CACH SYNDROME: A CASE REPORT

Abstract:

CACH syndrome (ChildhoodAtaxiawith Central Nervous System Hypomyelination), alsoknown as Vanishing White Matterdisease, is a rare geneticleukodystrophycaused by mutations in the EIF2B genes, which lead to impaired control of proteinsynthesis and the cellular stress response. It mostcommonlypresents in childhood as progressive cerebellarataxia, oftentriggered by an infectiousepisode, trauma, or stress.

We report the clinical case of an 8-year-old female patient hospitalized for ataxia in the pediatricneurology and neurometabolicdisorders unit of the Pediatrics II Department at the Children'sHospital of Rabat, in whom the diagnosis of CACH syndrome wasestablished and geneticallyconfirmed.

CACH syndrome is a rare geneticpediatricleukodystrophycharacterized by cerebellarataxia, frequentlytriggered by stress or infection. Diagnosisisbased on characteristicbrain MRI findings and confirmed by genetictesting. Early recognition of the diseaseallowsavoidance of aggravatingfactors and optimization of symptomatic management.

Keywords:Ataxia – CACH – Leukodystrophy – Leukoencephalopathy – Vanishing White Matter – EIF2B gene

Introduction

CACH syndrome (ChildhoodAtaxiawith Central Nervous System Hypomyelination), alsoknown as Vanishing White MatterDisease, is a rare geneticleukoencephalopathybelonging to the group of myelindisorders. First described in the late 1990s, this condition resultsfrom mutations in one of the five EIF2B genes (EIF2B1 to EIF2B5), which encode the subunits of the translation initiation factor eIF2B. These mutations lead to impaired control of proteinsynthesis and increased glial cellsensitivity to stress, explaining the progressive deterioration of cerebral white matter.

Clinically, the diseasemostoftenmanifests in childhoodwith progressive cerebellarataxia, spasticity, and cognitive impairments of variable severity. Its course ischaracterized by acute episodesoftentriggered by febrile infections, trauma, or emotional stress. Brain MRI is a key diagnostic tool, revealing diffuse hypomyelination and a cavitaryappearance of the white matter. Genetic confirmation through identification of an EIF2B gene mutation establishes the definitivediagnosis.

CACH syndrome isextremely rare in Morocco, withvery few cases reported in the literature. Here, we report the case of an 8-year-old girl presentingwith acute cerebellarataxia, ultimatelydiagnosedwithgeneticallyconfirmed CACH syndrome, and showing notable clinicalimprovementaftercorticosteroidtherapy. This case highlights the importance of consideringthis rare disorder in anychildpresentingwithunexplainedataxia and emphasizes the value of imaging and moleculardiagnosis in management.

Case Report

The patient is an 8-year-old girl with no significantpersonal or familymedicalhistory, born of a non-consanguineousmarriage. Herpreviouspsychomotordevelopmentwasconsidered normal, with no delays in milestones or priorneurologicalepisodes. Shewasadmitted for acute cerebellarataxia, whichappeared a few daysafterafebrileupperrespiratory tract infection.

Initial clinicalexaminationrevealed a moderatestatic and dynamiccerebellar syndrome, including postural instability, a broad-basedgait, enlargement of the base of support, and dysmetria on finger-to-nose and heel-to-shintesting. Deep tendon reflexes werepreserved and brisk, with no associatedmotordeficit. Cognitively, the patient showedimpairments in higherfunctions, with attention deficits, difficultiesrecognizingconventionalsigns, and ideationalslowing, indicatingmoderate cognitive impairment. No disturbances of consciousness or pyramidal signswereobserved.

Standard laboratory tests (completeblood count, serumelectrolytes, liver and kidneyfunction) were normal. Metabolic investigations, including lactate and ammonialevels, werewithin normal limits, ruling out metabolic or mitochondrial encephalopathy.

Brain MRI showed diffuse white matterlesionspredominantly in the fronto-parietalregions, with a cavitary and hypomyelinatedappearance, sparing the gray matter and basal ganglia. Thesefindingswere suggestive of a hypomyelinatingleukoencephalopathy consistent with CACH syndrome.

Genetictestingrevealed a pathogenic mutation in the EIF2B gene, confirming the diagnosis of CACH syndrome.

Therapeutically, the patient received a bolus of methylprednisoloneduring the acute phase (30 mg/kg/day for threedays), followed by gradualtapering. The course wasmarked by improvement in neurologicalsymptoms, with partial recovery of walking and reduction of ataxia, although relapses occurredfollowinginfectiousepisodes.

Regular neurological and cognitive follow-up wasestablished, alongwithrehabilitative care and preventivemeasures to avoidtriggering stress factors (infections, trauma, intense emotions).

