Stormorken syndrome caused by *STIM1* mutation: A case report and literature review

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Abstract. The aim of the present case study was to identify the genetic cause of a patient with a clinical presentation of tubular aggregate myopathy (TAM)/Stormorken syndrome (STRMK) and review the published clinical data of patients with TAM/STRMK. A child with thrombocytopenia and hyperCKemia at the Children's Hospital of Soochow University were recruited in the study. Peripheral blood samples of the infant and her parents were collected, and then whole-exome sequencing was performed. Detection of the stromal interaction molecule 1 (STIM1) level of the child was performed using western blot analysis. In addition, a literature review was performed based on a thorough retrieval of published literature from the PubMed database, as well as domestic databases. In the present study, the c.326A>G mutation in a *STIM1* allele (p.H109R) was identified only in the child, as opposed to the unaffected parents. The level of STIM1 was not decreased in the child. Among the mutation sites identified in previous studies, there were 46 cases across 30 families of *STIM1* EF-hand mutations, 21 cases across 14 families of *STIM1* CC1 mutations and 20 cases across 8 families of calcium release-activated calcium channel protein 1 mutations, in which 7 parents had the same mutation site as the patient described herein. On the whole, it is demonstrated that TAM/STRMK is an extremely rare disease with autosomal dominant inheritance. Patients often have multisystemic signs. Gene detection at an early stage is helpful for diagnosis. Long-term exercise training may also have a certain curative effect.

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Abbreviations: TAM, tubular aggregate myopathy; STRMK, Stormorken syndrome; STIM1, stromal interaction molecule 1; SOCE, store-operated Ca2+ entry; PBS, phosphate-buffered saline; RRs, reference ranges; TA, tubular aggregate; CK, creatine kinase

Key words: STIM1, Stormorken syndrome, tubular aggregate myopathy, thrombocytopenia, hyperCKemia

Introduction

Tubular aggregate myopathy (TAM) is a progressive muscle disease that mainly affects the muscle of the proximal lower limbs and results in myasthenia, myalgia and exercise intolerance (1,2). The term Stormorken syndrome (STRMK) is used when TAM is combined with thrombocytopenia, bleeding tendency, mild anemia, hypocalcemia, asplenia, miosis, dyslexia, ichthyosis and a short stature. TAM overlaps with STRMK and differs in severity and age of onset (3). Some patients with STRMK may exhibit only TAM-related clinical manifestations, and the phenotypical spectrum ranges from asymptomatic hyperCKemia to myalgia, progressive muscle weakness and the contracture of muscle (1).

Studies have reported that TAM/STRMK is a rare autosomal-dominant inheritance disease with mutations in stromal interaction molecule 1 (*STIM1*) or calcium release-activated calcium channel protein 1 (*ORAI1*) (4,5). *STIM1* or *ORAI1* both encode key factors of store-operated Ca2+ entry (SOCE), and thereby direct a plethora of Ca2+-dependent cellular pathways and functions, including muscle contraction (6,7). Functional analyses have demonstrated that TAM/STRMK arise from gain-of-function mutations in *STIM1* or *ORAI1* (8,9).

The TAM/STRMK case described in the present study is the second case in China identified to date, at least to the best of our knowledge. The present study describes the case of a pediatric patient with TAM/STRMK at the Children's Hospital of Soochow University, Suzhou, China and also provides a review of the literature on TAM/STRMK. The aim of the present study was to explore the clinical features, diagnosis and treatment of TAM/STRMK in order to aid in its early identification.

Case report

Clinical assessment. The present study abided by the principles of the Declaration of Helsinki. All clinical, laboratory and molecular biological examinations and treatment programs were performed after obtaining informed consent from the parents of the child and were approved by the Ethics Committee of the Children's Hospital of Soochow University.

Clinical general information. A 2-year-old Chinese girl was born to a gravida 2 para 2 (G2P2) woman via caesarean

section at term, with a birth weight of 3,250 g, a body length of 50 cm, a normal Apgar score and timely vaccination. The child had a history of convulsions, long-term thrombocytopenia, hyperCKemia and repeated skin petechiae and ecchymoses from the age of 1 month. The girl was admitted to the Children's Hospital of Soochow University due to petechiae and ecchymoses that were scattered across the skin of the whole body. A physical examination revealed a temperature of 36.5˚C, a pulse of 112 bpm, a respiratory rate of 26 breaths per minute, a body length of 82 cm and a weight of 11.2 kg, and petechiae and ecchymoses were noted over the skin of the whole body. Eye movements were normal. Chest, cardiac and abdominal examinations did not reveal any abnormalities. No marked muscular weakness was noted in her extremities, and Kernig's and Brudzinski's signs were negative.

