Clinical Case Reports International

Case Report
Published: 26 Jan, 2022

Case Report: The First Glass Syndrome in Indonesian Children

Saputra DR[1], Mangunatmadja I[2], Nurfitri E[1] and Sulistyowati A[1]*

[1]Department of Pediatrics, Fatmawati Hospital, Indonesia

[2]Department of Child Health, Cipto Mangunkusumo Hospital, Indonesia

Abstract

SATB2-Associated Syndrome (SAS) or glass syndrome is a condition that affects several body systems. It is mainly characterized by intellectual disability, severe speech problems, and dental abnormalities, other abnormalities of the head and face, and behavioral problems. Genetic testing is mandatory to confirm the disease. We report or case of 5-year old boy who suffered from neurological regression, seizure, behavioral problem and ultimately, encephalopathy. Later his genetic testing detected a mutation detected a missense point mutation which causes an amino acid change from Asn to Ser at position 268 in *SATB2* gene location. Currently, this mutation is classified as heterozygous variant of uncertain significance. The *SATB2* gene is known to play a key role in brain and skeletal development, thus this was consistent with our case that developed mainly neurological problems.

Introduction

SATB2-Associated Syndrome (SAS) or glass syndrome is a condition that affects several body systems. It is mainly characterized by intellectual disability, severe speech problems, and dental abnormalities, other abnormalities of the head and face, and behavioral problems [1]. It was first reported in a 16-year-old male in 1989 and termed as glass syndrome at that time [2]. This is a rare condition. Its prevalence is still unknown [1]. The registry of this disease just started in 2016. Not many cases of glass syndrome have been confirmed worldwide. Up to July 2020, 194 individuals with SAS from more than 17 countries had enrolled at a website registry for SAS on www.*SATB2*gene.com.

No specific laboratory tests are available for SAS. Genetic testing is mandatory to establish the diagnosis, which alteration in *SATB2* gene has been identified as pathogenic cause. It is a challenge for pediatrician or medical practitioner to confirm the diagnosis, especially in limited resources country for genetic testing. Thus, early diagnosis is quite challenging. We hereby describe a child with developmental regression and seizure who was suspected as glass syndrome. As far as we know, this is the first case of glass syndrome that has ever been confirmed in Indonesia.

Case Presentation

A 5-year-old was referred to Fatmawati Hospital, Jakarta with the working diagnosis of chikungunya disease. His chief complaint was the weakness of lower limb that caused him difficulty on walking. He also suffered from mild fever atonic epilepsy. By the time he was admitted in our hospital, initially he was diagnosed as transverse myelitis and epilepsy. Later he was treated with high dose corticosteroid and antiepileptic drug. He was discharged two weeks later, with no significant improvement of both legs.

He was born during normal labor, a term for gestational age and within normal range of birth weight and birth length. His basic immunization was complete. He reached developmental milestone normally. He was able to walk by the age of 13 to 14 months and talk fluently in full sentences by the age of 3 years old. He was a delightful and happy child. Prior his symptoms, he used to play with and take care of his older brother who suffered from global delay development.

He underwent appendectomy two years earlier and showed no other significant health problems in the past. He was the last child of three, from non-consanguineous parents originated from Nias, a small island in the west Indonesia. His second brother is suffered from some neurological problems, including global delay development, microcephaly and intellectual disability.

OPEN ACCESS

Correspondence:
Irawan Mangunatmadja, Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, E-mail: irawanma2802@gmail.com

Received Date: *29 Dec 2021*
Accepted Date: *18 Jan 2022*
Published Date: *26 Jan 2022*

Citation:
Saputra DR, Mangunatmadja I, Nurfitri E, Sulistyowati A. Case Report: The First Glass Syndrome in Indonesian Children. Clin Case Rep Int. 2022; 6: 1270.

