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CASE REPORT

ACTA2 mutation is responsible for multisystemic smooth muscle dysfunction syndrome with seizures: A case report and review of literature

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Abstract

BACKGROUND

ACTA2 gene is a specific gene that encodes actin α2. Multisystem smooth muscle dysfunction syndrome (MSMDS) is a multisystem disease characterized by aortic and cerebrovascular lesions caused by *ACTA2* gene mutations. There have been many reports of cardiac, pulmonary and cerebrovascular lesions caused by MSMDS; however, few studies have focused on seizures caused by MSMDS.

CASE SUMMARY

Our patient was a girl aged 7 years and 8 mo with recurrent cough, asthma and seizures for 7 years. She was diagnosed with severe pneumonia, congenital heart disease, cardiac insufficiency, and malnutrition in the local hospital. Cardiac ultrasonography revealed congenital heart disease, patent ductus arteriosus (with a diameter of 0.68 cm), left coronary arteriectasis, patent oval foramen (0.12 cm), tricuspid and pulmonary regurgitation, and pulmonary hypertension. Cerebral magnetic resonance imaging and magnetic resonance angiography indicated stiffness in the brain vessels, together with multiple aberrant signaling shadows in bilateral paraventricular regions. A heterozygous mutation (*c.536*G>A) was identified in the *ACTA2* gene, resulting in generation of *p.R179H*. Finally, the girl was diagnosed with MSMDS combined with epilepsy. The patient had 4 episodes of seizures before treatment, and no onset of seizure was reported after oral

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administration of sodium valproate for 1 year.

CONCLUSION
MSMDS has a variety of clinical manifestations and unique cranial imaging features. Cerebrovascular injury and white matter injury may lead to seizures. Gene detection can confirm the diagnosis and prevent missed diagnosis or misdiagnosis.

Key Words: Multi-systemic smooth muscle dysfunction syndrome; *ACTA2* gene; Seizures; Gene detection; Case report

Core Tip: Multisystem smooth muscle dysfunction syndrome (MSMDS) is a disease caused by *ACTA2* gene mutation. We report a case of MSMDS complicated with epilepsy. Since birth, the child developed several system dysfunctions, including dyspnea, congenital heart disease, and malnutrition. Brain magnetic resonance imaging (MRI) and magnetic resonance angiography showed cerebrovascular stiffness. It was accompanied by multiple abnormal signaling shadows around the bilateral ventricles, which may have been the focus of the seizures. Reviewing the literature and imaging reports, head MRI shows that abnormal signals and vascular malformations should be paid more attention to, which may lead to seizures in older patients.

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INTRODUCTION

Multisystem smooth muscle dysfunction syndrome (MSMDS), initially reported by Milewicz *et al*[1] in 2008, is a serious genetic disease caused by mutations in the *ACTA2* gene. It is characterized by aortic and cerebrovascular diseases, persistent ductus arteriosus, congenital mydriasis and organ dysfunction dependent on smooth muscle function, including the bladder and intestinal tract[2]. The diagnosis and treatment are still a challenge as few cases induced by *ACTA2* mutation are available. In this case report, we present a patient with MSMDS induced by *ACTA2* mutation combined with seizures. We summarize the clinical manifestations, laboratory test findings and molecular features. At the same time, we searched PubMed for related cases from 1980 to 2020 by using the keywords "multi-system smooth muscle dysfunction" and "*ACTA2*", and summarized the clinical characteristics, laboratory results and molecular characteristics of these cases.

CASE PRESENTATION

Chief complaints

A girl aged 7 years and 8 mo came to our department for repeated cough, shortness of breath for 7 years and one convulsion. There were four convulsions within 2 d after admission. No fever, vomiting, diarrhea and other symptoms were found.

History of present illness

The patient had convulsions shortly after waking up in the morning, for no obvious reason. They were characterized by generalized tonic–clonic seizures and relieved spontaneously within 2 min.

History of past illness

The patient had a paroxysmal cough after catching a cold, combined with cyanosis in the mouth and lips, and shortness of breath since 8 mo of age. Chest radiography indicated increased pulmonary markings in both lungs. Cardiac ultrasonography indicated congenital heart disease, patent ductus arteriosus (PDA), patent oval foramen and pulmonary hypertension. She was admitted to the local hospital several times for the treatment of severe pneumonia, congenital heart disease, heart insufficiency, and malnutrition. These conditions showed remission after symptomatic treatment.

Personal and family history

The child was born by cesarean section at 38 wk. Her parents and one of her brothers were healthy.