Family history. In the family, only the patient had thrombocytopenia and long-term hyperCKemia. The parents were not inbred, and there was one sibling sister, who was in good health. There was not familial history of the disorder.

Laboratory tests. Blood tests revealed that the patient's white blood cell count was high ($11.2x10^9$/l; reference range (RR), $4.0\text{-}10.0x10^9$/l). She had low platelet counts ($16x10^9$/l; RR, $101\text{-}320x10^9$/l), anemia (hemoglobin, 90 g/l; RR, 110-140 g/l), normal calcium serum levels (2.27 mmol/l; RR, 2.25-2.67 mmol/l) and very high levels of creatine kinase (CK; hyperCKemia; 498.6 U/l; RR, 25-225 U/l). Antinuclear antibody tests revealed positive results for anti-SSA, anti-AMA-M2 and anti-Ro-52 antibodies. Alanine aminotransferase, aspartate aminotransferase and serum creatinine levels were normal. Fibrinogen, prothrombin time and activated partial thromboplastin time were normal. Trace element serum levels, ammonia serum levels, ceruloplasmin serum levels, fibrinogen, prothrombin time, activated partial thromboplastin time, tandem mass spectrometry and cerebrospinal cultures did not reveal any obvious anomalies. In the bone marrow assessment, nucleated cell hyperplasia was markedly active, megakaryocytes were visible and platelets were rare. An abdominal computed tomography scan revealed normal structures of her liver, gallbladder, pancreas and spleen. Brain magnetic resonance imaging and a 24-h electroencephalogram revealed no abnormalities. Blood and urine tandem mass spectrometry and hemolysis examinations were normal.

Whole-exome sequencing and mutation detection. Genomic DNA was extracted from 200 μl peripheral blood, using a Qiagen DNA Blood Midi/Mini kit (Qiagen GmbH). The extracted DNA was fragmented with DNase and purified via the magnetic bead method, followed by ligation of the adaptor sequence and PCR amplification. The PCR products were validated using an Agilent 2100 Bioanalyzer (Agilent Technologies, Inc.). PCR was performed using Takara PrimeSTARMax DNA Polymerase (Takara Biotechnology, Co., Ltd.) under the following thermocycling conditions: An initial denaturization at 95˚C for 5 min, followed by 35 cycles of denaturation at 95˚C for 3 sec, annealing at 60˚C for 30 sec and extension at 72˚C for 30 sec. A final extension was performed at 72˚C for 5 min. Sequencing of the genomic DNA of the family was performed using the Novaseq6000 platform (Illumina, Inc.). The original data were obtained following sequencing of all exons. The Burrows Wheeler Aligner algorithm was used to compare the reference sequence (UCSChg19), and GATK version 3.7.0 (https://software.broadinstitute.org/gatk/) and VarScanversion 2 software (http://dkoboldt.github.io/varscan/) were used to identify mutations, e.g., single nucleotide polymorphisms (SNPs) and InDels, including detection, annotation and statistical analysis. The pathogenicity of variants was analyzed according to the American College of Medical Genetics and Genomics standards and guidelines (10).

Construction. The STIM1 domain was searched on UCSC (http://genome.ucsc.edu/). The STIM1 bioconservative analysis view was structured using T-Coffee (https://www.ebi.ac.uk/Tools/msa/tcoffee/). The 3D structures of STIM1 and mutated proteins were constructed in SWISS-MODEL (https://swissmodel.expasy.org/).