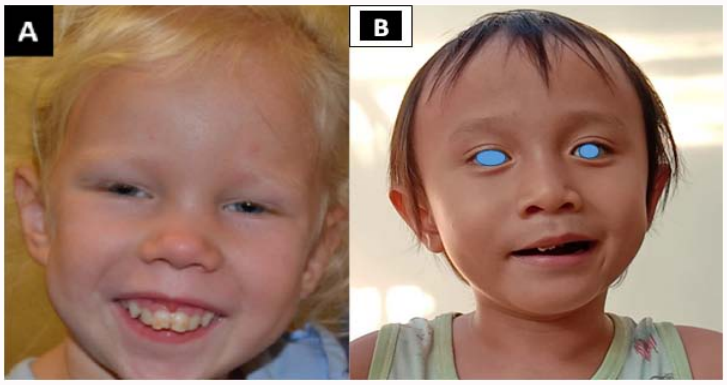

Figure 1: Comparison pictures of facial features of patients with SATB2-associated syndrome. A. Credit: Gene Reviews. B. Our 5-year-old patient.

UNCLEAR RESULT
Variant(s) of uncertain significance (VUS) identified

INTERPRETATION

A heterozygous variant of uncertain significance was identified in the SATB2 gene. **The genetic diagnosis of autosomal dominant Glass syndrome is possible.**

No clinically relevant copy number variations related to the described phenotype were identified.

SEQUENCE VARIANTS

GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
SATB2	NM_001172509.1:c.803A>G	p.(Asn268Ser)	rs375141410	heterozygous	PolyPhen: Benign Align-GVGD: C0 SIFT: - MutationTaster: Disease causing Conservation_nt: weak Conservation_aa: high	gnomAD: - ESP: - 1000 G: - CentoMD: -	Missense Uncertain significance (class 3)

Variant annotation based on OTFA (using VEP v94). * AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function; splicing predictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). *** based on ACMG recommendations.

Figure 2: Genetic test result patient conducted by Centogene of the, a genetic diagnostic company based in Germany.

A month after hospitalization, the atonic seizure was more frequent. He could not talk and communicate clearly, even though was still full alert and aware of surroundings. Other significant change of behavior was self-injury behavior by banging his own head to the wall. Those conditions were getting worse in the following months. He suffered from worsening motoric and communication regression, frequent atonic epilepsy and repetitive self-injury behavior. Genetic counseling was then conducted.

Upon physical examination during his first admission, his vital sign was normal; the occipitofrontal circumference was in normal range. He was conscious and alert. He also presented irregular dentition but no special facial features. There was no apparent bone abnormalities, no spasticity but he had profound weakness especially in lower limb. His motoric scores were 4 on upper extremities and 3 on lower extremities. Patellar reflex was normal, and Babinski signs were negative. Other neurological examinations resulted normal.

Blood tests were normal, including liver and kidney functions. Vitamin D 25-OH total was 26.8 ng/mL, slightly below lower reference value. The analysis of cerebrospinal fluid revealed normal and no microorganism evident of blood and cerebrospinal fluid cultures. The EMG and whole spine CT scan were normal. Head MRI suspected subarachnoid hemorrhage late subacute DD/inflammation of meningen, and also mild dilatation of the ventricles. EEG resulted abnormal epileptiform activity. On the evaluation EEG a few months later, the epileptiform activity subsided but showed general hipofunction.

Later on, the next generation sequencing-based whole exome sequencing was performed for genetic analysis (the process was performed by Centogene®, German). The EDTA-treated peripheral blood was collected with informed consent of the patient's guardians. The genetic test resulted a heterozygous variant of uncertain significance in the *SATB2* gene. The genetic diagnosis of autosomal dominant of glass syndrome is possible. The family was suggested to conduct genetic testing, but it was postponed due to financial restraint. After diagnosis, special education and symptomatic treatment were performed, including multidrug antiepileptic treatment. Physical rehabilitation and chest therapy was also applied to the patient for his hemiparesis and thick respiratory mucous.

Five months after onset, he had only limited activity on the bed. Awareness to surroundings was becoming lessened. Involuntary

movement appeared predominantly rather than atonic seizures. He was admitted repeatedly to the hospital due to pneumonia and sepsis because of the long period of immobilization. The patient eventually died 7 months after the first symptoms. The cause of death was sepsis.

Discussion

SATB2-Associated Syndrome (SAS) or originally called as glass syndrome is a multisystem disorder, mainly with neuro-developmental anomalies, such as intellectual disability, speech delay or behavioral problem [3]. Even some features can be described using the acronym *SATB2*, those are severe speech anomalies, abnormalities of the palate, teeth anomalies, behavioral problems with or without bone or brain anomalies, and onset before age of 2 [1].

