

## Seizures and Cerebellar Calcification in a Child with Autoimmune Polyendocrine Syndrome 3A

A 6-year-old girl, born to consanguineous parents, presented to us with polyuria and weight loss for two weeks. Six months prior, she had multiple episodes of generalized seizures for which she was on antiepileptic drugs. She had history of developmental delay in all domains after the age of one year, and at presentation she had a developmental age of about three years.

On examination, she had proportionate short stature, dysarthria, ataxic gait, increased tone, and exaggerated deep tendon reflexes in the lower limbs. Investigations showed random blood sugar of 369 mg/dL, HbA1C of 10.5%, and ketonuria. TSH was >100 mIU/mL, and Free T4 was 0.364 (Normal 0.97-1.67 ng/dL). Anti-TPO (thyroid peroxidase) antibody was elevated (813.59 IU/mL) and anti-GAD (glutamic acid decarboxylase) antibody was >2000 IU/mL. Serum levels of calcium, phosphorus, parathormone and cortisol were normal. Non-enhanced computed tomography scan of the brain showed bilateral symmetrical calcification and mild atrophy of the cerebellar folia (**Fig. 1**). Magnetic resonance imaging of brain showed mild cerebral atrophy, marked cerebellar atrophy and bilateral symmetrical cerebellar calcification. The child was diagnosed to have Autoimmune Polyendocrine Syndrome Type 3A due to the presence of hypothyroidism and Type 1 diabetes mellitus [1].

The neurological manifestations (developmental delay, seizures, dysarthria, ataxia, spasticity along with cerebellar atrophy and calcification on neuroimaging) observed in this child can be attributed to long-standing untreated hypothyroidism with onset in early childhood. The common neurological manifestations seen in early onset hypothyroidism include intellectual disability, impaired motor development with involvement of the pyramidal and extrapyramidal systems, cerebellar dysfunction, strabismus, sensorineural hearing loss and intracranial calcification. There have been reports of children with hypothyroidism presenting with intellectual impairment, spasticity and deformity of lower limbs mimicking cerebral palsy with spastic diplegia [2]. The



**Fig. 1** Non-contrast CT Scan of the brain showing bilateral symmetrical calcific foci in the cerebellum.

severity of these symptoms has been linked to delay in diagnosis and treatment of hypothyroidism, especially in the early childhood. These manifestations may not show an improvement even after initiation of treatment; although, progression is halted. Hypothyroidism is known to cause calcification in the basal ganglia, subcortical areas and rarely in the cerebellar folia, probably due to metabolic derangements [3]. The differential diagnosis for this pattern of calcification includes hypoparathyroidism, hypothyroidism, pseudohypoparathyroidism and idiopathic disorders such as Fahr disease. Low levels of thyroid hormones may also contribute to epilepto-genesis by mitochondrial dysfunction and oxidative stress due to their role in the development and function of GABAergic neurons [4].

Hypothyroidism being a treatable condition should be ruled out in any child presenting with symptoms like developmental delay, seizures, spasticity, cerebellar dysfunction with neuroimaging findings such as intracranial calcification and cerebellar atrophy.

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## Two Novel Heterozygous *MCCCI* Mutations in a Neonate with Asymptomatic 3-methylcrotonyl-coenzyme A Carboxylase Deficiency

Isolated 3-methylcrotonyl-coenzyme A carboxylase deficiency is a rare metabolic disorder inherited as an autosomal recessive trait [1]. We report features of patient with asymptomatic 3-methylcrotonyl-coenzyme A carboxylase deficiency and two novel heterozygous *MCCCI* mutations.

The proband, a girl, was born in the 41th week of gestation with a weight of 2.85 kg to non-consanguineous parents. On the fourth day of life, tandem mass spectrometry was performed, revealing that the level of 3-hydroxyisovaleryl-carnitine (C5-OH) was high (2.74  $\mu$ M; reference range <0.6  $\mu$ M). C5-OH levels were repeated in dried blood spot, and it was again high (3.23  $\mu$ M). Due to persistently elevated level of C5-OH, blood samples from the proband, her parents and her elder brother were tested for genetic- and mutation-analysis, after informed consent. Genetic analysis of the proband showed two heterozygous novel missense mutations (*MCCCI* NW\_020166.3: c.1570G>C (p.D524H) and *MCCCI* NW\_020166.3: c.601C>T (p.P201S)) in the

*MCCCI* gene. The father was heterozygous for c.601C>T (p.P201S) and the mother was heterozygous for c.1570G>C (p.D524H). The elder brother was heterozygous for c.601C>T (p.P201S). At 11 months of age, the proband was still asymptomatic, and with normal growth and development.

In general, most newborns with isolated 3-methylcrotonyl-coenzyme A carboxylase deficiency detected on screening appear clinically normal and healthy. Features such as vomiting, ketosis, poor oral intake, irritability, lethargy and hypotonia are reported in up to 15% of patients; majority (92.5%) of infants show completely appropriate age-matched development [2].

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