Clinical and pathogenic themes in Hereditary Spastic Paraplegia

This scientific commentary refers to "The clinical, molecular and imaging spectrum of adaptor protein complex 4-associated hereditary spastic paraplegia: A cross-sectional analysis of 156 patients", by Ebrahimi-Fakhari et al Brain 2020.

Genetic classifications of neurodegenerative diseases appear to many clinicians to have taken on a life of their own, with an ever-growing list of numbered genes and unusually named proteins. The Hereditary Spastic Paraplegias (HSPs) are no exception, with over 80 "spastic gait" (SPG) loci now recognised in genes encoding proteins such as spastin, paraplegin and strumpellin. This genetic heterogeneity, with many genes identified in single families only, is associated with significant phenotypic heterogeneity and makes diagnosis and treatment difficult. One solution is to look for commonalities in the clinical features and underlying pathogenic mechanisms. In this issue of *Brain*, Ebrahimi-Fakhari and co-workers use a multinational approach to study a large cohort of patients with SPG47, SPG50, SPG51 and SPG52, all of whom have loss of function of subunits of the adaptor protein complex 4 (AP-4), and in so doing bring clarity to the field of childhood-onset complex HSPs (Ebrahimi-Fakhari et al, 2020).

HSPs are a heterogeneous group of monogenic neurological conditions with the core clinical features of bilateral lower limb spasticity, hyperreflexia and extensor plantar responses (Shribman et al, 2019). They can present from infancy to adulthood and can have autosomal dominant, recessive or X-linked inheritance. The commonest forms – SPG4, 3A and 31 – are dominant with a fairly pure phenotype. However, patients may also present with additional neurological impairments including cognitive deficits, ataxia, dysarthria, neuropathy and seizures. Treatment for HSP is symptomatic with no disease-modifying therapies available, and the symptoms and disability progress slowly, in keeping with the underlying neurodegeneration.

The study by Ebrahimi-Fakhari and colleagues is significant by virtue of its detailed analysis of a large cohort of patients with bi-allelic mutations in *AP4B1* (SPG47), *AP4M1* (SPG50), *AP4E1* (SPG51) and *AP4S1* (SPG52). A total of 156 patients from 101 families in 19 countries were recruited, demonstrating the value of international registries for rare disorders. Whilst the mean age of onset was in the first year of life, the mean age at diagnosis was almost 10 years later. Clinical analysis revealed a core phenotype, which Ebrahimi-Fakhari and colleagues labelled the "AP-4 deficiency syndrome". This comprised postnatal microcephaly, early-onset developmental delay with delayed motor milestones and speech delay, intellectual disability, initial hypotonia progressing to spastic diplegia and then tetraplegia with contractures, foot deformities and epilepsy. A key MRI brain finding was thinning of the corpus callosum in 90% of cases, often associated with ventriculomegaly, and sometimes with colpocephaly and periventricular white matter signal abnormalities (Figure).

Genetic analysis revealed bi-allelic variants in all patients, with 82% carrying homozygous variants in keeping with the fact that the majority were born to consanguineous parents. *AP4B1* and *AP4M1* mutations accounted for just over 70% of cases. Most variants were frameshift or nonsense mutations predicted to lead to truncated protein and loss of function. Exploration of genotype-phenotype correlations revealed that disease severity and major phenotypes were equally represented amongst the four subtypes, demonstrating that SPG47, SPG50, SPG51 and SPG52 share a common AP-4 deficiency syndrome phenotype. The presence of epilepsy was associated with worse outcomes.

Considerable efforts have been made to investigate the molecular pathogenesis underlying HSPs in order to explain the length-dependent axonopathy of corticospinal upper motor neurons, and a number of converging pathogenic themes have emerged (Blackstone, 2018). Key mechanisms implicated include organelle shaping and biogenesis, as well as membrane and cargo trafficking. Loss of function of the AP-4 protein complex fits into these themes. Adaptor proteins (AP-1 to AP-5) form heterotetrameric protein complexes that are involved in selective incorporation of transmembrane cargo proteins into vesicles, and which assist their intracellular trafficking. The AP-4 complex is made up of four subunits (β4, ε, μ4 and σ4), and mediates protein trafficking from the trans-Golgi network to early and late endosomes. Recently, the same group have published work showing that the ATG9A protein, which is important in autophagy, is mislocalised in cellular models of AP-4 HSP. In iPSC-derived cortical neurons, they found evidence of altered autophagosome turnover and reduced neurite outgrowth and branching, suggesting neuronal development may play a role in pathogenesis (Behne et al, 2020). Autophagic dysfunction in this form of HSP is of interest because the two commonest forms of complex autosomal recessive HSP (SPG11 and 15), plus two other rare variants (SPG48 and SPG 49), also have underlying autophagy defects.

