Shwachman Diamond Syndrome with Arrhythmia as the First Manifestation: a Case Report and Literature Review

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Objective: Analyze the different clinical manifestations and genetic characteristics of Shwachman diamond syndrome (SDS).

Methods: The clinical data of a case of neonatal onset Shwachman diamond syndrome with arrhythmia as the first manifestation were retrospectively analyzed, and the relevant literature was reviewed to summarize the clinical manifestations, genetic characteristics and treatment of Shwachman diamond syndrome.

Results: The patient, female, age 1 month 24 days, with ventricular arrhythmia as the first manifestation, accompanied by growth retardation, liver damage, and persistent decrease in peripheral blood neutrophil count (< 1.5 × 10^9/l), no pancreatic exocrine gland dysfunction at the initial stage of the disease. Gene detection showed that the SBDS gene chr7:66,459,197, c.258+2T > C homozygous variation.

Conclusion: Although the classic manifestations of Shwachman diamond syndrome are pancreatic exocrine insufficiency, pancreatic adiposis and unexplained neutropenia, its clinical manifestations are complex and diverse, involving multiple systems. For suspected children, early genetic examination is helpful for subsequent diagnosis and treatment.

Keywords: Shwachman diamond syndrome, arrhythmia, case report

Shwachman diamond syndrome is a rare autosomal recessive disorder. The most common clinical manifestation is diarrhea, followed by agranulocytosis. May be accompanied by anemia at the same time; Low hematopoietic function of bone marrow; Liver lesions include liver enlargement and elevated transaminase; Bone deformity; Growth retardation; Abnormal development of neuromotor function, etc. Now we review and analyze the clinical data and genetic characteristics of a case of SDS with arrhythmia as the first manifestation treated in our department in May 2020 and literature review.

Public publication of case reports has obtained informed consent from guardians and medical institutions of children.

Case Report

Proband. The patient, female, age 1 month 24 days, was hospitalized after 50 days due to arrhythmia. Arrhythmias (specific types cannot be provided) were found in the physical examination of the child on the third day of birth, and the parents did not pay attention to them. Later, arrhythmia was found during physical examination in the outpatient department of our department, and the ECG showed ventricular premature beats with bigeminy coupled rhythm. He was admitted to the hospital. The child was G2P1 (embryo was stopped once), full-term spontaneous delivery, birth weight: 3.26kg, no history of hypoxia and asphyxia, and the mother had hypothyroidism during pregnancy, and was treated with oral Euthyrox. Breastfeeding, denies the history of similar diseases in the family. Admission physical examination: length: 48cm (< P3),
weight: 3.7kg (< P15). Good mental reaction, heart rate: 142 beats/minute, irregular rhythm, clear breathing sound of both lungs, soft abdomen, 1.5cm under the liver ribs, soft texture, the spleen is not touched, and the neurological examination is normal. Auxiliary examination: Blood routine: WBC:5.17 × 10^9/L, NEUT%:11.6%, LYM%:72.7%, NEUT:0.66 × 10^9/L, HGB:104g/L, PLT:293 × 10^9/L. The morphology of peripheral blood smear cells was normal, and bone marrow puncture was not performed. ALT:39.2U/L, AST: 67.3 U/L, ALP:410 U/L, TBIL, DBIL, IBIL are normal. Myocardial enzyme, troponin, coagulation function, complete items of TORCH, thyroid function, blood lactate, hematuria tandem mass spectrometry screening were normal. No chromosome number or structure abnormality was found by karyotype analysis. Abdominal ultrasound showed that the liver was swollen and the echo was normal. No obvious abnormality is found in spleen and pancreas. No pathological changes were found on cranial MRI. Cardiac ultrasound showed patent foramen ovale with a diameter of 1.8mm. 24-hour ambulatory electrocardiogram showed that the total number of ventricular premature beats was 8284 times, including 126 times of ventricular premature bigeminy coupled rhythm, and frequent ventricular premature bigeminy coupled rhythm. The etiology of arrhythmia in the child is unknown. It is suggested to have cardiac electrophysiological examination, but the guardian refuses to accept invasive examination. Based on the arrhythmia of unknown cause in the child, growth retardation, abnormal liver function and neutropenia were combined at the same time. Full exon sequencing was performed for children and their parents. Results: The proband’s SBDS gene chr7:66,459,197, c.258+2T> C homozygous variation, the mother was heterozygous, and the father did not find the variation. QPCR verified that there was a pseudogene in SBDS, and qPCR SYBR Green I dye method was used to verify the copy number variation, It was found that the proband and his father had a heterozygous deletion variation near the position of chr7:66,459,197 of SBDS gene, and the proband’s mother had no such variation. Point mutation and fragment deletion constitute compound heterozygosity, which conforms to the autosomal recessive mode of inheritance. The results are shown in Figures 1 and 2.

