Posterior Circulation Stroke due to Atlantoaxial Instability in *CHST3*-Related Skeletal Dysplasia

A Case Report

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Abstract

Case: An eight-year-old boy presented with acute encephalopathy due to posterior circulation ischemic stroke. He was found to have vertebral artery stenosis secondary to atlantoaxial instability (AAI) due to an os odontoideum. Occipitocervical fusion was performed 4 weeks after stroke. The child improved neurologically and regained independent ambulation. He had indications of an underlying spondyloepiphyseal dysplasia with joint luxation and whole-exome sequencing diagnosed *CHST3*-related skeletal dysplasia.

Conclusion: As far as we know, this AAI due to an os odontoideum is a previously unreported complication of *CHST3*-related skeletal dysplasia. Occipitocervical fusion yielded good clinical results with the 1-year follow-up.

Introduction

Posterior circulation ischemic stroke (PCIS) is ischemia related to the posterior circulation arteries, including the vertebral artery (VA), basilar artery (BA), and posterior cerebral arteries and their branches[1]. PCIS because of VA insufficiency or dissection caused by atlantoaxial instability (AAI) is rare in both children[2-8] and adults.[9] *CHST3*-related skeletal dysplasia is a rare genetic disorder associated with short stature, congenital joint dislocations, and joint stiffness[10,11]. We report the association of PCIS with AAI due to an os odontoideum in a child with *CHST3*-related skeletal dysplasia and discuss the nuances in management.

The patient and parents were informed that data concerning the case would be submitted for publication and they provided consent.

Case Report

An 8-year-old male child, born of nonconsanguineous union, presented in a drowsy state with complaints of multiple episodes of vomiting over 3 days—quadriparesis, aphasia, and inability to swallow for 2 days. The family denied any history of recent trauma or febrile episode. He had suffered school absenteeism due to recurrent headache and vomiting for the preceding 18 months. On examination, the child had normal facies and no cleft palate and had spontaneous eye opening, but he was unable to vocalize or obey commands. He had neck stiffness, appendicular hypotonia, and hyperreflexia. Cranial nerve examination revealed absent gag. He had clinical features suggesting an underlying skeletal dysplasia, including short stature, elbow contractures, genu valgum, and scoliosis (Figs. 1-A and 1-B), but the acute neurological presentation necessitated that we defer a detailed genetic workup until stabilization. On imaging, he was diagnosed to have acute PCIS due to mechanical occlusion of both VA secondary to os odontoideum. Bilateral PCIS was evident on MRI brain with gliotic infarcts involving the right inferior cerebellar cortex (posterior-inferior-cerebellar-artery territory) and in left superior cerebellar cortex (left superior-cerebellar-artery territory) (Fig. 2). Prothrombin time, activated partial thrombopastin time, and serum homocysteine levels were normal. CT angiography showed BA stenosis and right VA hypoplasia with stenosis (Fig. 3-A). CT revealed os odontoideum (Fig. 3-B). Digital subtraction angiography revealed bilateral VA occlusion at the junction of V2-V3 with bilateral PCA embolism along with collaterals supplying PCA territory. Lateral cervical radiographs in flexion and extension revealed AAI (Fig. 4-A). Detailed ophthalmological evaluation, 2D-echocardiogram, and pure tone

This is a retrospective study and all interventions were carried out in the normal course of treatment, institutional review approval was waived.

All authors have contributed to the study design, methodology, writing and revisions of the manuscript and have approved the final version submitted.

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSCC/B363).