Severe speech anomalies

SAS patients might have varied clinical features; however some are consistently described, such as Intellectual Disability (ID) [1]. ID was mostly found in patients with large deletion based on molecular testing [3]. Language development is often reported (95%) and frequently in severe form [1,4]. Eighty two percent of SAS patients have a limited vocabulary under ten words or absent speech by 10-years-old. A study from Japan resulted that 3 patients had not acquired meaningful words at 5-years-old [5]. For our case, intellectual disability and limited speech were not observed in the patient. However it was apparent in patient's brother. Unfortunately, we cannot conduct genetic testing for patient's brother to confirm the diagnosis due to financial problem.

Typically there is no developmental regression among SAS patients. This differs from our case which showed significant regression in motor and speech development during his last 5 months of life. Our patient formerly had reached normal motor and speech milestones, which rapidly declined during his illness. At the end, he lost his communication ability, verbally and nonverbally, and also only lay on his bed due to his limb weakness and encephalopathy. We found one case with an 8.6-Mb deletion of 2q32.2-q33.1, including *SATB2* gene, which reported to have ID regress from mild to severe and speech from poor to absent between the ages of 6 years and 12 years [6]. Even though developmental regression is scarce for *SATB2* gene anomaly, it still likely to occur. This variability of genotypic features might influence the variability of its phenotypic symptoms and prognosis.

Abnormalities of the palate

Half of individuals with SAS have cleft palate. While micrognathia was found in 42% of SAS individuals. Higher proportions was reached for cranial dysmorphism and dental anomalies, 89% and 72%, respectively [1]. A study by Fitz Patrick et al. [7] showed translocation involving locus 2q32-q33 in cleft palate, using high resolution FISH mapping. It supports the evidence of *SATB2* gene involvement in the process of palatal fusion [7,8]. As for our case, no palatal and distinctive craniofacial abnormalities were found. But we found prominent forehead and high anterior hairline in our patient, as for 53% of SAS patients [3]. The comparison pictures are depicted in Figure 1.

Teeth anomalies

Thirty-six percent of individuals with SAS have abnormal size or shape of upper central incisors. They might also have dental crowding (36%), hypodontia (16%), delayed primary dentition (6%), and/or 4% have diastema.8Radiologic findings showed some delayed permanent root formation, delayed or missing second bicuspids, and malformed teeth [9]. While in our case, irregular dentation was found and he still did not grow any permanent teeth.

Behavioral issues with or without bone or brain MRI anomalies

Some behavioral issues has been reported in SAS patients, including emotional problems, hyperactivity, sleep problems, and conduct problems [10,11]. Nonspecific brain abnormalities are found in half of affected individuals, including enlarged ventricles, agenesis of corpus callosum, enlarged perivascular spaces, and abnormal myelination in white matter [3]. In our case, the patient later developed repetitive self-injury behavior. There were no emotional nor conduct problems before and after genetic diagnosis of abnormality of *SATB2* gene. Brain MRI indicated mild ventricular enlargement. When we evaluated head CT scan a few months later, it revealed communicating hydrocephalus (*ex vacuo*). It seemed that the ventricular enlargement was worsening. However it is still unexplainable whether it was due to the genetic abnormalities or other comorbidities.

Epilepsy is not a predominant feature for SAS, but it occurs in some patients. Among 101 individuals with *SATB2*-associated syndrome, 41 (41%) individuals were identified as having at least one abnormal Electroencephalography (EEG), mostly in form of epileptiform discharge. Six patients with clinical seizures needed aggressive management with polytherapy [12]. For our case, as the epilepsy was featured at first had atonic epilepsy at first but then eventually, his EEG also confirmed for epileptiform activity on the brain. However during his illness, the patient was getting unaware of surroundings, the seizure subsided as well as the epileptiform wave. Later EEG changed to general hipofunction of the brain. It shows total damage of all area of the brain. It was consistent with his appearance during this time that had already lost his motoric and speech ability, and only lay on the bed.