Expression analysis. The bottom blood cells were obtained by the centrifugation of peripheral blood (centrifugation conditions, 4 ml, 4˚C, 1,509.3 x g). The blood cells were frozen and dissolved, and treated using Red Blood Cell Lysis Buffer (Shanghai Acmec Biochemical Co., Ltd.). The products were washed with phosphate-buffered saline (PBS) buffer (ABclonal Biotech Co., Ltd.) and treated with RIPA lysis buffer (ABclonal Biotech Co., Ltd.). The protein concentration was measured using a BCA Protein Quantification kit [Yeasen Biotechnology (Shanghai) Co., Ltd.]. The samples (10 μg protein/lane) were resolved by 10% SDS-PAGE and electroblotted onto Immobilon-P transfer membranes (ABclonal Biotech Co., Ltd.). The membrane was blocked at 4˚C overnight with 5% skim milk, and incubated with primary antibodies at room temperature for 1 h, and then incubated with secondary antibodies at room temperature for 1 h. STIM1 rabbit polyclonal antibody (diluted 1:1,000, cat. no. A19894, ABclonal Biotech Co., Ltd.) was used as a primary antibody. Anti-rabbitIgG-HRP (diluted 1:1,000, cat. no. AS080, ABclonal Technology, Wuhan, Hubei, China) was used as a secondary antibody. GAPDH rabbit polyclonal antibody (cat. no. AC027, ABclonal Technology, Wuhan, Hubei, China) as the loading control. The membranes were again washed three times with TBS and the color reaction was carried out by incubating the membranes with chromogenic substrate for peroxidase, 4-chloro-1-naphtol and H_2O_2. Protein bands were visualized using an Enhanced Chemiluminescence Detection kit (Beyotime Institute of Biotechnology), and images were captured using Image Lab software version 3.0 (Bio-Rad Laboratories, Inc.).

Literature search. The literature review was based on a thorough retrieval of studies from PubMed, China National Knowledge Infrastructure (CNKI; https://www.cnki.net/) and Wanfang Standards Database (WFSD; http://www.wanfangdata.com.cn/). The key terms used in the search included Stormorken, *STIM1* and TAM. Clinical, laboratory, therapeutic and outcome data were collected.

Treatment. After admission, the patient was administered intravenous immunoglobulin 500 mg/(kg/day) for

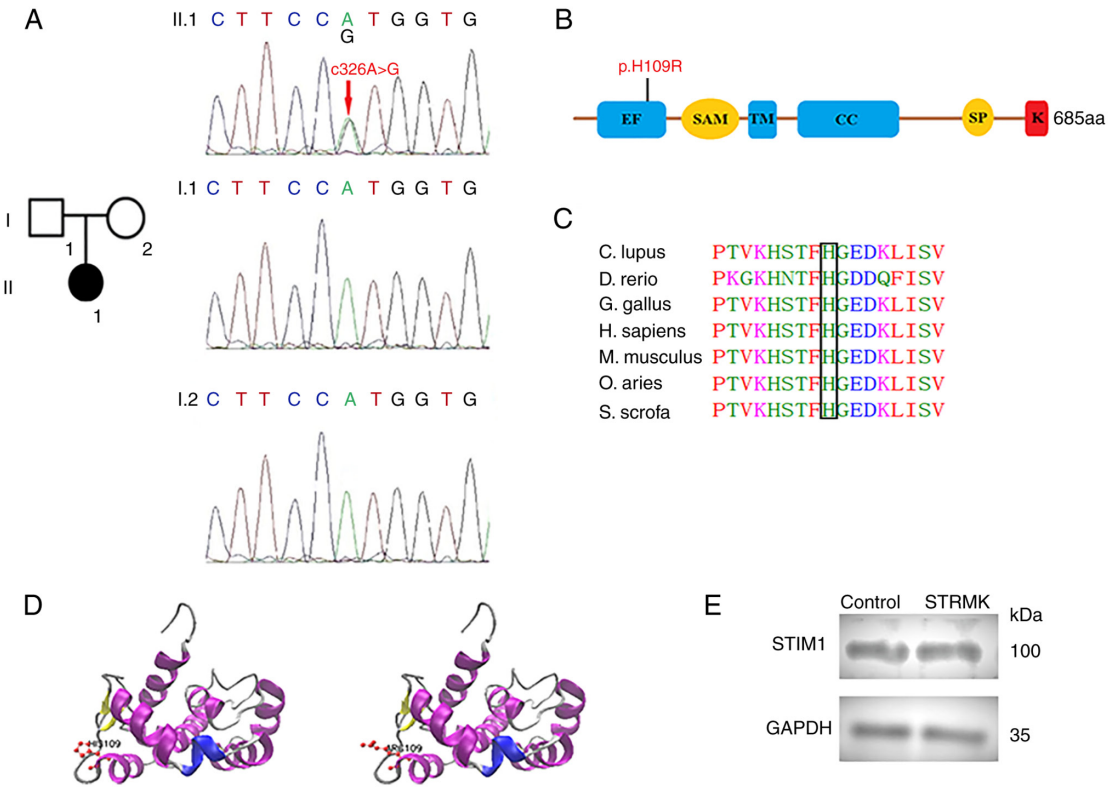

Figure 1. Genetic analysis of *STIM1*. (A) Information on the pedigree and Sanger sequencing results. The mutation was present in affected patient and absent in the unaffected parents, indicating that it was a spontaneous mutation. (B) Schematic representation of the STIM1 domains. The arrow indicates the position of the substitution in the EF-hand domains. (C) Amino acid sequence conservation of STIM1. The affected amino acids have been highly conserved during evolution. (D) 3D structures of STIM1 and mutated proteins. (E) STIM1 exhibited a comparable level compared to the control *in vitro*, as indicated using western blot analysis. STIM1, stromal interaction molecule 1; EF, EF-hand domain; TM, transmembrane domain; CC, coiled-coil domain; SP, serine- and proline-rich domain; K, polylysine.