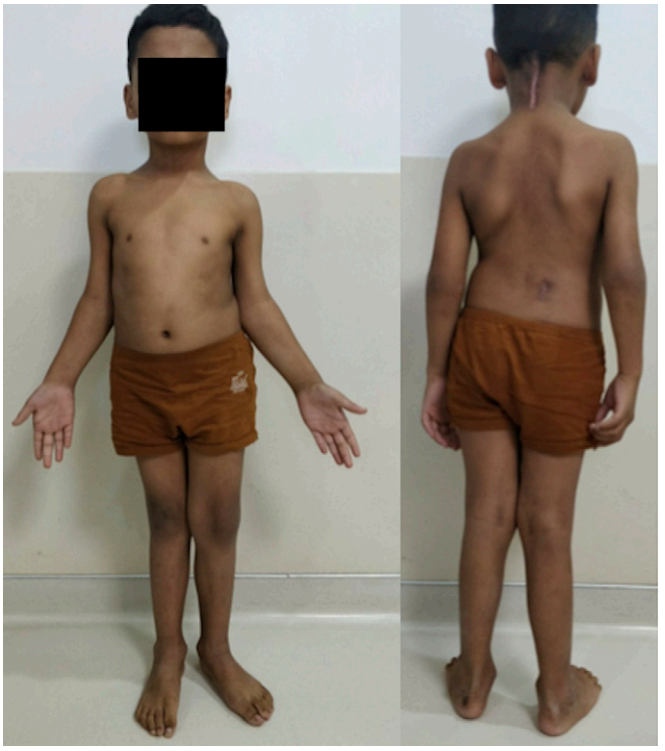

Fig. 1-A

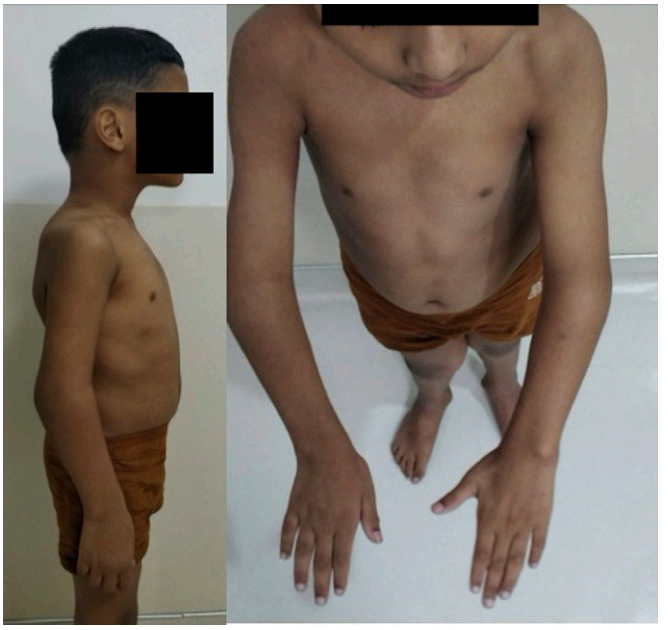

Fig. 1-B

Fig. 1-A Clinical picture: Note bilateral cubitus valgus, genu valgum and scoliosis, postoperative scar. **Fig. 1-B** Clinical picture: Note bilateral elbow fixed flexion deformity.

audiometry were normal. Clinical and imaging studies suggested the possibility of spondyloepiphyseal dysplasia associated with joint dislocation (Fig. 4).

He had 2 episodes of generalized seizures during the first week of admission. Over the 2 weeks of hospitalization, he gradually regained normal sensorium, swallowing, and speech, with no further episodes of seizures, although he remained quadriparetic.

Treatment

The child was started on low molecular-weight heparin and aspirin because of PCIS during initial admission at the primary center. Deglutition concerns and poor sensorium necessitated nasogastric-tube insertion, although leviteracetam was started to control the seizures. He was immobilized in a cervical collar after diagnosis of AAI and was discharged at 2 weeks after