Age of onset before 2 years

Despite of broad variation of clinical features in individuals with SAS fail, developmental delay is almost universally reported. They tend fail to reach normal developmental milestones from infancy [3,13]. Delay development with some nonspecific signs may exist from infancy, such as facial dysmorphism, hypotonia, feeding difficulties, growth restriction, genital abnormalities, and thin skin or hair [1,13]. In our case, the patient had no reported abnormalities during infancy. He grew normally until the age of five, and then started to suffer from developmental regression. It was quite different for other cases of SAS or glass syndrome. It might be due to the difference of location or variant of gene abnormalities. But further research regarding this topic is still needed.

Genetic alteration

Glass syndrome or SAS diagnosis is established by molecular genetics testing's, including karyotyping, Chromosomal Microarray Analysis (CMA), multigene panel, genomic sequencing, whole exome sequencing and current next generation sequence [1,3]. Originally *SATB2* gene was identified as causative gene on abnormalities in 2q32-q33 associated with isolated cleft palate [7]. The *SATB2* alteration consists of large deletions, intragenic deletions and duplications, translocations with secondary gene disruption, missense point mutations, and gonadal/somatic mosaicism. *SATB2*, which is a kind of matrix attachment region-binding transcription factor, plays

a key role in brain and skeletal development. Human patients with *SATB2* haploinsufficiency have shown some neurological symptoms, such as cognitive deficits, developmental delay, and developmental speech and language problem [1,3,13].

A study stated 120 unique variants have been identified in *SATB2*, and the most common ones were single nucleotide variants inducing the occurrence of a stop codon (42.5%), and next were the missense variants (25.8%) [14]. The mutation detected in our case (c.803A>G (p.Asn268Ser)) is a missense point mutation. This mutation causes an amino acid change from Asn to Ser at position 268. It is classified as variant of uncertain significance (class 3) according to the recommendations of Centogene and American College of Medical Genetics and Genomics (ACMG). The genetic test result is presented in Figure 2. This classification of VUS can be explained by the limited number of patients of glass syndrome worldwide. As far as we know, this kind of missense point mutation has not been reported previously.

The wide variability of phenotype manifestation might be related to the wide variability of the gene mutation. However, a study reported that individuals with missense variants in *SATB2* gene have clinical features indistinguishable from those with clear loss-of-function mutations [15]. The type of mutation might change upper to pathogenic class if more cases were found and conformed to the same phenotype and genotype abnormalities. These broad variation in phenotypic penetrance could be explained due to complicated functions of *SATB2* related to specific genetic mechanism affecting the *SATB2* locus [3]. The *SATB2* function shift at different developmental stages and complex interactions with related proteins may be involved in the pathogenesis of variable manifestations in SAS patients, which plays great role in neurologic development [1,13]. In our patient, the craniofacial and bone manifestations are very subtle, not to mention almost none. Main problem was related to neurological problems, including developmental regression, behavioral problem, seizure and encephalopathy. However, very limited data regarding encephalopathy with *SATB2* gene. So far there is only one report on 15-months-old baby who suffered from encephalopathy and developmental regression. Later her genetic tests revealed mutations in the *SERAC1* gene and *SATB2* gene [16]. Even though the authors were unable to distinguish between mutations on those two genes with the neurological manifestation, it was hypothesized that *SATB2* plays more significant role in phenotypic manifestation.

Diagnosis and management

Diagnosis for SAS can be quite challenging in patients and can only be confirmed by genetic testing. Today next generation sequencing technologies are available for clinical genetic diagnosis. However the test is not widely available worldwide and still perceive as expensive procedure in some countries. So far, *SATB2* gene was known as de novo mutation [1]. In our case, it could not be proven yet whether the mutation is *de novo* or inherited mutations. Actually, it can be differentiated by conducting parental genetic testing. The elder brother who has intellectual disability and other neurological problems is a perfect candidate for the same testing. Unfortunately, we could not do those testing's due to family financial restraint. Since almost all SAS patients have *de novo* genetic mutations, it is unlikely for risk for the sibling. However, the risk to siblings can be slightly greater because of the possibility of parental germline mosaicism [1].