supportive treatment, and methylprednisolone was added at 2 mg/(kg/day) for 5 days; carbazochrome sodium sulfonate 20 mg/(once/day) was administered to prevent bleeding, vitamin C was administered to improve vascular permeability, and other comprehensive treatments were applied. No new skin bleeding points occurred in the child, and her platelet count was progressively maintained >60x10^9/l after two consecutive reexaminations. The patient was discharged after 8 days with improved symptoms. At the last follow-up, the patient's platelet count was 68x10^9/l, CK levels were 501.4 U/l and no related manifestations of muscle weakness were found. Comprehensive language and exercise training was conducted at home, with regular outpatient follow-up visits at the Department of Child Health care and Rehabilitation, Children's Hospital of Soochow University. The quality of life of the child was the same as that of a healthy individual during the non-pathogenic period, specifically, the motor function is normal, and can communicate and play normally with children of the same age.

Molecular genetics analysis. To identify the disease, exome sequencing was performed on the patient and her parents, and the c.326A>G transition in an *STIM1* allele (p.H109R) was identified (Fig. 1A). The mutation was present in the affected patient and absent in the unaffected parents, indicating that it was a spontaneous *STIM1* mutation in the patient. The mutation was predicted to be harmful by protein function prediction software (http://www.mutationtaster.org/). Mutations associated with TAM/STRMK were found upon consulting the HGMD database (http://www.hgmd.org/). The variant located in the EF-hand (Fig. 1B) supposedly led to constitutive STIM1 unfolding and oligomerization (11). The affected amino acids in this residue was evolutionarily conserved (Fig. 1C), which indicated an important functional role. The 3D structures of STIM1 and mutated proteins were constructed in SWISS-MODEL (https://swissmodel.expasy.org/) (Fig. 1D). No differences in STIM1 expression levels were observed between the case in the present study and the healthy control (the healthy control was selected from a 2-year-old healthy Chinese girl without clinical manifestations of STRMK) (Fig. 1E); thus, the present study reached similar conclusions as those of a previous study (9).

Literature review. The literature search revealed only a few reported cases of suspected TAM/STRMK worldwide, comprising 52 families and 87 cases in total. Among these, 30 families (46 cases) had STIM1 EF-hand mutations, 14 families (21 cases) had STIM1 CC1 mutations, and 8 families (20 cases) had ORAI1 mutations (1,4,8,9,11-24). TAM/STRMK was mainly induced after STIM1 EF-hand, STIM1 CC1 and ORAI1 mutations. The mutation sites identified in previous studies (including the present case) are summarized in Table I. A total of 7 patients had the same mutation site as the patient described herein, and the phenotypic and histopathological data of the patients with STRMK with c.326A>G (p.H109R) mutations were collated (Table II) (9,15,22,24).

Table I. Summary of mutation sites reported in previous studies (1,4,8,9,11-24).

STIM1 EF-hand (N=46)	*STIM1* CC1 (N=21)	*ORAI1* (N=20)
c.216C>A(p.H72Q) (10)	c.910C>T(p.R304W) (18)	c.290C>G(p.S97C) (3)
c.239A>C(p.N80T) (2)	c.911 G>A(p.R304Q) (3)	c.292G>A(p.G98S) (6)
c.242G>A(p.G81D) (3)		c.319G>A(pV107M) (7)
c.251A>G(p.D84G) (3)		c.412C>T(p.L138F) (1)
c.252T>A(p.D84E) (2)		c.551C>T(p.T184M) (1)
c.262A>G(p.S88G) (1)		c.734C>T(p.P245L) (2)
c.274C>G(p.L92V) (1)		
c.286C>G(p.L96V) (1)		
c.293A>G(p.Y98C) (1)		
c.322T>A(p.F108I) (2)		
c.322T>C(p.F108L) (1)		
c.325C>A(p.H109N) (4)		
c.326A>G(p.H109R) (8)		
c.343A>T(p.I115F) (5)		
c.1095G>C(p.K365N) (1)		
c.312A>T(p.K104N) (1)		

(N), mutation numbers; *STIM1*, stromal interaction molecule 1; CC, coiled-coil domain.