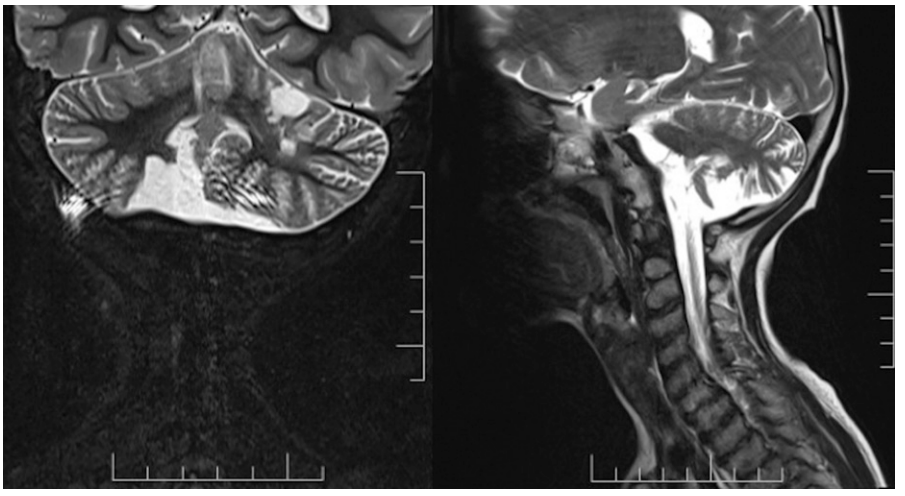

Fig. 2

MRI. T2 coronal and sagittal brain MRI image showing large gliotic cerebellar infarcts in right PICA territory and left SCA territory, os odontoideum, reduced vertebral height with endplate irregularity and sclerosis.

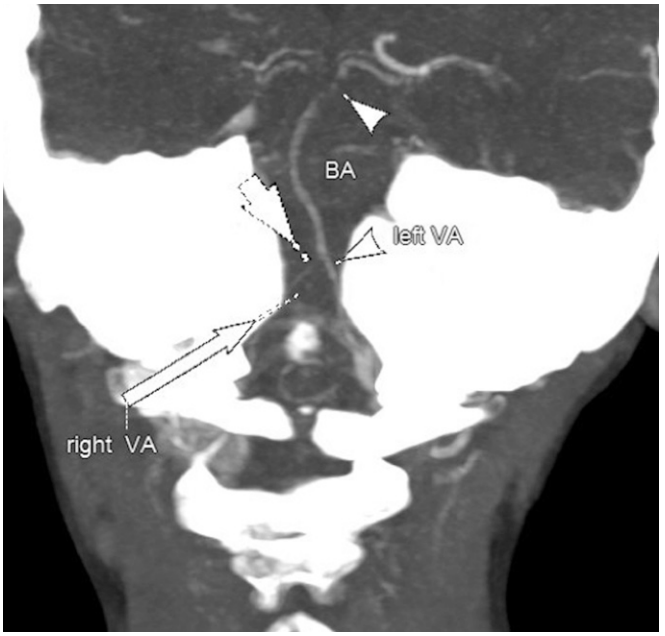

Fig. 3-A

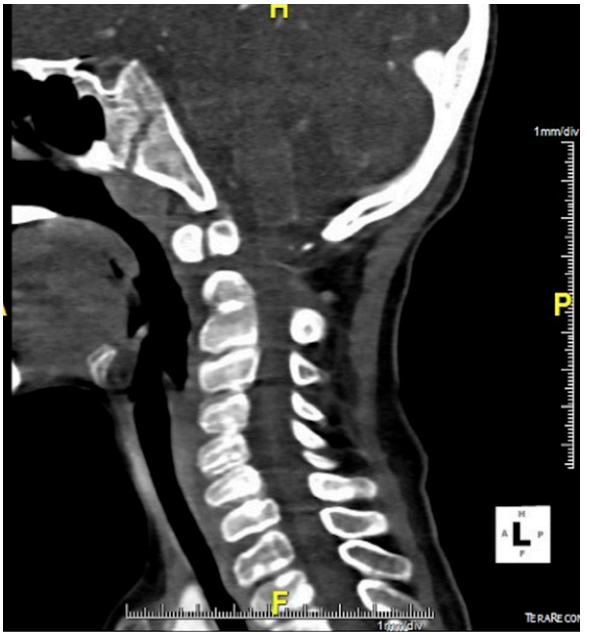

Fig. 3-B

Fig. 3 CT angiography. **Fig. 3-A** CT sagittal multiplanar reconstruction with os odontoideum. **Fig. 3-B** Coronal Maximum Intensity Projection showing severe stenosis of hypoplastic right Vertebral Artery and thrombosis of the distal basilar artery (broad arrow).

initial treatment and readmitted at the tertiary center for occipitocervical fusion surgery 2 weeks later when low molecular-weight heparin was stopped. Preoperative planning was performed using nonorthogonal multiplanar reconstruction of thin cut reformatted CT to assess the feasibility of C2 and occipital fixation. Fiber-optic intubation was performed avoiding neck movements. The surgery was performed without intraoperative neuromonitoring, in view of the recent history of seizures and cerebrovascular accident in the child. Gardner Wells tongs were applied, and the patient was positioned prone on a horse-shoe attachment. Two-kg weight skeletal traction was applied over a pulley. Lateral fluoroscopic images were obtained to confirm satisfactory reduction of C1-2. Occipitocervical fusion was performed with an occipital plate with C2 pedicle and laminar screws (Fig. 5). Iliac crest autograft was used for fusion. Although delayed extubation and prolonged ventilator support was anticipated, the child was extubated immediately postsurgery and had an uneventful course in hospital without complications and was discharged on the fifth postoperative day.