Physical examination

After admission, the patient's temperature was 37.0°C; pulse, 112 bpm; respiration, 29 breaths/min; blood pressure, 98/60 mmHg; body weight, 18 kg; height, 118 cm; and head circumference, 50 cm. She was conscious, but presented with an appearance of malnutrition. The subcutaneous fat was thin. No swelling was noticed in the tonsils. No cyanosis was identified in the mouth and lips. No obvious edema was observed. her language, intelligence and movement showed slight delay. Congenital mydriasis was noticed. The pupils showed a diameter of 5 mm, and were no longer sensitive to light reflex. The heart rate was 112 bpm. The cardiac sound was loud, P_2 showed accentuation. Persistent machinery murmur (III/6) was identified in the left sternal border. The pulmonary respiration in both lungs was coarse, without dry or moist rales. The abdomen was soft, and the liver was palpable under the ribs (1.0 cm). The boundary was sharp, and the texture was soft. No tenderness was felt. For nervous system examination, the neck was soft, and the pathological signs were negative. The myodynamia and muscular tension were normal, and the tendon reflex was normal. Appetite, sleeping, urination and defecation were normal.

Laboratory examinations

Blood analysis revealed leukocytosis 8.58 × 10^9/L with the neutrophils as the major cells (68%). The hematocrit and platelet count were normal. The level of procalcitonin increased slightly (1.42 ng/mL). Serum C-reactive protein was 33.84 mg/L (normal range < 8 mg/L). Stool occult blood test was positive. Electrocardiography showed sinus rhythm and axis deviation to the right. Chest X-ray showed thickened texture in both lungs, together with patchy blurred shadows and enlarged heart shadow. There was obvious protrusion in the pulmonary artery segment, plump edge of the right heart, and left heart margin beyond the midline of the clavicle. There were no abnormalities in liver and renal function determination, cardiac enzymes, electrolytes, blood glucose and organic acid. The score based on the Wechsler Intelligence Scale was 75.

Imaging examinations

The video electroencephalogram findings showed background activity of 6–7 c/s in consciousness. The bilateral activity was symmetric, with no obvious spike/sharp wave. No paradoxical discharge was noticed in the presence of flash stimulation. Cardiac ultrasonography revealed congenital heart disease: PDA with a diameter of 0.68 cm, left coronary arteriectasis, patent oval foramen with a diameter of 0.12 cm, tricuspid and pulmonary regurgitation, and pulmonary hypertension. Cranial magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) indicated stiffness in the brain vessels, together with multiple aberrant signaling shadows in bilateral paraventricular regions (Figure 1).

Gene sequence analysis

For the gene sequencing, venous blood samples (3 mL) were collected from the patient and her parents using a tube containing EDTA after obtaining informed consent. The study protocols were approved by the Ethical Committee of our hospital (approval No. 2016066). The pathogenic gene was detected by whole exon sequencing, and verified by Sanger technique. A heterozygous mutation (*c.536G>A*) was identified in the *ACTA2* gene, which resulted in generation of *p.R179H* (Figure 2, Table 1). No mutations were identified in the *ACTA2* gene in her parents.

Table 1 Gene sequencing data of the *ACTA2* in the patient

Item	Results
Nucleotide changes	*c.536*G>A
NM No.	NM_001613.2
Homozygous/heterozygous mutation	Heterozygous mutation
Amino acid changes	*p.R179H*
Minor allele frequency	N/A
Pathogenicity	Pathogenic mutation
Disease/phenotype	Multi-systemic smooth muscle dysfunction syndrome
Genetic type	Autosomal dominant
Mutation source	Newly identified

