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Case Report

ACTA2 leukovasculopathy: A rare pediatric white matter disorder ☆,☆☆

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ABSTRACT

A 3-year-old girl presented with ataxia, dilated pupils, and behavioral change prompting work up for stroke. Her medical history included chronic mydriasis and patent ductus arteriosus requiring aortoplasty. Magnetic resonance imaging of the brain demonstrated confluent white matter signal abnormality concerning for leukodystrophy. Magnetic resonance angiography revealed a cerebral vessel arteriopathy with a “broomstick appearance” and other neuroradiographic findings consistent with ACTA2 mutation. Pathogenic Arg179His ACTA2 mutation was confirmed in the patient. ACTA2-related leukovasculopathy should be considered during workup of patients with abnormal white matter (eg, leukodystrophies), childhood stroke, and arteriopathies. Recognizing the combination of commonly associated physical and medical conditions associated with radiographic features of this neurogenetic condition will prompt appropriate care and screening for comorbidities associated with this disorder.

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Introduction

Smooth muscle cells form a lattice-like cellular matrix within blood vessels providing contractile functioning and homeostasis of vascular tone. Smooth muscle cells also synthesize

proteins (eg, collagen, elastin, and proteoglycans) important for muscle remodeling and repair. Vascular smooth muscle cells are comprised in part by tissue-specific $\alpha 2$ -smooth muscle actin which is encoded by ACTA2 [1].

ACTA2 mutations can result in abnormalities in the underlying protein matrix of smooth muscle cells which can lead to fibrotic vessel walls [1] leading to suboptimal physi-

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ological contractile functioning in response to typical stimuli. Malformation of brain structures in this disorder is postulated to occur from mechanical compressive deformations caused by stiffened blood vessels on adjacent brain tissue (eg, stiff basilar artery vessels resulting in indentation of the pons) and also from embryological neuronal migration alterations caused by the influence of abnormal actin cytoskeleton [2]. Arg179His mutations in ACTA2 have been linked to a cerebral arteriopathy involving small and large vessel abnormalities with characteristic neuroradiographic findings which include dilatation of the proximal internal carotid arteries, occlusion or narrowing of the distal internal carotid arteries, straightened or “broomstick-like” appearance of vessels originating from the circle of Willis and absence of lenticulostriate collaterals typically seen with Moyamoya disease [2,3]. Other clinical manifestations of this mutation include childhood stroke, brain parenchymal abnormalities, patent ductus arteriosus (PDA), congenital mydriasis (iris flocculi), and thoracic aortic aneurysms [4–6].

Depicted in our case is a 3-year-old who presented with 72 hours of ataxia and behavioral changes who was found to have computerized tomography (CT) and magnetic resonance imaging (MRI) brain imaging findings initially suggestive of a diffuse leukodystrophy, without acute ischemic changes. Magnetic resonance arteriography (MRA) revealed characteristic findings associated with ACTA2 cerebral arteriopathy, which was subsequently confirmed genetically. The patient was evaluated for alternative causes of leukodystrophy typically seen in a child her age. The combination of white matter disease, along with recognizable anatomical and vascular abnormalities seen in ACTA2 cerebral diseases is valuable to recognize in order to screen for other associated systemic anomalies with this disorder and to provide clinical guidance on the risk of stroke.

Case report

A previously healthy 3-year-old Hispanic female presented to our tertiary care facility with 3 days of intermittent ataxia, behavioral changes, and dilated pupils. Her past medical history was relevant for an uneventful full-term gestation, chronically dilated pupils, and large PDA requiring aortoplasty at 5 months of age and frequent pulmonary infections. Symptoms observed by caretakers included intermittent ataxia, decreased speech, fluctuating mental status, and activity level with additional reports that she would cry intermittently without clear cause. She had prior normal development with no previous neurologic history including no history of seizure, stroke, muscle weakness, or ataxia. Electroencephalogram showed predominately right occipital slowing but no electrographic correlate to suggest clinical behaviors were secondary to seizure activity. All laboratory workup on the patient was negative including: *Infectious workup*: complete blood count, erythrocyte sedimentation rate, C-reactive protein, and cerebrospinal (CSF) profile. *Metabolic workup*: toxicology screen, thyroid panel, complete metabolic profile, muscle creatinine kinase, copper, folate, vitamin B12, acylcarnitine, profile, arylsulfatase A, very long chain fatty acids serum, and CSF lactate.