Four weeks postoperatively, the child was referred to a clinical geneticist to delineate the etiology of the underlying skeletal dysplasia. On enquiry, the parents denied the child to have any antenatal abnormal scans or postnatal complications. The measurements at birth were unavailable. The parents noticed the child to be shorter than his peers at 3 years, followed by progressively increasing stiffness of his back since 5 years of age. His intelligence was normal. The child had proportionate short stature (111.1 cm, <3rd percentile as per WHO growth charts). Neurological examination revealed no residual weakness or sensory deficit, although there was mild gait instability and hyperreflexia in all extremities. Whole-exome sequencing, a sophisticated genetic tool to detect >90% to 95% of the genetic errors that lead to these group of disorders, revealed compound heterozygous mutations in the *CHST3* gene, in *trans*; thus, confirming the diagnosis of autosomal recessive *CHST3*-related skeletal dysplasia[10]. Both variants, c.735C>G p.(Tyr245*) and c.835C>T p.(Gln279*), resulted in premature stop codons and were classified as likely pathogenic. Genetic counselling was done.

Outcome

One year postoperatively, the child was self-ambulatory with no residual weakness or sensory deficit, with a slightly wide based gait and hyperreflexia in all extremities. There were no other cerebellar signs, no visual, speech, or swallowing dysfunction. Radiographs showed satisfactory reduction and fusion with no implant loosening (Fig. 5).

Discussion

Nontraumatic AAI can occur in certain genetic conditions such as Down syndrome, Morquio syndrome, certain SED, and diastrophic dysplasia—to name a few[12]. PCIS due to AAI and os odontoideum in children is extremely rare and a delayed diagnosis has been reported[2-9]. Previous case reports are summarized in Table I. In our patient, the circle of Willis was "complete" type with good-sized bilateral posterior communicating arteries along with few other collaterals from bilateral internal carotid arteries. Because there were bilateral cerebellar infarcts, these were most likely thromboembolic infarcts from posterior circulation because of local compression at C1-C2 due to AAI. There were no anterior circulation infarcts, ruling out cardiac thromboembolism or from any other systemic source. There is postulation of some intrinsic abnormality in the VA and collateral circulation in these cases[2-9]. The proposed