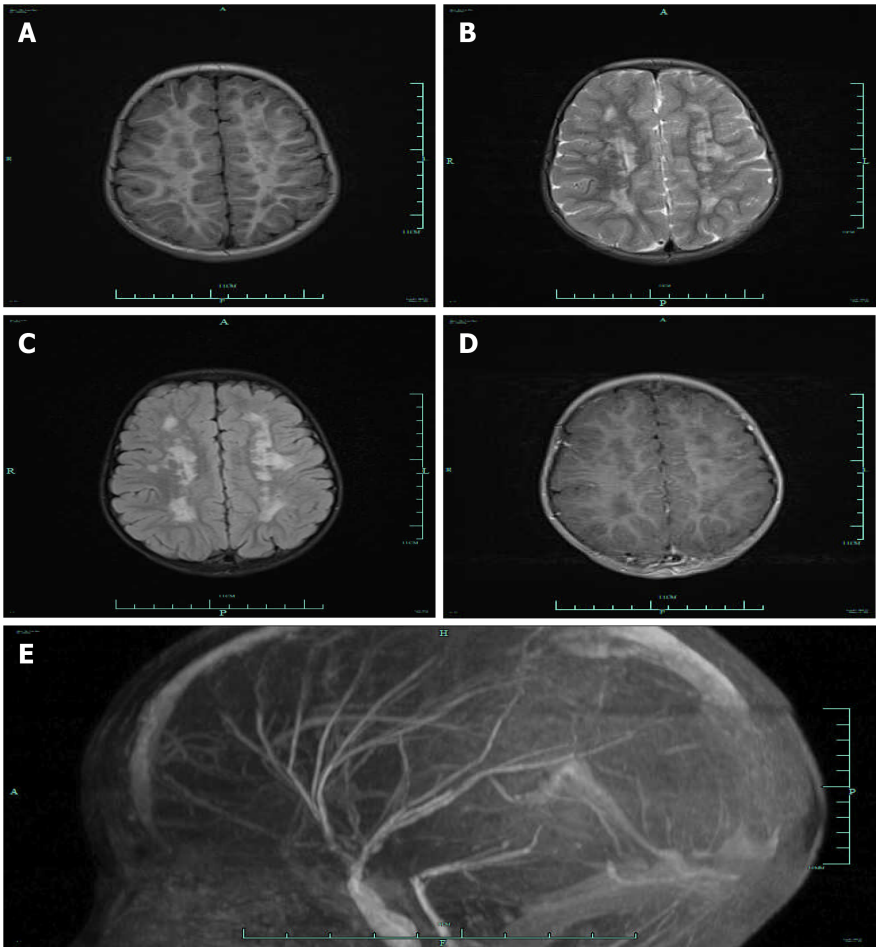

Figure 1 Cerebral magnetic resonance imaging (axial T1-weighted, T2-weighted, fluid attenuated inversion recovery images) for the patient with multi-systemic smooth muscle dysfunction syndrome multiple. A-C: Cerebral Magnetic resonance imaging showed multiple aberrant signal shadows in bilateral paraventricular; D: There was no enhancement in contrast-enhanced scan; E: Lateral projection of magnetic resonance angiography indicated abnormally straight course of intracranial arteries.

FINAL DIAGNOSIS

MSMDS.

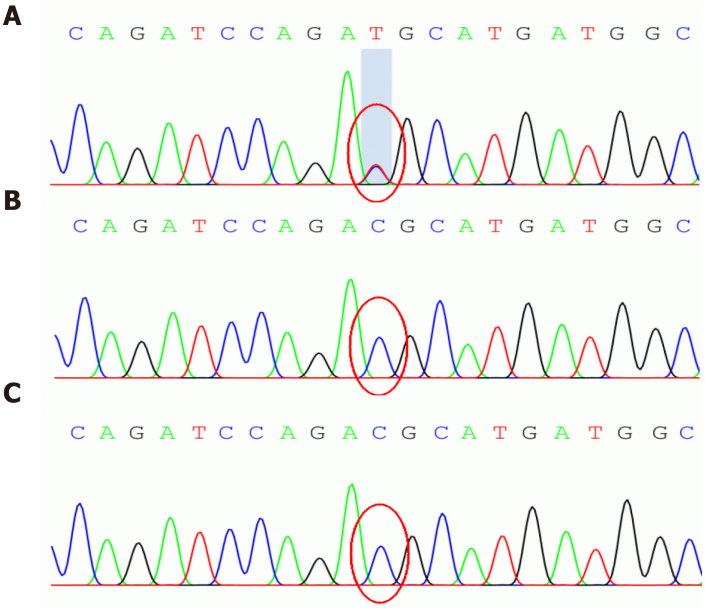

Figure 2 Sequencing analysis results for the patient and her parents. The gene sequence map of the child showed the change of *c.536*G>A (the nucleotide cytosine mutation of coding region 536 became thymine). No mutation was identified in the sequencing data of her father and mother. A: The patient; B: Her father; C: Her mother; Green shadow indicated mutation sites.

TREATMENT

To date, there is no standardized treatment for MSMDS. For children with MSMDS, we reviewed and screened the conventional treatment strategies for related symptoms, and administered the following treatments to alleviate the patient's conditions. Sildenafil was utilized to decrease pulmonary hypertension[3]. Fructose diphosphate sodium was used to nourish the cardiac muscles[4]. Oral administration of sodium valproate was given for the treatment of epilepsy[5].

OUTCOME AND FOLLOW-UP

The patient was followed up every 3 mo after discharge. Recurrent coughing and purplish relapse could usually be improved after anti-infective treatment, and she has not shown seizures until now, through oral administration of sodium valproate (5 mL, bid).

DISCUSSION

We searched "multiple system smooth muscle dysfunction" and "*ACTA2*" in PubMed and Medline, and reviewed the clinical symptoms and imaging of the previous cases. Besides our case, we searched PubMed for a total of 19 published articles involving 37 MSMDS patients. Details of these cases are summarized in Table 2[1,2,6-22]. According to the analysis of these patients, the youngest was age 3 d[8] and the oldest 41 years [12]. The main clinical manifestations were congenital fixed mydriasis and PDA. Thirty-seven patients had congenital pupil dilation and 35 had PDA. Four patients had convulsions. Twenty-five patients had abnormal signals of white matter on MRI findings. Thirty-seven patients underwent gene sequencing analysis. In total, 28 cases had Arg179His mutation, five Arg179Cys mutation, and two each Arg179Leu and Asn117Lys mutation.