Discussion

The case in the present study had thrombocytopenia and hyperCKemia, and the dominant missense variant, p.H109R in *STIM1* was identified in this patient. The mutation was present in the affected patient and absent in the unaffected parents, indicating that it was a spontaneous *STIM1* mutation in the patient. The level of STIM1 was not decreased in the case described herein. Previous studies have demonstrated that the variant probably results in constitutive STIM1 unfolding and oligomerization, further impairing SOCE, and further changing resting cell Ca^{2+} levels, which first affects skeletal muscle as it is susceptible to changes in Ca^{2+} levels (4,25). The mechanism may be related to the fact that TAM/STRMK patients due to *STIM1* mutations mostly present with muscular involvement.

Shahrizaila *et al* (17) first reported 4 patients with STRMK from one British family in 2004. To date, a total of 8 patients with TAM/STRMK with c.326A> G (p.H109R) have been identified, including the present case. In total, 7 patients with c.326A> G (p.H109R) were all found in childhood. The other 7 patients had a typical TAM-related phenotype, apart from the present patient. By contrast, the patient in the present study only had hyperCKemia, which was also the main reason for the absence of muscle biopsy. Compared with other patients, patient 3 (Table II) had an obvious muscle phenotype. However, the patient did not have obvious abnormalities in the early stages, and the clinical symptoms gradually worsened as the age of the last follow-up increased. Other cases have also exhibited this phenomenon. Patient 1 (Table II) was a 53-year-old male who required intermittent ventilation treatment at night and could not walk normally. The patient described herein was <3 years of age at the last follow-up and only exhibited hyperCKemia. This phenomenon suggests that the severity of TAM/STRMK clinical manifestations is associated with age. The patient in the present study was diagnosed earlier than the other 7 patients, mainly due to its recurrent thrombocytopenia/bleeding tendency. Platelet analyses of the patient with heterozygous *STIM1* R429C mutation revealed a reduced Ca^{2+} store content, a partially impaired SOCE and a secretion defect, which further caused decreased platelet cohesion and platelet dysfunction (19,26). This may account for the bleeding tendency in children with STRMK. Three patients (including the patient in the present study) with c.326A>G (p.H109R) had thrombocytopenia/bleeding tendency. The other 2 patients (patient 5 and 6) (Table II) began to develop muscle weakness at 3 years and >10 years of age. The case described herein lacked the TAM-relevant performance and was <3 years old at the last follow-up, which may be related to her long-term and medium-intensity exercise training. Further follow-up observations are required.

STRMK has a variable degree of multisystemic signs, including muscle weakness, miosis, thrombocytopenia, hyposplenism, ichthyosis, a short stature and dyslexia (4). A literature review suggested that the type and site of TAM/STRMK mutations do not determine the clinical presentation and that the genotype-phenotype correlation remains loose. The case in the present study first manifested thrombocytopenia/bleeding tendency and convulsion, and was misdiagnosed with thrombocytopenia or epilepsy. Following treatment for thrombocytopenia, there was no significant improvement. The case was diagnosed with TAM/STRMK by combining the previous clinical history of the child, the clinical characteristics, laboratory examinations and exome sequencing. Currently, the diagnosis of TAM/STRMK is dependent on clinical features, hyperCKemia, routine blood examination, muscle biopsies, muscle histochemical analysis, gene sequencing and other related assessments (11).

Some patients with TAM/STRMK develop the disease in early life, and patients can develop motor dysfunction as the

Table II. Phenotypic and histopathological data of patients with STRMK with the c.326A>G (p.H109R) mutation (9,15,22,24).