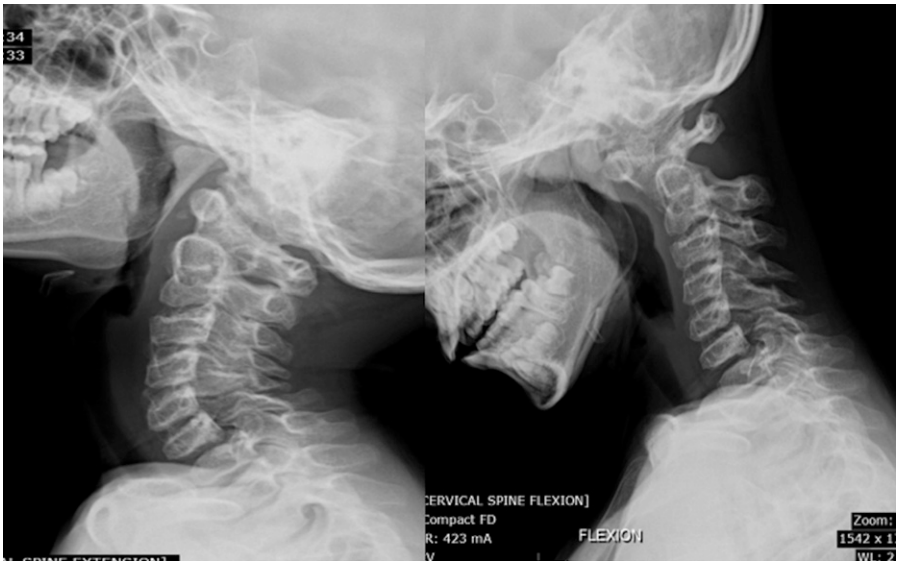

Fig. 4-A

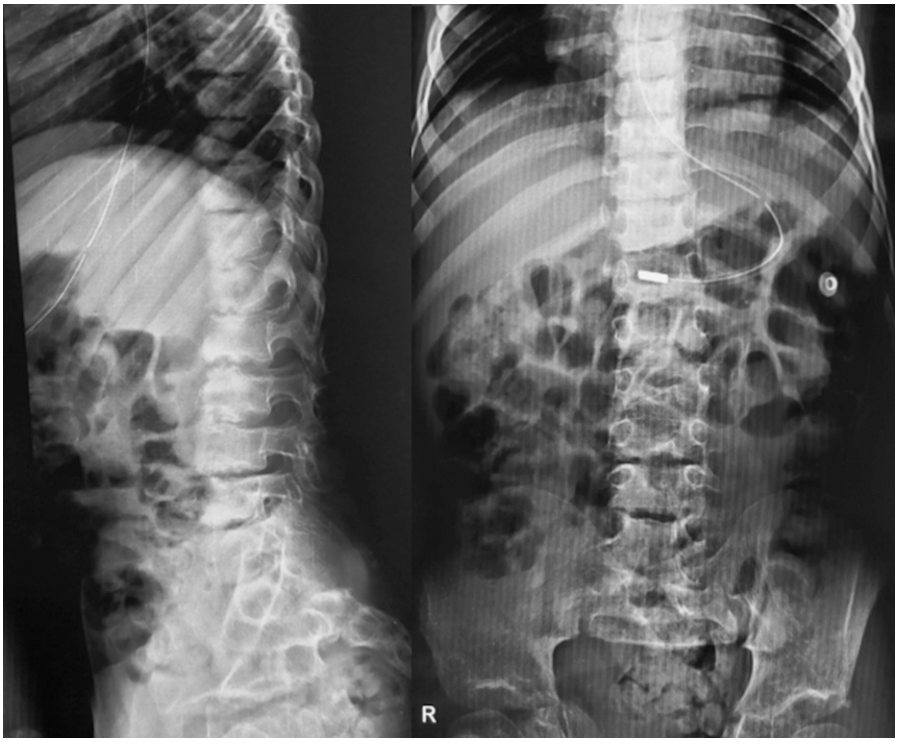

Fig. 4-B

Fig. 4 Preoperative skeletal survey. **Fig. 4-A** Flexion and extension radiograph of cervical spine showing atlantoaxial instability with osodontoideum. **Fig. 4-B** Radiographs of thoracolumbar spine (lateral and frontal view): irregular superior and inferior vertebral end plates with normal intervertebral disc space. Thoracolumbar interpedicular distance seem normal.

pathoanatomy is stretching or kinking of the VA with intimal damage, thrombus formation, and microemboli or dissection[2-9]. In this case, there may be a combination of factors—the primary reason being the AAI as because of the os odontoideum with VA thrombus formation due to the stretch on the vessel and antegrade thromboembolism to the BA (Fig. 3-A) The congenital hypoplasia of the right VA may have accentuated the pathology by limiting the establishment of a collateral circulation.

We are not aware of previous reports of children with skeletal dysplasia presenting with PCIS due to AAI. *CHST3*-related skeletal dysplasia (OMIM #143095) is reviewed in Table II[10,11,13]. AAI due to os odontoideum has not been described in