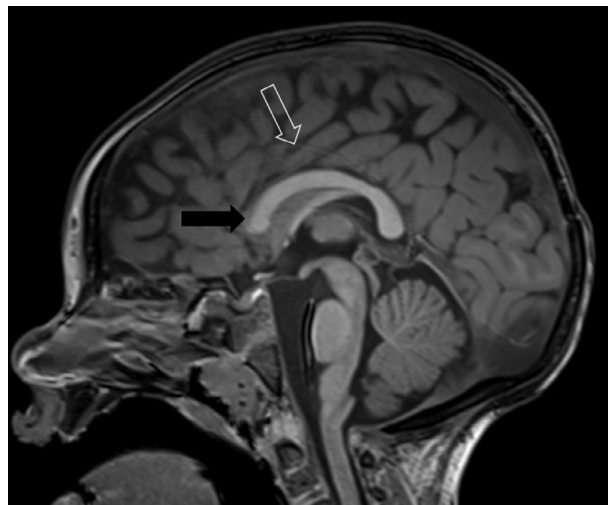


Fig. 1 – Sagittal T1-weighted image of the brain in the midline demonstrates a slightly foreshortened and curved appearance of the anterior corpus callosum (black arrow) and radial gyral pattern of the pericallosal gyri (white arrow).

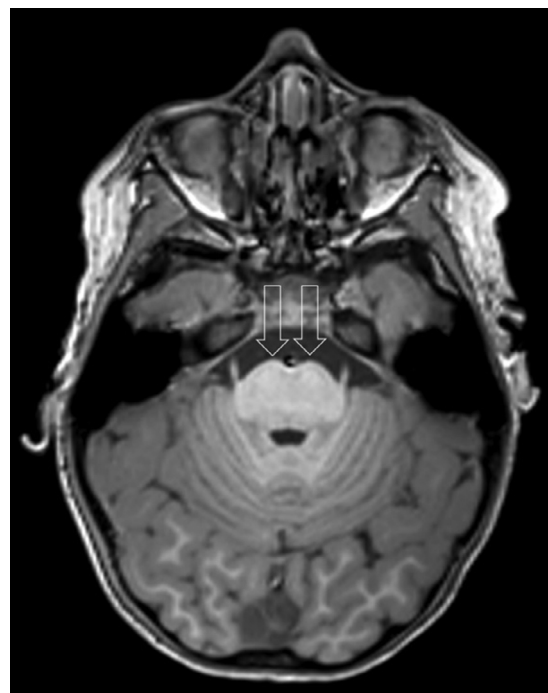


Fig. 2 – Axial T1-weighted image of the brain depicts a “twin peaks” appearance of the anterior pons (arrows).

Autoimmune workup: serum and CSF autoimmune panels, CNS Demyelinating Disease evaluation.

MRI of the brain showed a foreshortened corpus callosum with a radial paramedian pericallosal gyral pattern (Fig. 1). The basilar artery impression on the pons was slightly pronounced (Fig. 2). The anterior corpus callosum exhibited a “V” configuration on the axial images (Fig. 3). Peritrial (Fig. 3) and confluent centrum semiovale T2 hyperintensity (Fig. 4) were appar-

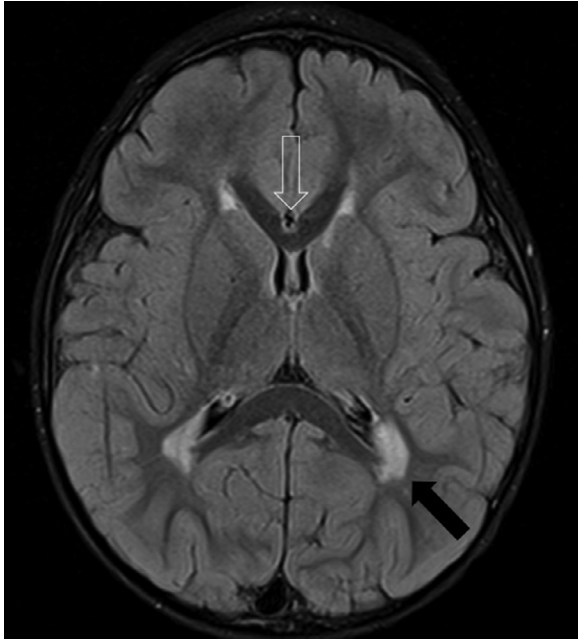


Fig. 3 – Axial FLAIR image of the brain shows a v-shaped anterior corpus callosum (white arrow). Peritrial gliosis is also visible (black arrow).

