

Case Report

SATB2-associated syndrome: a case report

Mehdi Issad^{*} , Victorin Ahossi, Emma Melli^{1b} , David Hoarau

Department of Odontology and Oral Surgery, Dijon-Bourgogne University Hospital, 14 rue Paul Gaffarel, 21000 Dijon, France

(Received: 23 October 2023, accepted: 5 January 2024)

Keywords:

SATB2-associated syndrome (SAS) / glass syndrome / facial dysmorphism / dental anomalies

Abstract – Introduction: SATB2-associated syndrome is an extremely rare genetic disorder. It is characterized by delayed neurocognitive development, craniofacial anomalies and dental defects. **Observation:** This case report highlights the craniofacial and dental phenotype linked to a mutation resulting in SATB2-associated syndrome affecting a 13-year-old boy. **Conclusion:** The diagnosis of this syndrome is very difficult. The management using a multidisciplinary strategy includes among others, oral hygiene maintenance, orthodontic treatment and intensive speech therapy.

Introduction

SATB2-associated syndrome, also known as Glass syndrome or SAS, is a genetic disorder first reported in 1989 [1]. It is caused by alteration of the SATB2 (Special AT-rich sequence-binding protein 2) protein on chromosome 2. This syndrome is extremely rare, with an estimated prevalence of 56 cases in France and 634 cases worldwide [2]. It is characterized by delayed neurocognitive development, craniofacial anomalies and dental defects. More recently, skeletal disorders and growth delay have been added to the description of the disease [3].

We present here the phenotypic description linked to a mutation resulting in SATB2-associated syndrome, our management and recent prospects for this syndrome.

Case report

A 13-year-old boy with SAS was referred by his geneticist to the odontology department of our hospital for comprehensive care in a center of expertise. He presented with facial dysmorphism associated with dental anomalies.

He was the only child of a non-consanguineous French couple. He was born at full term. The origin of the dysmorphism was investigated at birth, and the default diagnosis was an atypical Pierre Robin sequence. At the age of 9, exome sequencing revealed a heterozygous substitution mutation in the CUT1 domain of the SATB2 gene. The variation found on chromosome 2 was c.1196G>A, resulting in the Arg399His modification on the SATB2 protein (Tab. 1). This pathological mutation is responsible for the SATB2-associated syndrome (OMIM#612313) [4].

Clinically, the patient was hypotonic and underweight (38 kg for 1.59 m). Neurocognitively, he had a severe intellectual deficit, virtually no language, praxis disorders and difficulty falling asleep. From a craniofacial prospective, the palpebral slits were slanting downwards and outwards, and the ears were low set. His facial features included: a long, narrow face, a short upper lip, a pendulous lower lip, drooling due to lip incompetence and micrognathia. He presented with Ballard skeletal class II with mandibular retrognathia, left lateral deviation of the mandible and maxillary hypoplasia (Fig. 1). He had an ogival palate with sequelae from a cleft affecting only the hard palate, which was operated on at 1 yr.

On oral examination, the patient's dental hygiene was moderate, the periodontium was healthy and no decay were visible. Dental brushing was done by his parents. The teeth had a mottled appearance. We observed mandibular incisal dental crowding and macrodontia on teeth 11, 13, 55, 21, 75, 84, 85. Inter-arch examination showed Angle's class 2 division 1, increased overjet and deep overbite. (Fig. 2). Ventilation was buccal. Mastication was alternating unilateral but slow, and swallowing was normal. No parafunction was observed.

The panoramic radiograph showed a mixed dentition, inconsistent with the patient's age, persistent milk teeth including 52, 55, 62, 64, 65, 71, 72, 73, 74, 75, 81, 82, 83, 84, 85, tooth agenesis including 12, 14, 15, 18, 22, 24, 25, 31, 32, 33, 35, 38, 41, 42, 43, 45, 48. We observed taurodontism on the molars 55, 16, 65, 26, 75, 36, 85, 46 with elongation of the pulp chamber to the detriment of the root pulp and the dental root, and finally delayed development of the roots on 16, 26, 36, 46 (Fig. 3). We observed eruption delays on 17, 23, 27, 34, 37, 44, 47.

It was decided that the patient would receive semi-annual pediatric odontology consultations to maintain good oral health. Education in oral and dental hygiene was mentioned at every visit. No dental extraction had been performed but dental

* Correspondence: mehdi.issad@chu-dijon.fr

Results: Positive - Probable cause of clinical presentation identified				
Gene	Pathology	Mode of inheritance	Genetic Variation	Interpretation
SATB2	SATB2-associated syndrome (Glass syndrome)	Autosomal dominant	chr2:g.200193611C>T NM_001172509.1:c.1196G>A p.(Arg399His)	Pathogenic

Table I. Conclusion of exome sequencing.

scaling was performed every six months. During care, he was treated with nitrous oxide. Orthodontic treatment was initiated and is still ongoing. It consisted of placing a palatal expansion device and then performing orthodontic traction of the impacted right maxillary canine on the dental arch. Speech therapy led to improved sensitivity of the oral sphere, more efficient mastication and reduced drooling by increasing labial tone and learning a mouth-closure-swallowing sequence.

