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Case Report

CHEDDA syndrome: a case report and review of the literature for this newly described entity[☆]

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ABSTRACT

Congenital hypotonia, epilepsy, developmental delay, and digital anomalies (CHEDDA) is a recently identified neurodevelopmental syndrome which has only 8 reported cases to date since its existence was proposed in 2007. We report a case of CHEDDA syndrome identified in a newborn female with congenital anomalies including Pierre–Robin sequence, arthrogyposis, craniosynostosis, cleft palate, and cardiac abnormalities who subsequently developed epilepsy at 1 month of life. Diagnosis was identified by whole-exome sequencing identifying mutations in a conserved histidine-rich motif within the gene *Atrophia-1*. Radiologic findings of cerebral atrophy, hypoplasia of the cerebellum, and thinning of the corpus callosum were identified in this patient, consistent with other reported cases. Given the rarity of this condition, we report this case and its findings to increase awareness of CHEDDA syndrome as a possible underlying diagnosis for neonates who present with this constellation of symptoms and radiologic findings.

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Introduction

CHEDDA, which stands for congenital hypotonia, epilepsy, developmental delay, and digital anomalies, is a recently identified neurodevelopmental syndrome. The first case reported in literature was in 2007, when the existence of this new syndrome was proposed [1]. Since its introduction, 7 more cases have been reported, with subsequent genetic analysis of these individuals showing various missense and insertion mutations in a conserved histidine-rich motif within *Atrophia-1*

(*ATN-1*), which codes for transcriptional corepressors involved in nuclear signaling. Patients with CHEDDA present early in life, typically within the first 3 months after birth. Presentation is generally characterized by hypotonia, severe global developmental delay, and facial dysmorphism including a tall forehead with bitemporal narrowing, long philtrum, retrognathism, and bulbous nasal tip. Epilepsy and camptodactyly were also findings present in the majority of cases identified to this date. Radiologic findings commonly reported in 6 out of the 8 patients identified most recently show cerebral atrophy, thinning of the corpus callosum, absence of the falx

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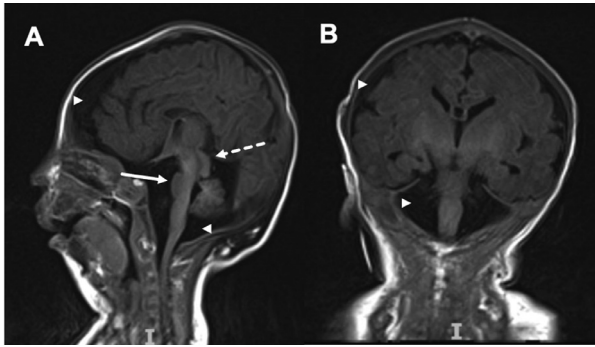


Fig. 1 – Sagittal (A) and coronal (B) T1-weighted brain MRI images from the second day of life reveals evidence of pontine hypoplasia (solid arrow) with relative preservation of vermis volume. Dysplasia of the tectum (dashed arrow) is also observed as well as prominent supratentorial and infratentorial subarachnoid spaces due to parenchymal volume loss, primarily due to loss of white matter (arrow heads). Myelination is consistent with age.

cerebri, hypoplasia of the cerebellar vermis, and polymicrogyria [1,2].

Case report

The patient was a 1-day old Caucasian female with no significant family history born to a G3P2 mother. Pregnancy was complicated by presence of anti-Kidd antibody, and prenatal ultrasound was notable for multiple fetal anomalies consisting of polyhydramnios, shortened long bones, suspected ventricular septal defect (VSD), enlarged fetal heart, micrognathia, and possible structural brain abnormalities (shortened falx cerebri) done at an external hospital. However, prenatal cell-free DNA screening and chromosomal microarray had previously returned normal, with no chromosomal microdeletions or duplications. At birth she was noted to have significant respiratory distress and required intubation and subsequent ventilation. Her respiratory distress was complicated by the presence of hypotonia as well as Pierre–Robin sequence, consisting of micrognathia, glossoptosis, and resulting airway obstruction which ultimately required mandibular distraction surgery and tracheostomy to achieve stable adequate oxygen saturation. In addition to the Pierre–Robin sequence, she was also noted to have multiple congenital anomalies including low set ears, craniosynostosis, cleft palate, arthrogryposis, and cardiac abnormalities of patent ductus arteriosus, right ventricular dilatation, and right ventricular hypertrophy shown on trans-thoracic echocardiogram.