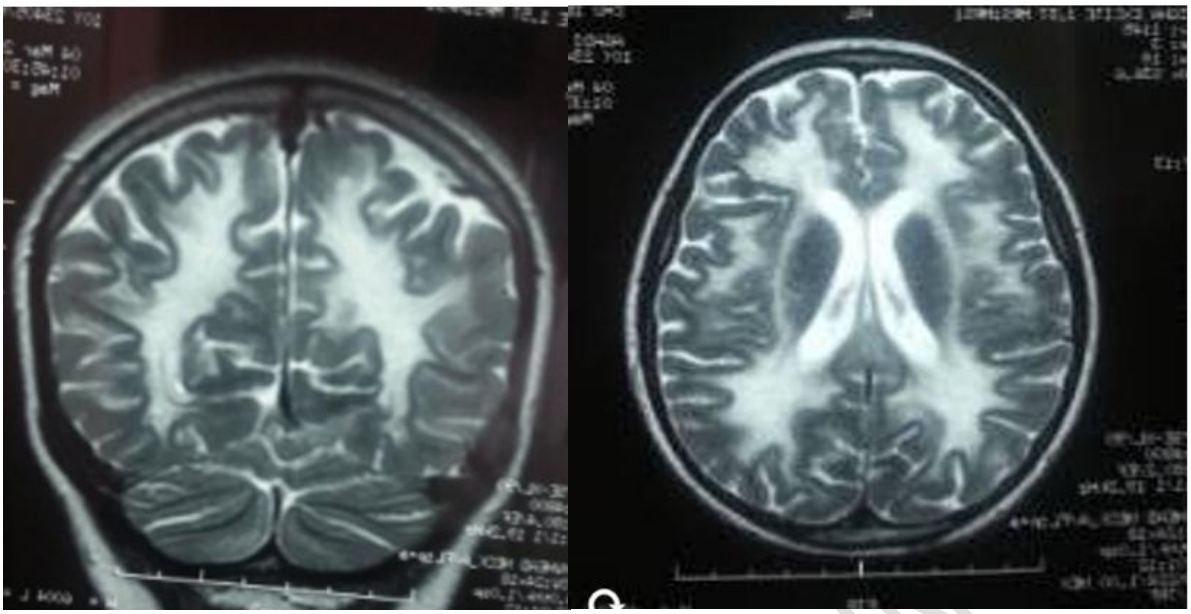

Figure 1 and Figure 2: There is a diffuse, bilateral, and symmetrical T2 and FLAIR hyperintense signal with T1 hypointensity of the white matter, predominantly in the fronto-temporal regions, sparing the U-fibers. Withinthishyperintense area, there are T2 hypointense bands, mainly in the frontal horns. This pattern is suggestive of diffuse supratentorial white matterinvolvement:leukodystrophy.

DISCUSSION:

This represents a newlycharacterizedclinicoradiologicalentity of leukodystrophy, initiallytermed CACH syndrome (ChildhoodAtaxiawith Central Nervous System Hypomyelination) and laterVanishing White Matter (VWM) disease. It isclassicallyassociatedwith:

- Onsetbetween 2 and 5 years of agewith a cerebello-spastic syndrome, oftentriggered or worsened by minor head trauma or a common viral infection, withaveragesurvival of 5 to 10 years;
- Diffuse supratentorial white matterinvolvement on MRI with a cavitaryappearance;
- Autosomalrecessiveinheritance;
- Neuropathologicalfindings of cavitary, orthochromaticleukodystrophywithincreasednumbers of oligodendrocytes, sometimeswith a foamyappearance.

Epidemiologically, a total of 148 cases have been reported to date. The exact prevalence of thesedisordersremainsunknown.

There are early infantile-onsetforms (Cree leukodystrophy), and evenneonatalforms, associatedwith extra-neurologicalsigns, which are rapidly fatal, as well as juvenile or adultforms (ovarioleukodystrophy), whichpresentwith cognitive or behavioraldisturbances and have a slower progression.

Mutations in the five genesencodingeachsubunit of the eIF2B translation initiation complex, whichregulatesproteinsynthesisunder cellular stress, have expanded the knownclinicalphenotype. The pathophysiologyinvolvesimpaired astrocyte maturation, leading

to increasedsusceptibility of white matter to cellular stress. Diagnosis relies on detection of mutations, mostcommonly in the **EIF2B5**gene. A defect in eIF2B activity (guanine nucleotide exchange factor, GEF) in patient lymphoblastsappears to have diagnostic value.

There is no specifictreatmentapartfrom "cellular stress prevention." Corticosteroids have sometimes been beneficialduring the acute phase. Prognosisispoorest in the earliest-onsetforms.

CONCLUSION:

CACH syndrome remains a very rare disorder. There is no specifictreatmentbeyondprevention of cellular stress. Corticosteroidsmayoccasionallybeusefulduring acute episodes.

REFERENCES :

- **Van der Knaap, M. S., Barth, P. G., Gabreëls, F. J. M., et al.** (1997). *A new leukoencephalopathywithvanishing white matter*. Neurology, 48(4), 845–855.

- **Van der Knaap, M. S., &Scheper, G. C.** (2006). *Vanishing white matterdisease*. The Lancet Neurology, 5(5), 413–423.

- **Schiffmann, R., Moller, J. R., &Trapp, B. D.** (1994). *Childhoodataxiawith diffuse central nervous system hypomyelination*. Annals of Neurology, 35(3), 331–340.

- **Moon, S. L., et al.** (2018). *EIF2B2 mutations in vanishing white matterdisease*. Brain, 141(11), 3192–3205.

- **Bugiani, M., et al.** (2010). *Leukoencephalopathywithvanishing white matter:areview*. Journal of Neuropathology&ExperimentalNeurology, 69(10), 987–1000.