Discussion

SAS is extremely rare. Diagnosis of this syndrome is difficult and delayed: the clinical signs are not very specific to this syndrome and are found in several genetic conditions (facial dysmorphism, clefts, dental anomalies). A definitive diagnosis requires exome sequencing by experienced and well-equipped geneticists. In a previous study, Zarate and al. found that there was an average time to diagnosis of 6.6 yr in a cohort of 72 patients [5].

Clinically, neurocognitive development delays and dental anomalies are consistently present. Three other elements are frequently found: hypersialorrhea (88%), facial dysmorphism (84%) and low bone mineral density (71%) [6]. On dental prospective, Scott and al. analyzed 37 patients with SAS. Delayed eruption (75%), bruxism (73%), and macrodontia (67%) were most often observed. Anterior dental injuries are common, possibly due to unsteady ambulation [7]. In another study, they analyzed 18 dental radiographs from patients with SAS. Most consistent radiological findings included delayed formation of the second mandibular bicuspid (83%), delayed development of permanent teeth roots (78%), malformed teeth (44%), and taurodontism (44%) [8]. According to Scott and al., association of delayed second bicuspid development, delayed permanent root development with taurodontism and malformed teeth should help the diagnosis and differentiate SAS from other neurodevelopmental syndromes [8].

In 2022, Li *et al.* described the dental phenotype of a 6-year-old child with the same mutation as our patient: a missense variation c1196G>A (p.Arg399His). Several

similarities were visible: Both patients presented dental crowding, no mandibular second bicuspid and underwent cleft palate surgery. Both orthopantomogram showed delayed formation of permanent teeth roots and taurodontism. More specifically our patient presented a hypotaurodontism according to Seow and Lai [9]. However, our patient also presented macrodontia, had no parafunction, no caries or chronic periapical periodontitis. This was probably explained by the patient's age and his autonomy, allowing for better dental hygiene. The c.1196G>A p.(Arg399His) mutation in the SATB2 gene has been described twice in the literature. So far, no study has correlated a mutation with a particular phenotype [6,10].

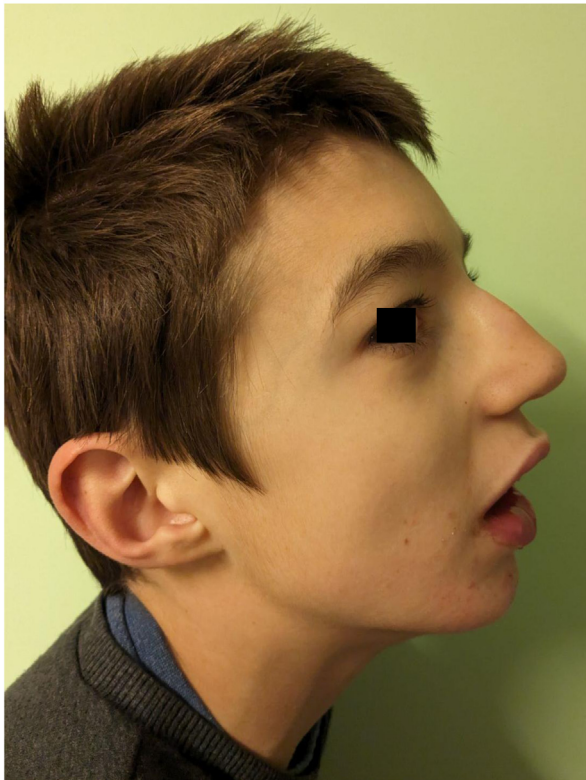
SAS management is therefore symptomatic, no specific treatment has proven effective. Monitoring guidelines have been proposed. Most studies recommend close dental follow-up with oral hygiene education and regular preventative care without describing a precise treatment plan [11,12]. Dental cares for these patients are difficult. Most received care by a pediatric dentist or in a special needs dentistry unit. Surgeries are often under general anesthesia [8]. Orthodontic treatment plan should be undertaken by an experienced practitioner in collaboration with an oral surgeon.

On other prospectives, syndrome sufferers have an increased risk of developing vascular disease and pulmonary hypertension [13]. They also have a particular metabolic profile. In fact, there is a reduction in the capacity to use glucose as an energy substrate [14]. This could contribute to neurological anomalies and developmental disorders. Finally, individuals with this syndrome show an increased response to certain hormones, such as estradiol.

The SATB2 gene is present on the long arm (q) of chromosome 2, it has been highly conserved throughout evolution. It is an essential gene for craniofacial patterning and cognitive development in humans [10]. It is an important epigenetic regulator during neurodevelopment [15]. More recently, this gene has also been described as playing a role in the oncogenesis of colorectal adenocarcinomas and intestinal neuroendocrine tumors [16].



(A)



(B)

Fig. 1. 13-year-old patient with SATB2-associated syndrome: (A) face front view (B) face profile view.