ACTA2 gene is located in the long arm of chromosome 10q23.31, which encodes the expression of actin α2. MSMDS is a serious disease caused by *ACTA2* mutation, which is characterized by familial thoracic aortic aneurysm and cerebrovascular lesions. Milewicz *et al*[1] summarized the clinical symptoms of the disease in 2010: (1) Visual system: congenital nonreactive mydriatic fixation; (2) Cardiovascular system: PDA, pulmonary artery dilatation or hypertension, thoracic aortic aneurysm; (3) Nervous system: cerebral infarction, hemiplegia, motor/mental delay; (4) Respiratory system:

Table 2 Clinical characteristics of 37 patients with multiple smooth muscle disorder syndrome

	Mutation type	Arg179His[1]	Arg179Cys	Arg179Leu	Asn117Lys
Total number of patients (unit: example)		28	5	2	2
Clinical features					
Visual system symptoms					
	Congenital mydriasis	28	5	2	2
	Retinal vessels twists and turns	13	1	1	0
Cardiovascular system					
	Patent ductus arteriosus	26	5	2	2
	Pulmonary hypertension	12	2	0	0
	Thoracic aortic aneurysm	9	0	0	0
	Pulmonary artery dilatation	10	1	0	0
Nervous system					
	Underdevelopment	11	1	0	0
	Cerebral infarction or hemiplegia	5	1	0	1
	White matter lesion	21	3	0	1
	Manifestations of moyamoya-like disease	19	4	1	0
	Epileptic seizure	4	1	0	0
Respiratory system					
	Dyspnea	14	3	1	0
	Asthma	3	0	0	0
Digestive system					
	Intestinal malrotation	5	2	0	0
	Poor intestinal peristalsis	5	1	0	0

[1]Including our patient. Data collected from references: Arg179His[1,2,6-10,15,17-21]; Arg179Cys[11,13,16,22]; Arg179Leu[14,17]; Asn117Lys[12].

shortness of breath, recurrent respiratory infection, bronchial asthma; (5) Digestive system: intestinal malrotation or intestinal dyskinesia; and (6) Other systematic manifestations: hypotonic bladder, congenital absence of abdominal muscle.

To date, the clinical pedigree of neurological manifestations of *ACTA2* mutations is not well described. The main symptoms are motor and/or mental delay, cerebral infarction and/or hemiplegia[11]. In the literature review, we found three patients with neurological epilepsy besides our case. The main imaging manifestations were cerebrovascular abnormalities and white matter signaling changes. The specificity of cerebrovascular disease was mainly epidural artery dilatation, intradural artery stiffness, large artery and distal microvascular malformation[10,15,22]. In our case, initial MRI showed that the blood vessels in the brain were stiff, and the white matter showed multiple signals. No changes in gray matter were found. With the increase of age, further attention should be paid to the occurrence of gray matter infarction. For the four convulsions in our case, we speculate that the possible mechanism is as follows: (1) Cerebrovascular rigidity and occlusion led to low regional cerebral blood flow and ischemic penumbra, in which surviving neurons repeatedly produced epileptic discharges; (2) Cerebrovascular lesions led to the loss of small vascular smooth muscle cells, thickening, stenosis and hardness of vascular wall, decrease of vasomotor activity, change of blood–brain barrier permeability and decrease of neuronal response threshold. It triggered increase in the excitability of neurons and albumin exudation. In the presence of albumin absorbed by astrocytes, the ability to buffer extracellular $K^+$and reuptake extracellular glutamate was affected, which eventually triggered the changes in neuronal microenvironment and epileptic electricity generation[23]; and (3) The change in signaling in the white matter. The white matter is an important part of the central nervous system and the gathering

place of nerve fibers in the brain, which undertake the functions of neural information sharing and information communication in various brain areas. The pathological changes in cerebral vessels cause ischemia and hypoxia in the white matter, which promotes the death of nerve cells. This facilitates new synaptic connections between neurons to form a new abnormal neural network, leading to seizures.

CONCLUSION

MSMDS caused by *ACTA2* mutation showed different clinical symptoms. Seizures may be one of the neurological manifestations in the evolution of the disease. The disease is characterized by multiple system involvement with no obvious specificity. Its diagnosis is still a challenge. Cranial MRI and MRA examinations are recommended in children with convulsions, which have important diagnostic value for the diagnosis of the disease. Gene sequencing is crucial to evaluate the patient population in order to provide accurate prognosis and genetic counseling. Pediatricians should be familiar with this rare disease and its prognosis.

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