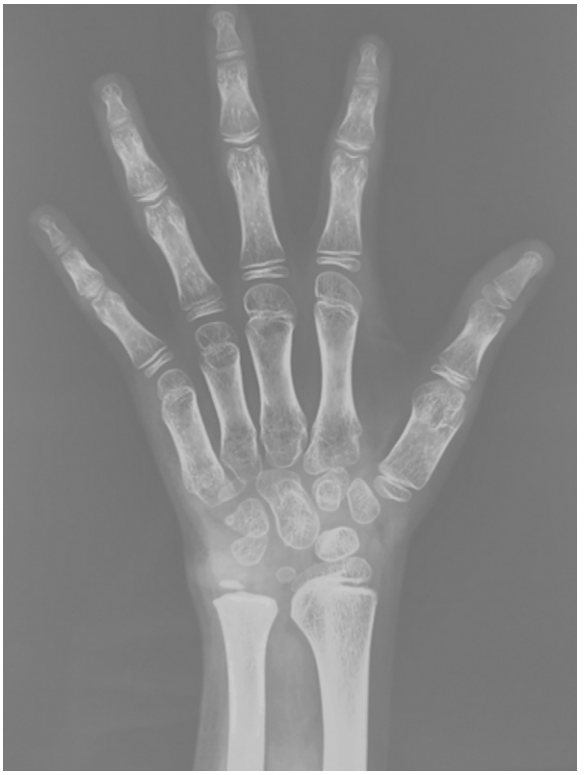

Fig. 4-C

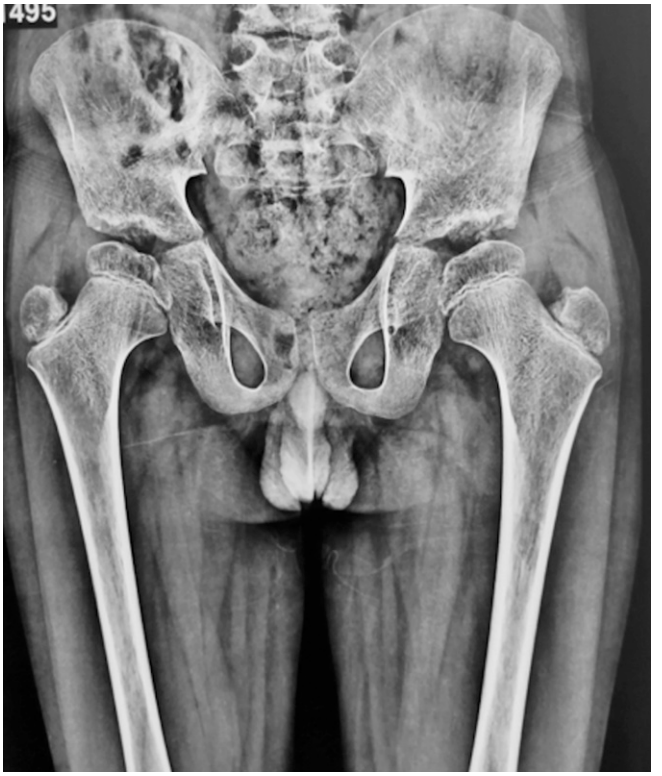

Fig. 4-D

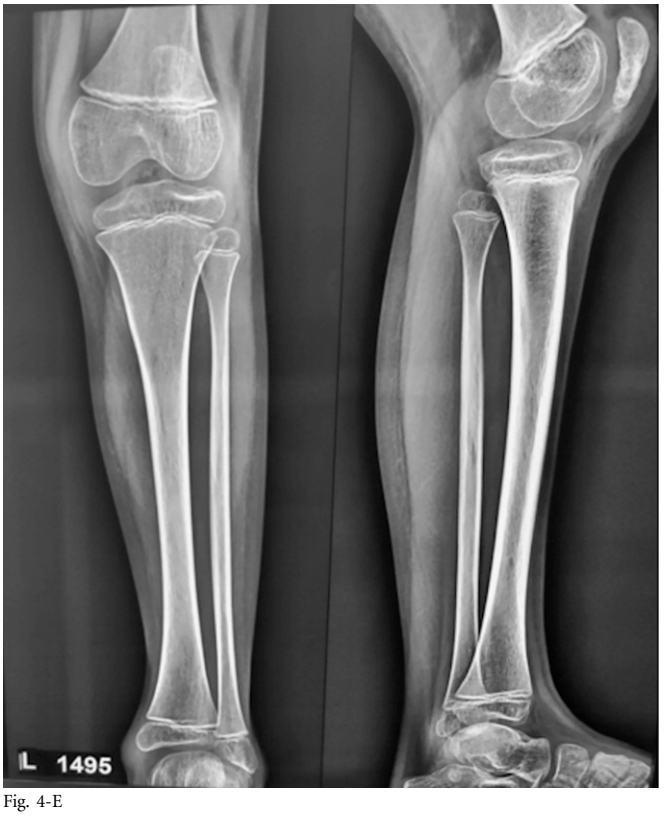

Fig. 4-E

Fig. 4-C Hand radiograph: Pisiform has not appeared (normally appear between 8 and 12 years of age), corroborating the chronological age with the skeletal age. **Fig. 4-D** Radiograph of Pelvis with both hips (frontal view): Trigonal pelvis, small femoral capital epiphysis, and proximal metaphyseal widening with foreshortening of the