After diagnosis, the patient was discharged from the hospital and given oral vitamin C and fructose diphosphate sodium nutritional myocardial treatment. The child developed diarrhea symptoms at the age of 2 months, 5–10 times a day, and a small amount of fat balls can be seen in Stool routine. At the age of 6 months, liver enzymes increased progressively, ALT:112–347 U/L, AST:110–286 U/L, and the neutrophil counts were all Above 0.6 × 10^9/L, but always below 1.5 × 10^9/L, anemia has been corrected. At the age of 10 months, reexamination of cardiac ultrasound showed that the foramen ovale was closed, and the cardiac structure and function were normal. At present, the child is 22 months old, with a length of 73cm (< P3) and a weight of 9.2kg (< P15). He can walk alone and pronounce reduplicative sound. There has been no serious infection since the onset of the disease. The total number of ventricular premature beats decreased to about 2000 times, feel no discomfort. Continue to take oral Chinese medicine preparations to reduce liver enzymes, supplement pancreatic enzymes, supplement fat soluble vitamins, outpatient follow-up and other treatments.

Informed written consent was obtained from patients and their guardians for the publication of the case details and any accompanying images.

Literature Review

From January 1st, 2000 to December 30th, 2021, relevant literatures were searched by PubMed, CHKD and CNKI databases with “Shwachman diamond syndrome” and “SDS” as keywords. The incidence rate of SDS in Europe and the United States is about 0.5/10^5–1.5/10^5.1 There are about 38 cases of children reported in China, mostly case reports and small sample data reports.2 The first clinical manifestations of SDS are: chronic diarrhea, granulocyte deficiency, skeletal deformity, and backward growth and development. It may also be combined with liver damage, abnormal development of motor function, and hypoplasia of myelin sheath in brain white matter. General children have no special face and are not accompanied by congenital heart malformations or other organ malformations. There are no reports of Shwachman diamond syndrome with arrhythmia as the first manifestation or with arrhythmia.

The cardiac conduction system is controlled by both sympathetic and parasympathetic nerves. Because of the unbalanced development of the sympathetic nervous system in infants, especially newborns, the immature development of the cardiac conduction system caused by the imperfect regulatory function, and the unstable electrophysiological function are the physiological basis for the occurrence of arrhythmias in infants.3 Clinically, supraventricular arrhythmia is more common. The causes of arrhythmia in infants and young children reported in the literature are as follows: 1. Various organic heart diseases: congenital heart disease, myocarditis, cardiomyopathy. 2. Systemic infectious diseases:
sepsis, severe pneumonia, enterogenous infection, etc. 3. Asphyxia and hypoxia. 4. Electrolyte balance is disordered. 5. Immune related diseases. 6. Genetic metabolic diseases.

This child has no fever, no infection and poisoning symptoms, no fatigue, shortness of breath, no history of hypoxia and asphyxia, and normal myocardial enzymes, troponin, electrolytes, lactic acid, hematuria tandem mass spectrometry screening. Multiple electrocardiograms suggested: ventricular premature bigeminy coupled rhythm, no evidence of supraventricular tachycardia, no QRS complex prolongation and δ Evidence of wave existence. There was no evidence of cardiac arrhythmia in the family. Therefore, it is highly suspected that the arrhythmia of children is related to SDS. Because parents refused cardiac electrophysiological examination, there was no direct evidence to confirm the correlation between them.

SDS has special genetic heterogeneity. More than 90% of children with SDS have mutations in the SBDS gene on chromosome 7. SBDS gene product is a multifunctional protein composed of about 250 amino acids, which is mainly involved in the biosynthesis of glycosomes in the cell core and the stabilization of mitotic spindles. SBDS gene is widely expressed in bone marrow, pancreas, liver, brain and other organs with active metabolism. If SBDS gene mutation occurs, it will cause

![Figure 1](https://doi.org/10.2147/PGPP.S381695)

**Figure 1** Homozygous variation.
The severity of its clinical manifestations may be related to the degree of protein function loss. The heart is also an important organ with active metabolism, and few cases involve cardiac manifestations. I hope this report can attract the attention of medical colleagues to the cardiac function of SDS patients.

