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Serine metabolism disorder – one more metabolic aetiology of cerebral palsy

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Introduction: Cerebral palsy (CP) refers to a group of neurological disorders caused by damaage or abnormalities of the developing brain, disrupting its ability to control movement and maintain posture and balance. Usually attributed to labour occurrences, metabolic and genetic disorders are increasingly being identified as main aetiological factors. Serine metabolism disorder involving SLC1A4 gene encoding for ASCT1 transporter are being described as one of the metabolic aetiologies associated to cerebral palsy.(1,2).

Results/Case report: We present a 21-year-old female, born at term from non-consanguineous parents. Low Apgar scores, diagnosed with dystonic cerebral palsy. She developed progressive microcephaly, severe psychomotor delay, no language, non-epileptic startle episodes, agitation, scoliosis, oropharyngeal dysphagia and MALT gastric lymphoma.
Brain MRI showed marked postero-anterior graded hypomyelination, thin corpus callosum, mild brainstem hypoplasia. Metabolic investigation showed normal mitochondrial respiratory chain activity and mild mtDNA depletion (60%). Mitochondrial disorders gene panel and clinical exome were inconclusive.
The patient was proposed to trio whole genome sequencing (WGS) in ZOEMBA® - International genomic discovery study, and two probably pathogenic biallelic variants c.272T>C (p.Leu91Pro) and c.1277del (p.Gly426Glufs*22) were identified in SLC1A4 gene, encoding for ASCT1 transporter.

Conclusion: ASCT1 transporter is a brain serine transporter encoded by SLC1A4 gene, and responsible for SPATCCM - spastic tetraplegia, thin corpus callosum, and progressive microcephaly disorder (MIM #616657).
Serine, although a non-essential aminoacid, needs to by synthesized in the brain and shuttle from astrocytes to neuron by this transporter. The clinical phenotype of ASCT1 defect is similar to defects in L-serine biosynthesis.(2)
Serine supplementation therapy was proposed as a possible therapeutic tool but only if started before neurological damage occurs.(1)

References:
(1) Damseh N, et al. Mutations in SLC1A4, encoding the brain serine transporter, are associated with developmental delay, microcephaly and hypomyelinationJ Med Genet 2015;52:541–547. doi:10.1136/jmedgenet-2015-103104;
(2) Heimer G. SLC1A4 mutations cause a novel disorder of intellectual disability, progressive microcephaly, spasticity and thin corpus callosum. Clin Genet . 2015 Oct; 88(4):327-35. doi: 10.1111/cge.12637.

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