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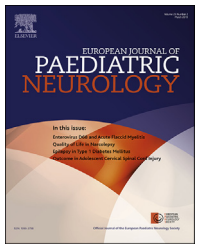

Editorial

# *GLUT1* deficiency and pediatric-onset hereditary spastic paraplegia: A new association

Glut1 deficiency (Glut1-DS) is a metabolic disease caused by mutations *SLC2A1*, encoding the glucose transporter type 1 (GLUT1) protein of the blood–brain barrier, with a frequency of approximately 1:80–90,000.[1,2] The first mutations identified were associated with the phenotype, characterized by infantile-onset seizures, delayed neurologic development, acquired microcephaly, and complex movement disorders. However, the phenotypic spectrum of this condition is continuously expanding, including atypical childhood absence epilepsy, myoclonic-atonic epilepsy, intermittent ataxia, paroxysmal exercise-induced dyskinesia or choreoathetosis, and alternating hemiplegia.[1] The diagnosis of Glut1 D is clinically established in a proband with suggestive clinical findings, normal blood glucose concentration, cerebro spinal fluid (CSF) glucose concentration <60 mg/dL, and the identification of a heterozygous pathogenic variant (or rarely, biallelic pathogenic variants) in *SLC2A1* by molecular genetic testing.[3]

In this issue, Nicita et al. describe two children featuring spastic paraplegia/paraparesis (HSP) associated with heterozygous *de novo* missense mutations in *SLC2A1* and discuss a novel approach in the diagnostic work-up of HSP patients.[4] HSPs are a group of genetic neurodegenerative diseases in which novel mutations are reported each year. The authors applied extensive targeted-re-sequencing (i.e. gene panel) on 140 pediatric and adult patients with pure and complex HSP. Two pediatric patients with *SLC2A1* missense mutations were found showing a prevalence of 1.4% of SLC2A1 mutations on the overall studied sample and a prevalence of 3% considering only pediatric-onset patients with HSP. The two children presented a neurologically impaired objective examination with pyramidal signs at lower limbs and gait and posture problems. The instrumental examinations showed an increase of central conduction time to the motor evoked potential and hypoglycorrhachia at the CSF analysis. Clearly, this study demonstrates the difficulty of associating HSP with Glut-1 based only on clinical symptoms, given the low prevalence of patients with HSP and SLC2A1 mutation. Therefore, this recent work of Nicita et al. recommends introducing the screening of SLC2A1 in the panels for gene sequencing in HSP patients, because the genetic analysis is essential for the diagnosis. Notably, a 10–14% of Glut1-D patients could not be diagnosed because the disease caused by deletions or duplications instead of missense mutations. In these cases, the clinician can be helped by the most obvious clinical manifestations of the disease. Importantly, the paper of Nicita et al. elaborates the diagnostic work-up of SLC2A1-related HSP, recommending screening of SLC2A1 in all patients with pure or complex HSP to avoid misdiagnosis of Glut1-D. In the second step, a lumbar puncture must be performed to confirm the hypoglycorrhachia, only in those cases with an incomplete or untargeted panel. Likewise, it is possible to diagnose a potentially treatable pathology thanks to the ketogenic diet. It is important to underline that in HSP early onset and subsequent symptoms and their severity can be different significantly among patients.[5] Clearly this fact emphasizes the great importance of genetic screening for diagnosis of HSP.

## REFERENCES

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