SPG11 and SPG15 are clinically very similar and have additional features of ataxia, parkinsonism, retinal abnormalities and cataracts. They are also characterised by thinning or loss of the corpus callosum on MRI, distinguishing them from almost all other forms of HSP. The similarity continues in that the SPG11 (spatacsin) and SPG15 (spastizin) proteins are part of a complex including AP-5, and have a key role in generating new lysosomes via autophagic lysosome reformation. Cellular models with SPG 11 and SPG15-related mutations have shown defects at different levels of the lysosomal-autophagy pathway (Vantaggiato et al, 2019). Spastizin and spatacsin interact with another complex autosomal recessive HSP (SPG48) protein, which is a subunit of the AP-5 complex (Hirst J et al 2015 & 2016), and patients with this disorder also have atrophy of the corpus callosum on imaging. AP deficiency disorders can thus be extended to include those featuring abnormalities in AP-4 and AP-5, and which present as neurodevelopmental disorders with a spectrum of central nervous system involvement. These in turn belong to the broader category of congenital brain disorders with underlying autophagic problems, a number of which also have evidence of corpus callosum atrophy on MRI (reviewed in Teinert et al. 2019). Why defective autophagic processes should have a selective effect on corpus callosal axonal development is unclear, but atrophy of the corpus callosum on MRI represents a useful tool for signposting these conditions.

This study highlights the value of international registries in making it possible to recruit a sufficient number of patients with rare diseases to allow meaningful conclusions to be drawn regarding clinical, imaging and genetic features. The identification of an AP4 deficiency syndrome should have an immediate impact on the field, with earlier diagnosis and more accurate genetic counselling for families. One relative weakness of the study is that it was cross-sectional in design. The hope is that the authors will continue their work by collecting prospective longitudinal data on the cohort, which will help clarify progression and prognosis. It will also assist in validating rating scales and potential biomarkers, which will be essential for future interventional trials. Given the pace of development of gene therapy approaches for other neurodegenerative disorders, the identification of common cellular mechanisms in HSPs should provide opportunities for interventions in well characterised cohorts such as this.

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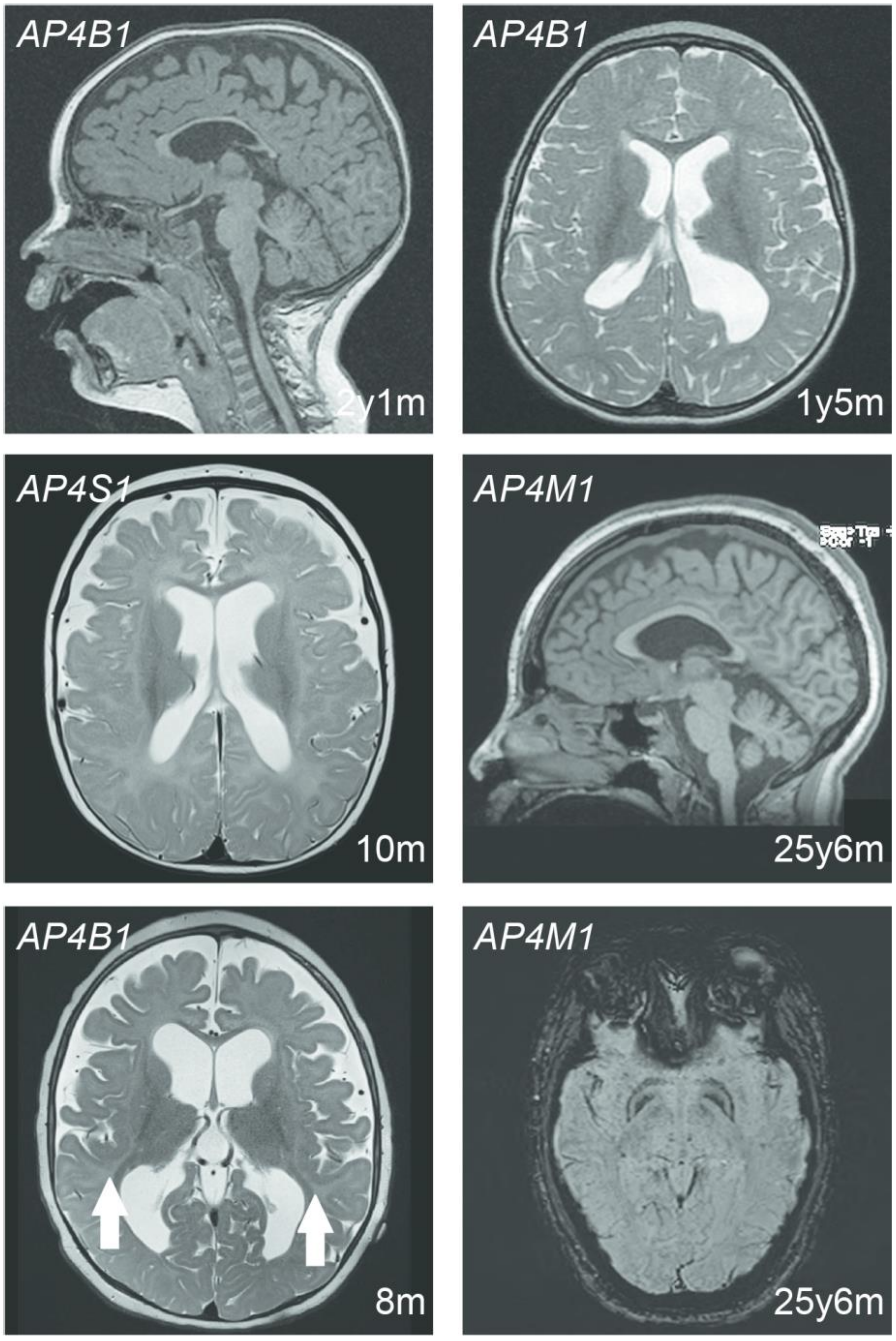
Figure. Key imaging features in AP4-hereditary spastic paraplegia. Upper left: Thinning of the corpus callosum. Upper right: Ventriculomegaly. Middle left: Cortical atrophy. Middle right: Cerebellar atrophy. Lower left: Bilateral perisylvian polymicrogyria (arrows). Lower right: Bilateral symmetrical hypointensity of the global pallidus suggestive of iron accumulation. Reproduced from Ebrahimi-Fakhari et al, 2020.



