

Multisystemic smooth muscle dysfunction syndrome: the first local case report

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Case presentation

In February 2020, a 7-year-old girl was brought to our institution. She had been experiencing dysphasia, dysphagia, and weakness in all four limbs for the past 5 days. She had no recent trauma, febrile illness or seizure. She had normal systolic blood pressure but diastolic pressure was persistently low for her age at 35 to 40 mm Hg. She had a Glasgow Coma Scale score of 11 (E4V1M6) with expressive aphasia. Pupils were equal but dilated at 5 mm and cranial nerves were grossly intact. The muscle strength of right lower limb power was the weakest, with a Medical Research Council (MRC) grade of 3, while others were at grade 4. She had brisk jerks over the lower limbs. Her medical history included premature birth at 34 weeks of gestation and surgical repair of a patent ductus arteriosus at 1 month of age. She also had recurrent urinary tract infections with megacystic bladder, managed since early infancy with intermittent bladder catheterisation. Magnetic resonance imaging of the brain was performed at the age of 5 years due to chronic headache and showed a large area of right frontal encephalomalacia that may have been due to a previous unknown insult.

Blood tests including complete blood count, electrolytes, inflammatory markers, lactate,

ammonia, dried blood spot test, homocysteine, and plasma amino acids were unremarkable. Clotting profile, protein C, protein S and antithrombin III, and antinuclear antibodies levels were normal. Magnetic resonance imaging of the brain revealed acute ischaemic stroke with diffusion restriction in the left superior frontal, precentral, cingulate cortices, and corona radiata. Magnetic resonance angiography showed the anterior cerebral artery and middle cerebral artery were replaced by pruned cerebral arteries with straightened appearance and multifocal stenosis (Fig 1). Transthoracic echocardiogram showed a dilated aortic root of 23 mm with mild aortic regurgitation. Magnetic resonance aortogram showed comparable measurement with no aortic aneurysm or dissection (Fig 2).

To account for all clinical manifestations of the patient, a rare condition, multisystemic smooth muscle dysfunction syndrome (MSMDS), was suspected. Genetic analysis confirmed the diagnosis with a *de novo* heterozygous mutation of *ACTA2* c.536G>A (Arg179His). No similar mutation was identified in her parents or younger sister.

Our patient was managed conservatively and prescribed oral aspirin. There have been five further episodes of ischaemic stroke or transient ischaemic

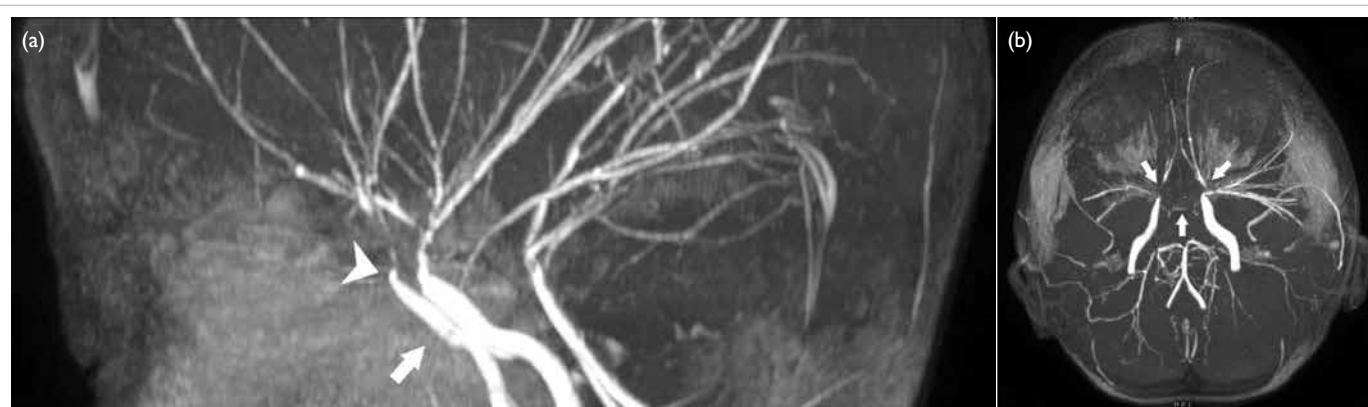


FIG 1. (a) Magnetic resonance angiogram of the brain showing bilateral ectasia of internal carotid arteries from cavernous to clinoidal segments (arrow) and stenosis of the carotid terminus [arrowhead]. (b) The course of intracranial arteries is abnormally straight. The circle of Willis appears absent (arrows)



FIG 2. Magnetic resonance aortogram showing dilated aortic root (arrow) and prominent ascending aorta

attack to date. Developmental assessments revealed mild-grade intellectual disability with regression of gross and fine motor skills. During the latest follow-up, she could walk unaided and manage oral feeding. Physical examination showed grossly full proximal power. The right-hand flexors were weak (Medical Research Council grading of 4/5) and right lower limb was spastic. The patient is being followed by a multidisciplinary team comprised of a neurologist, cardiothoracic surgeon, neurosurgeon, and ophthalmologist.

