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### CASE REPORT

### CACH SYNDROME: A CASE REPORT

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#### Abstract

CACH syndrome (Childhood Ataxia with Central Nervous System Hypomyelination), also known as Vanishing White Matter disease, is a rare genetic leukodystrophy caused by mutations in the EIF2B genes, which lead to impaired control of protein synthesis and the cellular stress response. It most commonly presents in childhood as progressive cerebellar ataxia, often triggered by an infectious episode, trauma, or stress. We report the clinical case of an 8-year-old female patient hospitalized for ataxia in the pediatric neurology and neurometabolic disorders unit of the Pediatrics II Department at the Children's Hospital of Rabat, in whom the diagnosis of CACH syndrome was established and genetically confirmed. CACH syndrome is a rare genetic pediatric leukodystrophy characterized by cerebellar ataxia, frequently triggered by stress or infection. Diagnosis is based on characteristic brain MRI findings and confirmed by genetic testing. Early recognition of the disease allows avoidance of aggravating factors and optimization of symptomatic management.

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#### Introduction:-

CACH syndrome (Childhood Ataxia with Central Nervous System Hypomyelination), also known as Vanishing White Matter Disease, is a rare genetic leukoencephalopathy belonging to the group of myelin disorders. First described in the late 1990s, this condition results from 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 protein synthesis and increased glial cell sensitivity to stress, explaining the progressive deterioration of cerebral white matter. Clinically, the disease most often manifests in childhood with progressive cerebellar ataxia, spasticity, and cognitive impairments of variable severity. Its course is characterized by acute episodes often triggered by febrile infections, trauma, or emotional stress. Brain MRI is a key diagnostic tool, revealing diffuse hypomyelination and a cavitory appearance of the white matter. Genetic confirmation through identification of an EIF2B gene mutation establishes the definitive diagnosis. CACH syndrome is extremely rare in Morocco, with very few cases reported in the literature. Here, we report the case of an 8-year-old girl presenting with acute cerebellar

ataxia, ultimately diagnosed with genetically confirmed CACH syndrome, and showing notable clinical improvement after corticosteroid therapy. This case highlights the importance of considering this rare disorder in any child presenting with unexplained ataxia and emphasizes the value of imaging and molecular diagnosis in management.

#### Case Report:-

The patient is an 8-year-old girl with no significant personal or family medical history, born of a non-consanguineous marriage. Her previous psychomotor development was considered normal, with no delays in milestones or prior neurological episodes. She was admitted for acute cerebellar ataxia, which appeared a few days after a febrile upper respiratory tract infection. Initial clinical examination revealed a moderate static and dynamic cerebellar syndrome, including postural instability, a broad-based gait, enlargement of the base of support, and dysmetria on finger-to-nose and heel-to-shin testing. Deep tendon reflexes were preserved and brisk, with no associated motor deficit. Cognitively, the patient showed impairments in higher functions, with attention deficits, difficulties recognizing conventional signs, and ideational slowing, indicating moderate cognitive impairment. No disturbances of consciousness or pyramidal signs were observed. Standard laboratory tests (complete blood count, serum electrolytes, liver and kidney function) were normal. Metabolic investigations, including lactate and ammonia levels, were within normal limits, ruling out metabolic or mitochondrial encephalopathy.

Brain MRI showed diffuse white matter lesions predominantly in the fronto-parietal regions, with a cavitary and hypomyelinated appearance, sparing the gray matter and basal ganglia. These findings were suggestive of a hypomyelinating leukoencephalopathy consistent with CACH syndrome. Genetic testing revealed a pathogenic mutation in the EIF2B gene, confirming the diagnosis of CACH syndrome. Therapeutically, the patient received a bolus of methylprednisolone during the acute phase (30 mg/kg/day for three days), followed by gradual tapering. The course was marked by improvement in neurological symptoms, with partial recovery of walking and reduction of ataxia, although relapses occurred following infectious episodes. Regular neurological and cognitive follow-up was established, along with rehabilitative care and preventive measures to avoid triggering 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. Within this hyperintense area, there are T2 hypointense bands, mainly in the frontal horns. This pattern is suggestive of diffuse supratentorial white matter involvement: leukodystrophy.**

**Discussion:-**

This represents a newly characterized clinicoradiological entity of leukodystrophy, initially termed CACH syndrome (Childhood Ataxia with Central Nervous System Hypomyelination) and later Vanishing White Matter (VWM) disease. It is classically associated with:

- Onset between 2 and 5 years of age with a cerebello-spastic syndrome, often triggered or worsened by minor head trauma or a common viral infection, with average survival of 5 to 10 years;
- Diffuse supratentorial white matter involvement on MRI with a cavitary appearance;
- Autosomal recessive inheritance;
- Neuropathological findings of cavitary, orthochromatic leukodystrophy with increased numbers of oligodendrocytes, sometimes with a foamy appearance.

Epidemiologically, a total of 148 cases have been reported to date. The exact prevalence of these disorders remains unknown. There are early infantile-onset forms (Cree leukodystrophy), and even neonatal forms, associated with extra-neurological signs, which are rapidly fatal, as well as juvenile or adult forms (ovarioleukodystrophy), which present with cognitive or behavioral disturbances and have a slower progression. Mutations in the five genes encoding each subunit of the eIF2B translation initiation complex, which regulates protein synthesis under cellular stress, have expanded the known clinical phenotype. The pathophysiology involves impaired astrocyte maturation, leading to increased susceptibility of white matter to cellular stress. Diagnosis relies on detection of mutations, most commonly in the EIF2B5 gene. A defect in eIF2B activity (guanine nucleotide exchange factor, GEF) in patient lymphoblasts appears to have diagnostic value. There is no specific treatment apart from “cellular stress prevention.” Corticosteroids have sometimes been beneficial during the acute phase. Prognosis is poorest in the earliest-onset forms.

**Conclusion:-**

CACH syndrome remains a very rare disorder. There is no specific treatment beyond prevention of cellular stress. Corticosteroids may occasionally be useful during acute episodes.

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