References:

Blackstone C. Converging cellular themes for the hereditary spastic paraplegias. Curr Opin Neurobiol. 2018 Aug; 51:139-146

Behne R, Teinert J, Wimmer M, D'Amore A, Davies AK, Scarrott JM et al. Adaptor protein complex 4 deficiency: a paradigm of childhood-onset hereditary spastic paraplegia caused by defective protein trafficking. Hum Mol Genet. 2020 Jan 15;29(2):320-334.

Ebrahimi-Fakhari D, Teinert J, Behne R, Wimmer M, D'Amore A, Eberhardt K et al. Defining the clinical, molecular and imaging spectrum of adaptor protein complex 4-associated hereditary spastic paraplegia. Brain 2020

Ebrahimi-Fakhari D, Saffari A, Wahlster L, Lu J, Byrne S, Hoffmann GF, Jungbluth H, Sahin M. Congenital disorders of autophagy: an emerging novel class of inborn errors of neuro-metabolism. Brain 2016 Feb;139(Pt 2):317-37

Hirst J, Edgar JR, Esteves T, Darios F, Madeo M, Chang J et al. Loss of AP-5 results in accumulation of aberrant endolysosomes: defining a new type of lysosomal storage disease. Hum Mol Genet. 2015 Sep 1;24(17):4984-96

Hirst J, Madeo M, Smets K, Edgar JR, Schols L, Li J et al. Complicated spastic paraplegia in patients with AP5Z1 mutations (SPG48). Neurol Genet. 2016 Aug 25;2(5):e98.

Shribman S, Reid E, Crosby AH, Houlden H, Warner TT. Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. Lancet Neurol. 2019 Jul 31. pii: S1474-4422(19)30235-2

Teinert J, Behne R, Wimmer M, Ebrahimi-Fakhari D. Novel insights into the clinical and molecular spectrum of congenital disorders of autophagy. J Inherit Metab Dis. 2019 Mar 10. doi: 10.1002/jimd.12084. [Epub ahead of print]

Vantaggiato C, Panzeri E, Castelli M, Citterio A, Arnoldi A, Santorelli FM et al. ZFYVE26/SPASTIZIN and SPG11/SPATACSIN mutations in hereditary spastic paraplegia types AR-SPG15 and AR-SPG11 have different effects on autophagy and endocytosis. Autophagy. 2019 Jan;15(1):34-57

Glossary of terms

Autophagy: Literally meaning "self-eating", this is a fundamental cellular catabolic pathway that delivers cytoplasmic cargo to the lysosome for degradation, allowing recycling of macromolecules and membranes.

Adaptor Proteins: Protein complexes essential for sorting of cargoes at the trans-Golgi network into vesicles for trafficking within the cell.

Colpocephaly: enlargement of the occipital horns of the lateral ventricles

SPG: Spastic Gait. The abbreviation used for the genetic classification of HSP