femoral neck. **Fig. 4-E** Radiograph of left leg (frontal and lateral view): small proximal tibial epiphysis and proximal metaphyseal widening of the tibia and fibula.

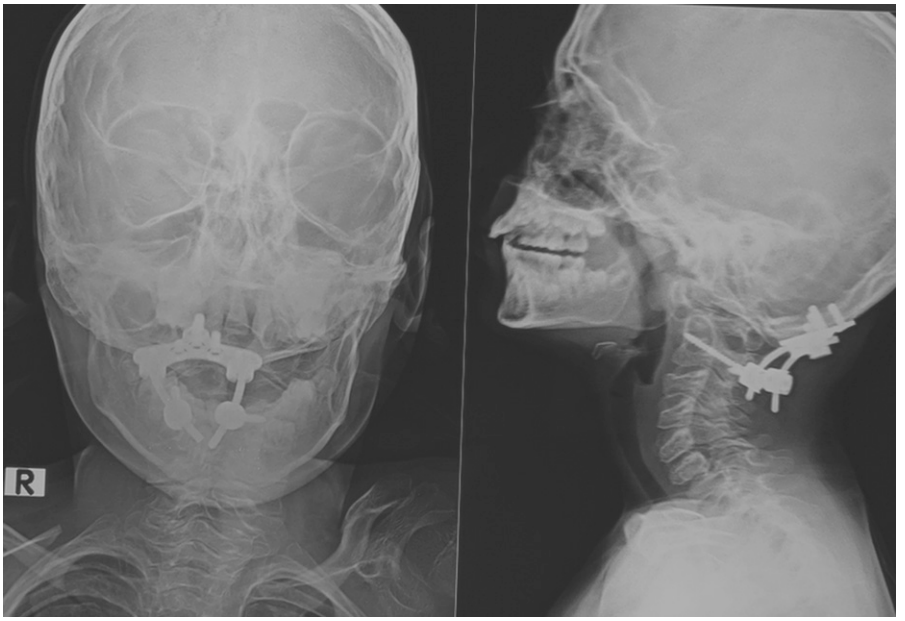

Fig. 5

Postoperative Radiographs at 1 year. AP and lateral radiographs showing occipitocervical fusion with C2-pedicle and lamina screws.

TABLE I Summary of Previous Case Reports of Atlantoaxial Instability (AAI) With Posterior Circulation Ischemic Stroke (PCIS) in children[2-8]