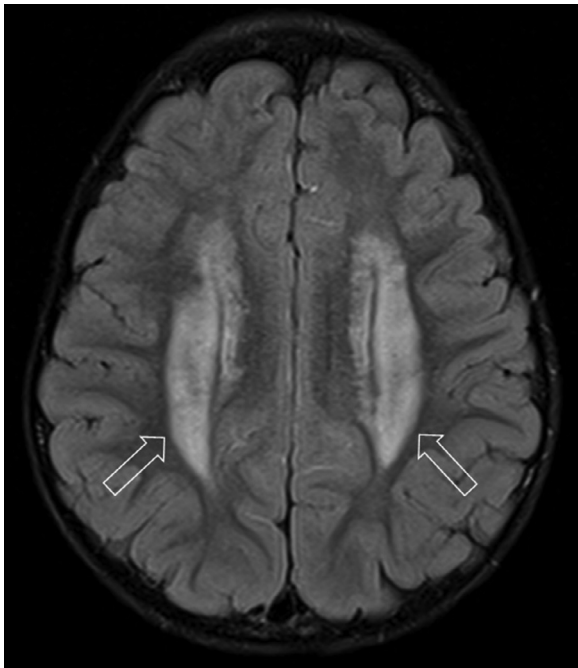


Fig. 4 – Axial FLAIR image of the brain reveals confluent gliosis (arrows).

ent. There was no contrast enhancement demonstrated with respect to the T2 signal abnormality, however, there was mild leptomeningeal enhancement of uncertain etiology. A time-of-flight MRA depicted a “broomstick-like” appearance of the bilateral middle cerebral arteries (Fig. 5) with beading of the peripheral branches (Fig. 6). There was fusiform dilatation of

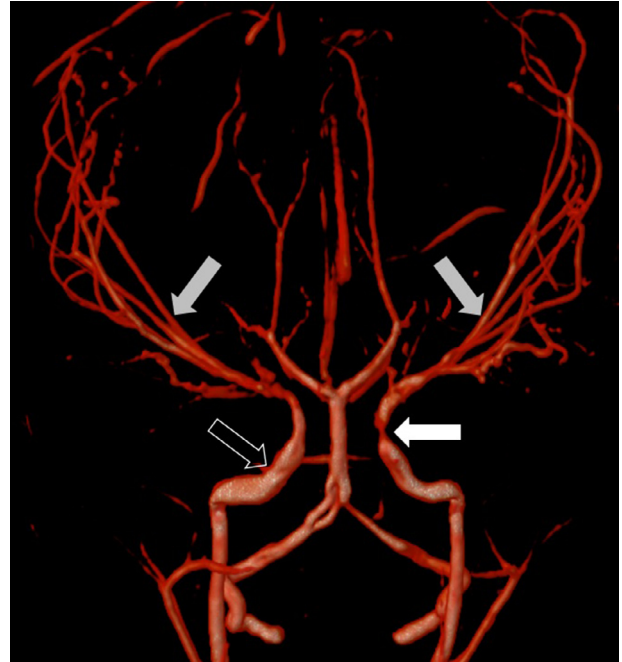


Fig. 5 – Time-of-flight MRA exhibits straightened middle cerebral arteries (gray arrows). Aneurysmal dilatation of the right internal carotid artery (white outline arrow) as well as focal stenosis of the left internal carotid artery (white solid arrow).

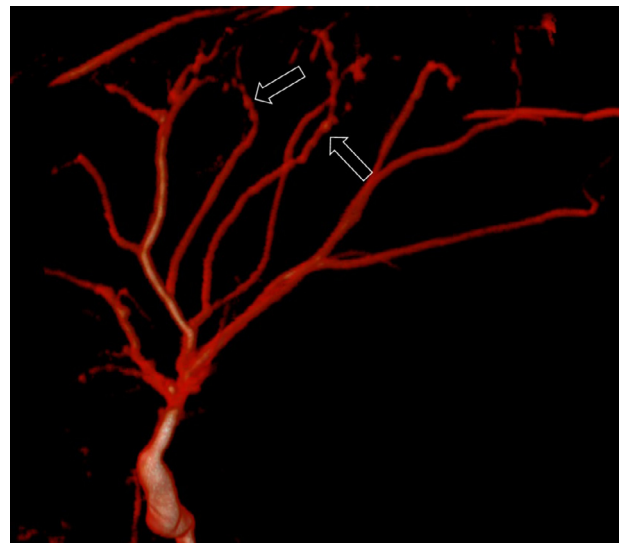


Fig. 6 – Time-of-flight MRA of the right middle cerebral artery shows beading aneurysms (arrows).

the right internal carotid artery and focal stenosis of the left internal carotid artery (Fig. 5).