In conclusion, SATB2-associated syndrome is extremely rare. The diagnosis of this syndrome is very difficult, and requires exome sequencing as the clinical signs are not very



(A)



(B)



(C)

Fig. 2. 13-year-old patient with SATB2-associated syndrome: (A) endobuccal view with maxillary teeth showing macrodontia (B) endobuccal view with mandibular teeth showing dental crowding (C) Dental occlusion showing Angle's class 2 division 1, increased overjet and deep overbite.

specific. The cares are interdisciplinary and symptomatic. Dental follow-up must be carried every 6 months to 1 yr for life by a pediatric dentist or in a special needs dentistry unit.

Acknowledgments

We are greatly thankful to Suzanne Rankin for her help in translating the manuscript.



Fig. 3. The panoramic radiograph at age 13 showing a mixed dentition, persistent milk teeth including 52, 55, 62, 64, 65, 71, 72, 73, 74, 75, 81, 82, 83, 84, 85, tooth agenesis including 12, 14, 15, 18, 22, 24, 25, 31, 32, 33, 35, 38, 41, 42, 43, 45, 48, taurodontism on the molars 55, 16, 65, 26, 75, 36, 85, 46, delayed development of the roots on 16, 26, 36, 46 (triangle).

Funding

This research did not receive any specific funding.

Conflicts of interest

The authors declare that they have no conflict of interest.

Author contribution statement

All authors contributed equally in the article.

Ethics approval

Ethical approval was not required.

Informed consent

Written informed consent for patient information and images to be published was provided by the parents' patient.

References

1. Glass IA, Swindlehurst CA, Aitken DA, McCrea W, Boyd E. Interstitial deletion of the long arm of chromosome 2 with normal levels of isocitrate dehydrogenase. *J Med Genet* 1989;26:127–130.
2. Association Française du SATB2. AFSATB2. [cited 2023 Oct 1]. Available from: <https://www.associationfrancaisesatb2.org>
3. Zarate YA, Perry H, Ben-Omran T, Sellars EA, Stein Q, Almureikhi M, *et al.* Further supporting evidence for the SATB2-associated syndrome found through whole exome sequencing. *Am J Med Genet A* 2015;167A:1026–1032.
4. ClinVar. [cited 2023 Oct 1]. Available from: <https://www.ncbi.nlm.nih.gov/clinvar/>
5. Zarate YA, Smith-Hicks CL, Greene C, Abbott MA, Siu VM, Calhoun ARUL, *et al.* Natural history and genotype-phenotype correlations in 72 individuals with SATB2-associated syndrome. *Am J Med Genet A* 2018;176:925–935.
6. Zarate YA, Bosanko KA, Caffrey AR, Bernstein JA, Martin DM, Williams MS, *et al.* Mutation update for the SATB2 gene. *Hum Mutat.* 2019;40:1013–1029.
7. Scott J, Adams C, Beetstra S, Zarate YA. SATB2-associated syndrome (SAS) and associated dental findings. *Spec Care Dent Off Publ Am Assoc Hosp Dent Acad Dent Handicap Am Soc Geriatr Dent* 2019;39:220–224.
8. Scott J, Adams C, Simmons K, Feather A, Jones J, Hartzell L, *et al.* Dental radiographic findings in 18 individuals with SATB2-associated syndrome. *Clin Oral Investig* 2018;22:2947–2951.
9. Lai PY. Association of taurodontism with hypodontia: a controlled study. *Pediatr Dent* 1989;11:214–219.
10. Döcker D, Schubach M, Menzel M, Munz M, Spaich C, Biskup S, *et al.* Further delineation of the SATB2 phenotype. *Eur J Hum Genet* 2014;22:1034–1039.
11. Zarate YA, Fish JL. SATB2-associated syndrome: mechanisms, phenotype, and practical recommendations. *Am J Med Genet A* 2017;173:327–337.
12. Li X, Ye X, Su J. The dental phenotype of primary dentition in SATB2-associated syndrome: a report of three cases and literature review. *BMC Oral Health* 2022;22:522.
13. Zarate YA, Bosanko KA, Thomas MA, Miller DT, Cusmano-Ozog K, Martinez-Monseny A, *et al.* Growth, development, and phenotypic spectrum of individuals with deletions of 2q33.1 involving SATB2. *Clin Genet* 2021;99:547–557.
14. Zarate YA, Örsell JL, Bosanko K, Srikanth S, Cascio L, Pauly R, *et al.* Individuals with SATB2-associated syndrome with and without autism have a recognizable metabolic profile and distinctive cellular energy metabolism alterations. *Metab Brain Dis* 2021; 36:1049–1056.

15. Britanova O, de Juan Romero C, Cheung A, Kwan KY, Schwark M, Gyorgy A, *et al.* Satb2 is a postmitotic determinant for upper-layer neuron specification in the neocortex. *Neuron* 2008;57: 378–392.
16. Li Z, Yuan J, Wei L, Zhou L, Mei K, Yue J, *et al.* SATB2 is a sensitive marker for lower gastrointestinal well-differentiated neuroendocrine tumors. *Int J Clin Exp Pathol* 2015;8:7072–7082.