At present, there are more than 40 mutations in the reported SBDS gene, among which the most common forms are: c.258+2T > C, c.183–184TA > CT, and compound heterozygous mutation of [c.258+2T > C; c. 183–184TA > CT]. There are also reports that DNAJC21, EFL1 and SRP54 can also cause SDS like clinical manifestations. Like SBDS, they play a role in the maturation and assembly of ribosomal subunits, resulting in changes in ribosomal composition, structure or function. This child is a very special SBDs gene and its pseudogene point mutation and fragment deletion constitute a compound heterozygous variant.

**Discussion**

SDS was first reported by doctors Shwachman and diamond of Boston Children’s Hospital in 1964. It is a rare autosomal recessive disease. It was confirmed in 2003 that it was caused by SBDS gene mutation on chromosome 7. SDS can involve multiple organs, and its clinical manifestations are complex and diverse, which is very easy to miss diagnosis. The main clinical manifestations are summarized as follows:

1. Pancreatic exocrine enzyme deficiency: clinical manifestations include diarrhea, dyspepsia, growth retardation and fat soluble vitamin deficiency. It is reported that diarrhea symptoms are common in infants, and more than half of the children that the diarrhea symptoms can be improved to varying degrees with age.
2. Abnormal hematopoietic function of bone marrow: due to the failure of hematopoietic function of bone marrow, most children show varying degrees of hemocytopenia. About 90% of the children will have neutropenia. A small number of children will turn into myeloid leukemia. Myeloid leukemia and severe infection caused by neutrophil deficiency are the main causes endangering the lives of children with SDS.
3. Liver disease: about 80% of children show increased transaminase and liver enlargement. Liver damage often persists in infancy and tends to be normal after the age of 5.
4. Abnormal bone development: the abnormal bone development of children with SDS is mostly manifested by osteoporosis and the widening of the metaphysis of long bone. It may be related to abnormal calcium and phosphorus deposition caused by poor absorption of fat soluble vitamins.
5. Central nervous system abnormalities: studies have found that a small number of children with SDS will have varying degrees of cognitive impairment and behavioral disorders. At the same time, there are also abnormal signals in different degrees and parts of the brain MRI of this part of children.
Treatment of SDS

Allogeneic hematopoietic stem cell transplantation (allo HSCT) is the only radical treatment for SDS at present. For children who do not meet the requirements of hematopoietic stem cell transplantation, only symptomatic support treatment can be used: including oral trypsin preparation, fat soluble vitamins, trace elements, skimmed formula, and regular assessment of nutritional status. For severe anemia and thrombocytopenia, appropriate component blood transfusion should be given. Severe persistent neutropenia and children with recurrent infection can be treated with granulocyte colony stimulating factor.\textsuperscript{18,19}

Conclusion

The first onset of this child did not have typical diarrhea symptoms, but began with a rare arrhythmia. After laboratory examination, it was confirmed that there was mild liver damage, continuous reduction of granulocytes for unknown reasons, and accompanied by growth and development retardation. The final genetic test confirmed the diagnosis of SDS. We carried out ECG follow-up for 2 years, and the child did not have supraventricular tachycardia, no QRS complex prolongation and δ Evidence of wave existence. And the premature ventricular contractions in children decreased with age. Although the child did not have cardiac electrophysiological examination, it was still highly suspected that arrhythmia was related to SDS. It is hoped that this report can attract the attention of medical colleagues to the heart function of SDS patients.

In conclusion, the incidence rate of SDS is very low, and its clinical phenotypes are diverse. In addition to the common diarrhea and abnormal liver enzymes, it can also involve the center, kidney, testis, skin, heart and other organs. Early gene diagnosis is helpful to disease management, improve prognosis, and provide genetic guidance for future eugenics.

Abbreviations

SDS, Shwachman diamond syndrome; SBDS, Shwachman Bodian Diamond syndrome; CHKD, China Hospital Knowledge Database; CNKI, China national knowledge infrastructure; TORCH, It is the abbreviation of a group of pathogenic microorganisms. Toxoplasma, Others, Rubella.Virus, Cytomegalo.Virus, Herpes.Virus; allo-HSCT, allogeneic hematopoietic stem cell transplantation; MRI, Magnetic resonance imaging; QPCR, Real-time Quantitative PCR Detecting System.

Consent to Participate

Informed written consent of the patient and child guardian and permission of The Affiliated Hospital of Inner Mongolia Medical University have been obtained to publish case details and any accompanying images.

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Disclosure

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