Complete resolution of symptoms occurred within 48 hours without intervention and the child was discharged home at her previous baseline development and a normal neurologic exam (apart from mydriasis). The patient was

started on aspirin for anticoagulation. Mydriasis was determined to be long standing.

The concern for ACTA2 mutation raised following interpretation of the MRI resulted in sequencing of the ACTA2 gene which revealed a pathogenic Arg179His mutation.

Discussion

As the ACTA2 mutation impacts smooth muscle cells, it follows that several systemic functions relying on normal smooth muscle activity are disrupted. Accordingly, manifestations of an ACTA2 mutation can involve the arteries. This results in aortic dissections and aneurysms, coronary artery disease, and cerebrovascular disease. Contractility of the iris can be impaired, resulting in mydriasis. Smooth muscle dysfunction in the pulmonary vasculature can lead to pulmonary hypertension, and it is hypothesized that respiratory disease such as asthma, bronchiectasis, and emphysema result from alveolar smooth muscle dysfunction in ACTA2 mutation [7].

The initial presentation of an individual affected with a pathological ACTA2 mutation may vary. Our patient's history revealed salient key features strongly associated with ACTA2 mutation had been present including large PDA, and congenital mydriasis. These 2 findings along with aortic aneurysms have been found to be some of the most salient, by some estimates present in 85%-92% of patients diagnosed with the mutation [8]. Recurrent respiratory tract infections, which have been shown to be present in many cases of the condition, were also present in our patient. Other features that have been documented, though less prevalent, are bladder problems (eg, hypotonicity and hydronephrosis) and gastrointestinal dysfunction including chronic constipation and gallstones

The variable dilation or stenosis of vasculature has been hypothesized to be related to the inherent character of the vessel with mutated actin decreasing contractility, leading to dilation.

Other key radiological findings observed in our patient have likewise been documented in association with ACTA2 arteriopathy. A 2018 neuroimaging study of 14 patients with ACTA2 mutations outlined additional related congenital brain malformations namely a "V"-shaped corpus callosum on axial imaging, abnormal radial gyration of the frontal lobe, and a "twin peaks" pons, characterized by symmetric pontine indentations [3]. These findings were all apparent in our patient.

The initial neuroradiographic findings leading to a clinical suspicion for a leukodystrophy in our patient led providers to acquire extensive and expensive tests that could possibly have been avoided if initial suspicions were higher for ACTA2. As we better understand the different types of leukodystrophies, Ashrafi et al. have proposed that an expanded classification system is needed. Leukodystrophies have classically been classified based on MRI findings with hypomyelination or demyelination, but can also be based on pathologic findings (myelin disorders, astrocytopathies, axonopathies, microgliopathies, and vasculopathies) or molecular and metabolic characteristics (lysosomal, peroxisomal, mitochondrial, myelin proteins, genetic vasculopathies, DNA repair, and others). In this case, the MR imaging in the

absence of vascular imaging led to consideration of some of the MRI-based demyelinating leukodystrophies such as metachromatic leukodystrophy. When vascular imaging was completed, the pathognomonic cerebrovascular arteriopathy was essential in obtaining the appropriate diagnosis and pursuing genetic testing. Given our growing understanding of mechanisms that can lead to white matter changes, vascular imaging is easy to obtain and can be essential in diagnosing these vasculopathy-induced disorders.

ACTA2 mutation should be suspected in young patients presenting with stroke-like symptoms and abnormal neuroimaging in conjunction with other indicators of systemic smooth muscle dysregulation. Abnormalities in normal smooth muscle-dependent developmental pathways, such as PDA, increase suspicion for the disease. Diagnosis of ACTA2 arteriopathy is supported by radiological findings, common physical findings, and confirmation by genetic testing. It is imperative to consider additional MRI imaging sequences such as MRA in the workup of leukodystrophies that can provide pathognomonic features of this neurogenetic condition. This pathology also exhibits brain malformations which set it apart from other white matter disease disorders.

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