Author	Age, Years	Presentation	Diagnosis	Vertebrobasilar Anomalies	Surgery	Outcome
Fraser and Zimbler[2]	6/M	Gait ataxia, clumsiness of right upper limb, intermittent episodes of vomiting, headache, and dysarthria since a month	Os Odontoideum	Right VA occlusion at C2 Collateral vessels bypassing occlusion Left VA aneurysmal dilatation Basilar artery not opacifying but recanalized in 4 weeks	C1-C3 fusion (wiring) at 6 weeks	Persistent deficits at 3 months
Phillips et al.[3]	5/M	Induced by trauma, ataxia, nystagmus, vomiting, headache, left dysmetria, and left arm weakess	Odontoid Aplasia	Focal irregularities of both VA at C2 (R > L) Normal BA. Left AICA and left SCA occluded at origins	C1-C2 fusion (wiring) at 6 weeks	Improvement
Bhatnagar et al.[4]	5.5/M	Ataxia, vertigo, diplopia, nausea, vomiting, left hand weakness, and quadriparesis	Os Odontoideum	Left VA tortuosity and dilatation of C2 No information about BA and collaterals	C1-C2 fusion (wiring) + Halo at 6 weeks	Improvement at 3 months
Miyata et al.[5]	11/F	Headache, gait disturbance, and semicomatose	Os Odontoideum	Left VA normal Right VA narrow at C2 No information about BA and collaterals	FMD, Ventricular drainage Patient refused fusion	Improvement at 3 months
Sasaki et al.[6]	5/M	Headache, nausea, and vomiting	Os Odontoideum	Left VA tortuosity Obstruction of branches of BA	C1-C2 fusion (TAS) at 6 weeks	Improvement
Nandish et al.[7]	13/M	Painless loss of vision, occipital headache, and ataxia	Occipitalized C1 + C2-3 fusion	VA and BA normal right PCA occlusion (?embolisim from VA proposed as probable cause)	O-C3 fusion (Screw-Rod) Timing unreported	Improvement
Hu et at.[8]	15/M	Acute vertigo, ataxia, tinnitus right ear, nausea, and brief unconsciousness without any recent trauma	Os Odontoideum	Bilateral VA occlusion (intracranial portion) Proximal BA and Right PICA not opacifying	C1-C2 fusion at 3 months	Improvement

AICA = Anterior inferior cerebellar artery, BA = basilar artery, C1 = cervical vertebra 1, C2 = cervical 2 vertebra, C3 = cervical vertebra 3, F = female, L = left, O = Occiput, M = male, PCA = posterior cerebral artery, PICA = posterior inferior cerebellar artery, R = right, SCA = Superior cerebellar artery, VA = vertebral artery, and TAS = transarticular screws.

TABLE II Review of CHST3 Dysplasia[10-13]

Autosomal Recessive Inheritance	
Clinical features	
Skeletal	Congenital joint dislocations, classically involving the knee, hip, and/or the elbow joints
	Progressive joint stiffness and reduced range of movements (especially of the spine and elbow joints)
	Evolving kyphoscoliosis and short-trunk dwarfism
Extra-skeletal	Minor heart valve dysplasia
	Normal vision, hearing, and intellect
Radiological features	
Long bones	Spondyloepiphyseal dysplasia
	Small epiphyses and malalignment
Joints	Congenital joint dislocations (especially of the hip and knee)
	Elbow joint—dysplasia, contractures, and dislocations
Spine	Coronal clefts in the vertebrae (infancy)
	Superior and inferior vertebral notching
	Irregular vertebral end plates
	Progressive reduction of intervertebral disc space and subsequent fusion Kyphoscoliosis
	Thoracolumbar interpedicular widening from T12-L1
Feet	Clubfeet
Clinical differential	
Larsen syndrome	Features resembling CHST3-dysplasia: Multiple joint dislocations
	Features differentiating from CHST3-dysplasia:
	Autosomal dominant inheritance
	Typical facies
	Cleft palate
	Advanced bone age

this dysplasia previously, but it is unclear whether this is a true association or an independent AAI due to os odontoideum.

Previous reports have described variations in the timing of intervention and treatment modalities of PCIS with AAI[2-8] (Table I). Previous reports are either ambiguous or have described intervention 6 weeks to 3 months from diagnosis of the PCIS after initiation of medical treatment[2-8]. We performed surgery at 4 weeks after diagnosis of PCIS keeping in mind the importance of recovery from stroke. After multidisciplinary discussion, it was considered risky to stop antithrombotic treatment earlier than 4 weeks before craniovertebral surgery with the possibility of a recurrent thromboembolism. Hence, the child was placed in a cervical collar, and surgery was scheduled after initial stroke medical management was completed at 4 weeks, there being no tangible benefit for delaying the surgery to between 6 weeks and 3 months as has been previously reported[2-8]. Because of anatomical considerations, bilateral C1-2 transarticular screws and C1–C2 fusion with C1 lateral mass screws were not feasible, and OCF was performed.[14-17]

Conclusion

An as-yet unreported constellation of *CHST3*-related skeletal dysplasia with AAI with an os odontoideum, presenting with posterior circulation ischemic stroke is described. Occipitocervical fusion at 4 weeks after stroke yielded good clinical results with the 1-year follow-up. ■

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