Case of congenital fixed dilated pupils due to ACTA2 gene mutation - Multisystemic Smooth Muscle Dysfunction Syndrome.

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Dear editor,

Congenital mydriasis is an uncommon eye anomaly characterized by fixed dilated pupils that do not respond to light. There are various causes, such as tonic pupil, pharmacologic cause, and aniridia, in congenital mydriasis.\[1\] We report a case with congenital mydriasis diagnosed through genetic testing confirming the presence of ACTA2 mutation.

A 14-month-old girl had an unremarkable antenatal history. She was born at 35 weeks gestational age. Patent ductus arteriosus and ventricular septal defect were surgically repaired before the age of 1 year. She had a developmental delay due to a history of severe bronchopulmonary dysplasia.

She visited our hospital with fixed dilated pupils discovered during a neonatal ophthalmic examination. She could fix and followed an object with both eyes, and the Bruckner test was normal.

Pupils were 6 mm and nonreactive to light and 0.125% pilocarpine eye drops. Ophthalmic examination showed the absence of an iris between the collarette and pupillary border, creating a scalloped pupillary margin. (Figure 1A) Fundus examination showed arteriolar tortuosity in both eyes. (Figure 1B) Anterior optical coherence tomography reveals undevelopment of insufficient growth of the iris sphincter and dilator muscles. (Figure 1C)

In Magnetic resonance imaging (MRI) of the brain to discriminate cerebral abnormalities such as neuroblastoma, periventricular white matter hyperintensities in T2 image and tortuous cortical veins were revealed. (Figure 1D, E) MR angiography showed dilatation of internal carotid arteries, stretches of proximal cerebral arteries, and peripheral diffuse stenosis of peripheral arteries. (Figure 1F) Ultrasonography for the kidney showed normal size, shape, and echotexture of both kidneys. We obtained genetic mutation analysis of the ACTA2 gene, with identification of the c.535C>T, p.(Arg179Cys)(NM_001613.4), heterozygous mutation. Genetic test was conducted using target panel sequencing and confirmed the results through Sanger sequencing. We performed parental testing, but no genetic abnormalities were found.

Multisystemic smooth muscle dysfunction syndrome (MSMDS) is a rare genetic disorder that affects the smooth muscle cells in various systems of the body. MSMDS is often caused by mutations in the ACTA2 gene, which is responsible for producing the contractile protein alpha-actin in smooth muscle cells.\[2\] The condition can present with features such as aortic and cerebrovascular diseases, congenital mydriasis (fixed dilated pupils), and other vascular and systemic abnormalities. Ocular manifestations include the absence of pupillary sphincter and dilator muscles in the iris, as well as tortuosity of the retina, loopy arterioles, stenosis, and thrombosis of a peripheral arteriole.\[3, 4\] Extraocular manifestations involve brain abnormalities such as a dilated proximal artery, stenosis of a distal artery, atrophic cortex, and extensive periventricular T2 abnormality, along with cardiovascular...
issues like patent ductus arterioles, abdominal aortic aneurysm, and aortic dissection.[5]

Congenital mydriasis is an exceedingly uncommon abnormality of the pupils and is a prominent indicator for early diagnosis of this syndrome. This patient's case represents the first reported instance in Korea of discovering ACTA2 mutation in congenital fixed pupils, highlighting its significance. Ophthalmologists should closely cooperate with other specialists due to the potential risks of aortic and cerebrovascular diseases and other complications associated with this condition.

REFERENCE
Figure 1. Clinical features of Multisystemic Smooth Muscle Dysfunction Syndrome. (A) Fixed dilated pupils with absence of iris between the collarette and pupillary border creating a scalloped pupillary margin. (B) Fundus reveals arteriolar tortuosity. (C-1) Anterior optical tomography reveals aplasia of iris sphincter and dilator muscles. (C-2) Iris muscle structure in normal individuals (D) Axial T2 magnetic resonance imaging demonstrates periventricular white matter abnormalities. (E) Tortuous cortical veins can be detected in MRI. (F) MR angiography showed dilatation of internal carotid arteries, stretches of proximal cerebral arteries and peripheral diffuse stenosis of peripheral arteries.