is associated with severe language impairment, which is sometimes accompanied by aggressive or self-injurious behaviour when patients become frustrated with their inability to express themselves.² Self-injurious behaviours such as head banging are also a stereotypic behaviour common to ASD, where they often increase during new, painful or stressful situations. In the present case, the patient's behaviour was consistent with previous SBBYSS case literature. However, growing concern over the patient's self-injury led to formal psychological testing, which revealed multiple autism features as noted above in the investigations section and

in figure 3. During the review of SBBYSS literature, no previous publications were found in which patients with SBBYSS were evaluated for ASD although previous reports had noted self-injurious behaviour frequently occur in these patients, and severe communication difficulties have been reported in over 60% of SBBYSS cases.²

Interestingly, during the clinical interview, the patient's mother reported that the patient enjoyed social activity. Case studies have corroborated that parents typically felt children with SBBYSS enjoyed social interaction. During psychological evaluation of our patient, examiners had difficulty determining if he was indeed seeking social interaction during the clinical interview. One examiner expressed concern that the patient may have such severe impairments in communication that the scoring of social abilities was affected.

Though ASD is frequently comorbid with intellectual disability, it is often clinically challenging to assess if a patient's given symptoms are indicative of ASD or simply a product of their intellectual disability. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition specifies that 'to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level'.⁴ Our patient met the criteria for diagnosis of both ASD and intellectual disability via his low score of 49 on the Vineland Adaptive Behaviour Scale, indicating particularly severe impairment of his communication ability.

Genetic disorders account for over 10% of all cases of ASD.⁵ It is important to identify genetic disorders linked with ASD, both to guide treatment of patients with these syndromes as well as to facilitate diagnosis when assessing for underlying causes of ASD. Furthermore, the individual implications of treating ASD in those with a genetic disorder is profound as literature suggests that patients with ASD can experience improvement in their functioning via the use of applied behaviour analysis.⁶ Additionally, from a psychopharmacological perspective, certain treatments such as risperidone have

demonstrated efficacy in treating stereotyped behaviours, self-injury and aggression within the ASD population.⁷

Few studies have investigated the behavioural features of SBBYSS, however, this limited data suggest that behavioural features include traits which are similar to ASD including severe impairment in communication abilities and stereotypic behaviours. The presence of these behaviours in the case patient prompted psychological testing which was indicative of an ASD diagnosis thus establishing the first published comorbid diagnosis of ASD and SBBYSS. Importantly, the case patient experienced increased level of functioning after ASD-focused therapies. We recommend physicians treating patients with SBBYSS consider offering further workup for ASD, especially given the potential for improvement in function with ASD-focused treatments. Further studies are needed

to evaluate if ASD is a clinical feature of Say-Barber-Biesecker-Young-Simpson syndrome.

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Competing interests None declared.

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Learning points

- Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS) is a rare genetic disorder characterised by distinctive facial features, severe cognitive impairment and developmental delay.
- Reported behaviours in patients with SBBYSS are similar to those found in autism spectrum disorder (ASD).
- In this case, treatment as usual for ASD provided significant benefit to this patient with concomitant SBBYSS and ASD.
- ASD may be comorbid with SBBYSS.

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