Currently, there is no specific therapy or guidelines are available for SAS. Regular evaluations are recommended. High suspicion for SAS should be maintained for cases with ID with developmental delay and palatal, dental or bone deformities. Multidiscipline team consists of pediatric neurologist, genetician, dentist, orthopedic surgery, psychologist, physical and speech therapist, and others should be collaborating to provide optimum management for improving the quality of life of the patients. Our case had poor prognosis due to his loss of motoric control which forced him to be bed-ridden. His rapid deteriorating conditions in respiratory problems and consciousness level had worsening his condition in his last months of his life. Currently, we cannot ensure the role of *SATB2* mutation for his poor prognosis. However, *SATB2* gene raises concern for his deteriorating motoric and neurological conditions. More studies are needed to explore the disease progression of SAS. Molecular studies on different gene sets and different type of mutations may help to give more understanding of this disease.

Conclusion

We suspected the first case of SAS or glass syndrome in Indonesia by the genetic analysis. This is a new variant, never reported in previous studies. Because of varied phenotypic manifestations, limited cases reported, and lack of specific laboratory tests, SAS can be difficult to diagnose. Awareness of this disease should be promoted among health professionals. Continuous monitoring should focus on speech development, behavior and cognitive problems or other neurological issues. Next generation sequencing can help differentiate underlying diseases and predict the appropriate prognosis. In future, more clinical and molecular studies are needed for more exploration on SAS.

References

1. Zarate YA, Kaylor J, Fish J. SATB2-associated syndrome. In: Adam MP, Ardinger HH, Pagon RA, editors. Gene Reviews®. Seattle (WA): University of Washington, Seattle; 1993-2022.
2. 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(2):127-30.
3. Zarate YA, Fish JL. SATB2-associated syndrome: Mechanisms, phenotype, and practical recommendations. Am J Med Genet A. 2017;173(2):327-37.
4. 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(4):925-35.
5. Yamada M, Uehara T, Suzuki H, Takenouchi T, Yoshihashi H, Suzumura H, et al. SATB2-associated syndrome in patients from Japan: Linguistic profiles. Am J Med Genet A. 2019;179(6):896-9.
6. Gregoric KH, Krgovic D, Vokac NK. Specific behavioural phenotype and secondary cognitive decline as a result of an 8.6 Mb deletion of 2q32.2q33.1. J Int Med Res. 2016;44(2):395-402.
7. FitzPatrick DR, Carr IM, McLaren L, Leek JP, Wightman P, Williamson K, et al. Identification of SATB2 as the cleft palate gene on 2q32-q33. Hum Mol Genet. 2003;12(19):2491-501.
8. Zarate YA, Kalsner L, Basinger A, Jones JR, Li C, Szybowska M, et al. Genotype and phenotype in 12 additional individuals with SATB2-associated syndrome. Clin Genet. 2017;92(4):423-9.
9. Scott J, Adams C, Beetstra S, Zarate YA. SATB2-Associated Syndrome (SAS) and associated dental findings. Spec Care Dentist. 2019;39(2):220-4.
10. Kumar N, Zarate YA. Managing sleep and behavioral problems in a preschooler with SATB2-associated syndrome. Case Rep Genet. 2020;2020:1-4.

11. Cotton AP, Gokarakonda S, Caffrey AR, Zarate YA, Kumar N. Behavioral phenotype and sleep problems in SATB2-associated syndrome. Dev Med Child Neurol. 2020;62(7):827-32.

12. Lewis H, Samanta D, Orsell JL, Bosanko KA, Rowell A, Jones M, et al. Epilepsy and electroencephalographic abnormalities in SATB2-associated syndrome. Pediatr Neurol. 2020;112:94-100.

13. Zhu YY, Sun GL, Yang ZL. SATB2-associated syndrome caused by a novel SATB2 mutation in a Chinese boy: A case report and literature review. World J Clin Cases. 2021;9(21):6081-90.

14. Zarate YA, Bosanko KA, Caffrey AR, Bernstein JA, Martin DM, Williams MS, et al. Mutation update for the SATB2 gene. Hum Mutat. 2019;40(8):1013-29.

15. Bengani H, Handley M, Alvi M, Ibitoye R, Lees M, Lynch SA, et al. Clinical and molecular consequences of disease-associated *de novo* mutation in SATB2. Genet Med. 2017;19(8):900-8.

16. Su Y, Zhang H, Wang H, Wu B, Yang J, Zhou W, et al. Case report: Progressive cholestasis: Severe phenotype of MEGDEL syndrome with SszATB2-associated syndrome. Front Pediatr. 2021:9:713458.