On the first day of life, a head ultrasound was obtained which was unremarkable except for an incidentally noted choroid plexus cyst. Initial magnetic resonance imaging (MRI) of the brain at 2 days of age showed evidence of small brainstem and cerebellum, with markedly prominent supratentorial and infratentorial subarachnoid spaces (Fig. 1).

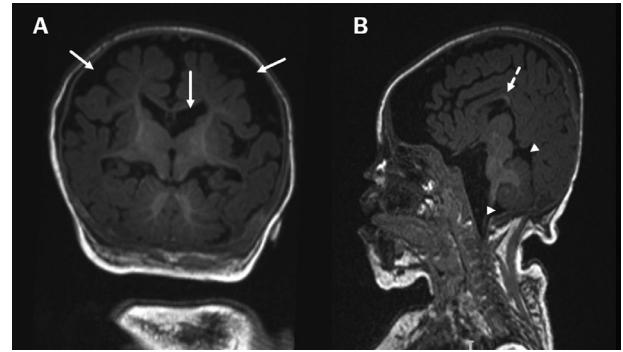


Fig. 2 – Coronal T1 (A) and sagittal T1-weighted brain MRI at 6 months of age shows further cerebral atrophy with increase in subarachnoid spaces and enlargement of the lateral and third ventricles (solid arrows), small corpus callosum (dashed arrow), and decrease in cerebrospinal fluid surrounding the cerebellum (arrowheads).

At 33 days of age, she additionally began to develop spells concerning for seizure activity characterized by right arm clonic movement which spread to all extremities. Video electroencephalogram confirmed seizure activity and identified it to be of bilateral centroparietal origin. Antiepileptic therapy was initiated, leading to a reduction of seizures. At that time, a diagnosis of Smith–Lemli–Opitz syndrome, which presents with slow growth, microcephaly, facial dysmorphism, cleft palate, heart defects, polydactyly, and underdeveloped genitalia in males was briefly considered, but her normal cholesterol levels were not consistent with the syndrome [3].

At 88 days of age, a genetic evaluation consisting of whole-exome sequencing which was initiated to assess for a unifying diagnosis underlying her multisystem symptoms returned positive for a change in the histidine repeat region of *ATN1*, identifying her diagnosis as consistent with the newly discovered CHEDDA syndrome. This variant was not identified in either parent, indicating that her mutation was likely spontaneous or due to germline mosaicism. She was also found to have a heterozygous pathogenic variant in the gene *ARSB*, which is known to be associated with Maroteaux–Lamy syndrome or mucopolysaccharidosis VI, an autosomal recessive syndrome characterized by macrocephaly, hydrocephalus, coarse facial features, macroglossia, cardiac valvular abnormalities, hepatosplenomegaly, and corneal clouding. However, as this syndrome is recessive and only one variant was identified, it is unlikely that her symptoms are due to this syndrome. Furthermore, to ensure that there was not a second variant that was missed, an arylsulfatase B enzyme analysis was obtained and returned within normal limits to rule out Maroteaux–Lamy syndrome [4].

Repeat MRI of the brain at 6 months of age for right parietal abnormality on electroencephalogram (EEG) performed for assessment of her continuing seizure disorder showed continuing global cerebral brain atrophy with marked increase in prominent subarachnoid spaces and lateral and third ventricles, small corpus callosum, and decrease in cerebrospinal fluid surrounding the cerebellum (Fig. 2). At that time, given guarded neurodevelopmental prognosis based upon prior case

reports of CHEDDA and imaging results, the decision was made to continue her on levetiracetam therapy rather than pursuing more invasive therapy.

Discussion

CHEDDA syndrome is an extremely rare autosomal dominant childhood disease, reportedly accounting for between 0.016%-0.037% of neurocognitive disturbances. So far, only 8 cases have been identified in the population to date [1,2]. Prognosis is unclear at this time, given the lack of data in current literature [2]. It presents early, typically within the first 3 months of life, with presentation generally characterized by global developmental delay, hypotonia, facial dysmorphisms, digital abnormalities, and development of epilepsy. Common radiographic findings in the few reported cases appear to show cerebral atrophy, thinning of the corpus callosum, and hypoplasia of the cerebellum [2]. In the case presented here, we observed primarily pontine hypoplasia with preservation of vermis length and morphology. In this regard, the imaging findings are distinct from other pontocerebellar hypoplasias. The tectum was noted to be dysplastic on MRI obtained at birth. Dysplastic tectum may be seen in other syndromes such as oculocerebrocutaneous syndrome, tubulinopathies, and lissencephaly-related midbrain and hindbrain malformations. Supratentorially, there was no sign of migration anomaly or corpus callosum dysgenesis. The corpus callosum was fully formed but diffusely thin, reflecting white matter volume loss.