Discussion

To the best of our best knowledge, this is the first identified case of MSMDs in Hong Kong. The *ACTA2* gene encodes the thin filaments alpha-actin of the contractile element of smooth muscle. In 2010, Milewicz et al¹ reported the first case series of patients with *de novo* missense mutation in the *ACTA2* gene. Arg179His is the most severe form of this vascular disease spectrum. The three cardinal clinical presentations are congenital mydriasis, patent ductus arteriosus/aortopulmonary window, and white matter lesions with cerebrovascular disease.

Less common mutation loci, including Arg179Cys, Arg179Leu and Arg179Ser, have been reported to cause MSMDs.²

Neurological aspect

Recurrent ischaemic stroke is the major debilitating manifestation in MSMDs patients. Up to 95% of these patients have periventricular white matter hyperintensities evident on magnetic resonance imaging, signifying ischaemic insult in these watershed areas of blood supply. The vasculopathies were once considered a variant of moyamoya disease. Nonetheless MSMDs has some unique features, namely dilatation from the cavernous to the clinoid segments of the internal carotid arteries, stenosis and occlusive disease of the distal intracranial circulation, and an abnormally straight course of intracranial arteries. Stenosis of major cerebral arteries arises as a result of significant intimal thickening and markedly increased collagen and smooth muscle cells in the medial layers of these vessels.³

Neurosurgical management similar to that applied in moyamoya disease has been extrapolated to patients with MSMDs and includes direct superior temporal artery to anterior cerebral artery revascularisation and indirect revascularisation such as encephaloduroarteriosynangiosis. Nonetheless patients with various *ACTA2* mutations respond less well to these operations. Almost half of affected patients who have undergone neurosurgical revascularisation continue to have major stroke episodes.⁴ After a case conference with neurosurgeons, anaesthesiologists, neurologists and the parents of our patient, we concluded that as surgery carried an exceedingly high risk with doubtful benefit, revascularisation was not considered.

Cardiovascular aspect

All reported cases of MSMDs have had a patent ductus arteriosus or aortopulmonary window with most requiring surgical ligation. Patent ductus arteriosus with diameter up to 20 mm in a neonate with MSMDs has also been reported.

Regalado et al² reported that among the various *ACTA2* mutations, Arg179His carries the highest risk of serious aortic events. By the age of 25 years, the cumulative risk of either elective aortic aneurysm repair or dissection is 100%.⁵ The group also suggested that elective surgical repair be considered when the aortic diameter reaches 4.5 cm.⁵ The benefit of drug therapy such as beta-blockers or angiotensin receptor blockers is unknown. It was not appropriate to prescribe either drug for our patient since further lowering of blood pressure would aggravate cerebral hypoperfusion leading to more stroke episodes.³

Apart from aortopathy, around half of MSMDs patients have peripheral arterial dilation involving the proximal internal carotid artery, common carotid brachiocephalic, subclavian, axillary and external/

internal iliac arteries. This might also explain the low diastolic pressure.

Other systems

All reported cases of MSMDs have had pupillary abnormalities, mostly fixed or nonreactive pupils. Iris hypoplasia or aniridia has also been reported. Pulmonary complications, though not yet evident in our case, are also common. Pulmonary arterial hypertension may present in early infancy and necessitate mechanical ventilation, vasodilator drugs or even lung transplantation. Asthma and chronic lung disease have also been reported.

About half of MSMDs patients have hypotonic bladders. Recurrent urinary tract infections and hydronephrosis, as in our case, have also been frequently identified. One-third of patients have gastrointestinal problems such as gut malrotation, gastroesophageal reflux disease or constipation.²

In conclusion, MSMDs can affect multiple systems with life-threatening complications. Patients with congenital mydriasis, patent ductus arteriosus and recurrent stroke may raise a clinician's suspicion of this rare condition and prompt early genetic investigations.

Author contributions

Concept or design: CH Ng.

Acquisition of data: CH Ng.

Analysis or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

The patient was treated in accordance with the Declaration of Helsinki and provided informed consent for all treatments and procedures, and consent for publication.

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