	Family 1				Family 2			
Period of onset	Patient 1 (father) Childhood	Patient 2 (son) Childhood	Patient 3 Childhood	Patient 4 Childhood	Patient 5 (son) Childhood	Patient 6 (mother) Childhood	Patient 7 Childhood	Patient 8 (present case) Childhood
Myasthenia	Upper and lower limbs, predominantly proximal	Lower limbs proximal, upper limbs mild and proximal	Ligature band muscle, lower limbs	Upper and lower limbs	Lower limbs proximal	Lower limbs proximal	Limb-girdle muscle weakness	-
Eye movement defects	Ophthalmoplegia, upwards gaze paresis	Ophthalmoplegia, upwards gaze paresis	-	Ophthalmoplegia, mild bilateral upper eyelid ptosis	-	-	-	-
Contractures	Neck, elbows, wrists, fingers	Neck, heels	Ankle joint	-	-	-	Elbows, wrists, heels	-
CK level	5x198 U/l	12x198 U/l	6x198 U/l	7x198 U/l	4.1x198 U/l	9.1x198 U/l	4x198 U/l	2.5x198 U/l
TA distribution	Mainly in type I fibers	In type I and type II fibers	Mainly in type I fibers	In type I and type II fibers	-	In type I and type II fibers	-	-
Special histological characteristics	Type I fiber predominance, type II fiber atrophy	Type I fiber predominance, type II fiber atrophy	Type I fiber predominance, type II fiber atrophy	Type I fiber predominance	-	Type I fiber predominance, type II fiber atrophy	-	-
Thrombocytopenia/ bleeding tendency	-	-	-	-	+	+	-	+
Prognosis	Intermittent ventilation treatment at night, not walking normally	Walking normally due to long-term exercise training	Progressive limb weakness, unable to run and climb up from the floor	Systemic muscle atrophy and weakness	Difficulty in climbing the stairs	Lower limb muscle weakness progressive aggravation, walking restriction	Normal walking	Normal walking

disease progresses; however, the life expectancy of patients is not markedly reduced. The child described in the present study had an early age of onset and now has no significant motor dysfunction and adverse prognosis. In patients with the p.H109R mutation identified in the literature, patient 2 had a milder clinical manifestation than his father (patient 1) at the same age (Table II), which may be related to the long-term moderate-intensity exercise training of patient 2. By contrast, patient 3 (Table II) was unable to perform physical training activities due to a fracture of the left greater trochanter of the femur, resulting in weight gain, which rapidly caused secondary muscle atrophy and weakness throughout the body. The phenomenon suggests that patients with combined muscular system involvement may be more effectively treated with timely exercise training of appropriate intensity. TAM, bleeding tendency and thrombocytopenia are factors that affect the quality of life of patients. Following the symptomatic treatment of the aforementioned conditions, they can live normally, or the disease may not affect their normal life. Long-term exercise cannot only reduce the average number of tubular aggregates (TAs) per fiber, the number of fibers containing TAs, and the average size of the few remaining TAs, but can also promote colocalization of STIM1 with ORAI1, significantly reduce the formation of TAs, increase Ca^{2+} influx via SOCE, and enhance muscle function and resistance to fatigue (27,28). Markello *et al* (16) hypothesized that compounds targeting the Ca(2+)-selective release-activated Ca(2+) channel may be beneficial for patients with TAM/STRMK. The case in the present study is now regularly followed up in outpatient clinics, and comprehensive long-term exercise and language training is performed at home. The patient has not yet exhibited typical TAM-related clinical manifestations.

TAM/STRMK is very rare and there is currently no effective cure. Patients with TAM/STRMK have multisystemic signs that are not easily distinguishable from other diseases. Overall, when encountering patients with thrombocytopenia of unknown a etiology, bleeding tendency and convulsions, whose causes are not readily apparent by relevant tests and whose therapies are not very useful, first, a careful assessment of the possibility of the development of TAM/STRMK should be conducted. Second, genetic testing must be obtained to assist in the diagnosis. At present, there is no effective radical cure for TAM/STRMK. Patients with TAM-related phenotypes should commence long-term exercise training as soon as possible. In addition, the further exploration of the pathogenesis of TAM/STRMK is warranted, and relevant targeted drugs need to be developed as early as possible.

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Availability of data and materials

The data that support the findings of this study are openly available at 'Mendeley Data' (http://dx.doi.org/10.17632/rjmn9x7fb9.3).

Authors' contributions

WS participated in the study design and in the writing of the manuscript. JHu and MLi participated in the collection of clinical data. JHuo performed the interpretation of the data. XZ participated in the data analysis, interpretation of the data and in the writing of the manuscript. WS and XZ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was reviewed and approved by the Ethics Committee of the Children's Hospital of Soochow University (Suzhou, China; Approval no. 2020CS059). All clinical, laboratory and molecular biological examinations and treatment programs were performed after obtaining informed consent from the parents of the children.

Patient consent for publication

All clinical, laboratory and molecular biological examinations and treatment programs were performed after obtaining informed consent from the parents of the children.

Competing interests

The authors declare that they have no competing interests.

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