So far, CHEDDA syndrome appears to be attributable to various *de novo* missense and insertion mutations in a histidine-rich motif of the gene, *ATN-1* [2]. While the precise function of *ATN-1* has yet to be determined, it is known to code for a transcriptional corepressor involved in nuclear receptor signaling. It has been shown that the mutations in this histidine-rich motif cause a toxic gain-of-function mutation in the Atrophin-1 protein, leading to neurotoxicity through dysregulation of various possible mechanisms required for neuronal plasticity and survival, including downstream suppression of transcriptional activation through the CREB pathway [2]. *ATN-1* has been shown to be highly expressed throughout the fetal brain during development. It is also widely expressed throughout the body in the heart, lung, and kidneys, as well as the reproductive organs [5]. It has been shown to interact with other important transcription factors which regulate gene expression, including colocalization with *MTG8*, a member of the *ETO* gene family, which is a proto-oncogene primarily implicated in acute myeloid leukemias [6,7]. *ATN-1* has also been shown to interact with several other suppressors and co-repressors, including *NR2E1*, *BAIAP2*, *FAT1*, and *PQBP1*, all of which have been implicated in neuronal migration, development, and patterning [8].

CHEDDA syndrome has been hypothesized to be associated with another congenital neurodevelopmental condition, Pallister-Killian Syndrome (PKS). PKS clinically presents similarly to CHEDDA syndrome, with severe cognitive impairment, congenital anomalies including cleft palate, polymicrogyria, limb abnormalities, and cardiac defects [9]. This syndrome is

caused by a mosaic tetrasomy of 12p, with a PKS critical region on 12p13.31 which contains *ATN-1*. It has been postulated that overexpression of *ATN-1* in a fashion similar to that present in CHEDDA syndrome may lead to dysregulation of the master transcriptional regulator CREBBP and subsequent downstream disruption in expression of the crucial developmental *HOX* genes, which potentially contributes to the similarities in clinical phenotype [2,10].

The presence of a mutation in *ATN-1* also suggests that CHEDDA may be related to dentatorubral-pallidoluysian atrophy (DRPLA), which is also associated with mutations in *ATN-1*. DRPLA presents with symptoms clinically distinct from those in CHEDDA and is associated with ataxia, myoclonus, seizures, and progressive intellectual deterioration in individuals younger than 20 years of age. In individuals who present with this syndrome who are greater than 20 years of age, primary symptoms are ataxia, choreoathetosis, dementia, and psychiatric disturbance [5]. Common radiologic findings in DRPLA are cerebellar and brainstem atrophy, and inheritance appears to be consistent with an autosomal dominant pattern, similar to CHEDDA. While the disruption in *ATN-1* in CHEDDA is missense or insertion repeats within a histidine-rich motif, DRPLA is associated with CAG trinucleotide repeat expansion in exon 5 of the gene [2,11].

ATN-1 has also been recognized to resemble a truncated form of the vertebrate arginine-glutamic acid dipeptide repeats protein, in which mutations in an analogous conserved histidine-rich motif have been shown to cause a similar neurodevelopmental disease identified as NEDBEH, or neurodevelopmental disorder with or without anomalies of the brain, eye, or heart. This condition is characterized by intellectual disability, delayed development, optic abnormalities such as colobomas or optic nerve hypoplasia, and cardiac abnormalities, most commonly ventral septal defects [12].

Given the rarity of CHEDDA syndrome and its related conditions, there is a relative dearth of research and data available to clinicians and researchers regarding this disease. Here, we have provided a summary of a new case of this rare syndrome, as well as highlights of clinical presentations and radiographic findings common to CHEDDA syndrome patients. Though this condition is extremely rare, it is important for physicians to be aware of this syndrome and consider it as a possible unifying diagnosis for patients presenting with this constellation of symptoms and radiologic findings.

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