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# Examples of High Scoring Conference Abstracts

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# *Precision gene therapy for aromatic l-amino acid decarboxylase (AADC) deficiency*

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Background
Classical aromatic L-amino acid decarboxylase deficiency (AADCd) is an ultra-rare genetic neurotransmitter disorder resulting from biallelic loss-of-function variants in DDC. The resulting defect in monoamine synthesis leads to profound infantile parkinsonism-dystonia, oculogyric crises (OGC), dysautonomia, and severe global developmental delay with most patients not achieving full head control. Whilst precision therapies are lacking for most neurodevelopmental disorders, recent advances have led to successful development of life-transforming gene therapy for patients with AADCd.

Objective
To describe the UK cohort of children who have received regional brain-targeted gene therapy for AADCd.

Methods
Retrospective review of case notes, neuroimaging and investigations from the Great Ormond Street Hospital neurotransmitter disorders multi-disciplinary service was undertaken.

Results
Seven children were identified with AADC deficiency. Five had received midbrain-targeted gene therapy (AAV2-hDDC), and two are progressing to putaminal gene therapy with eladocagene exuparvovec (Upstaza). All have classical AADCd with typical baseline CSF neurotransmitter metabolites. Age at treatment ranged from 6 years to 12 years 10 months (mean 9 years 7 months) with post-surgical follow up of 3.25-4 years. Rapid developmental progress was evident in 4/5 patients, with 4/5 children achieving independent sitting, 4/5 standing with support, and all achieving their first words of spoken language. Two are now walking with support. 4/5 patients had cessation of OGC within 3 weeks after gene therapy. Three patients remain free of OGC and mild/infrequent OGC recurred in two patients 1-2 years post gene therapy, either not requiring treatment or well-controlled with a monoamine oxidase inhibitor. 2/5 are fully weaned off AADCd medications. CSF dopamine metabolites normalised in 4/5 children.

Conclusions
Our UK cohort demonstrates that targeted gene therapy can significantly alter the natural history of AADCd. Given recent UK licensing of eladocagene exuparvovec (Upstaza) for classical AADCd, paediatric neurologists should be aware of this new disease-modifying precision therapy.

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# *Evaluating visual assessments for the design of clinical remyelination trials in multiple sclerosis in children*

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Objective
Therapies to promote myelin repair (remyelination) in multiple sclerosis (MS) are being explored in adults. Many such clinical trials include visual system assessments as outcome measures. We aimed to evaluate, from a selection of visual assessments, which demonstrated least variability over time in children to guide future trial design.

Methods
Longitudinal observational study of children with stable MS (cwMS) and controls, with baseline and month 6 visits. Participants underwent full-field and multi-focal visual evoked potentials (VEP), optical coherence tomography (OCT), Sloan letter low-contrast acuity and trivector Cambridge Colour Vision Test assessment.

Results
4 controls and 4 cwMS (16 eyes total) completed 6 months follow-up. Comparing control eyes between visits identified significant difference only in VEP amplitude (p=0.0156). Amongst cwMS, only 1.25% contrast acuity (p=0.0142) significantly differed. Between control and cwMS groups, over 6 months, significant difference in change scores was only observed for 1.25% contrast acuity (p=0.0400). Examining mean percentage change over 6 months, amongst controls, least change was seen in temporal pRNFL (0.140%), full-field VEP P100 (ffVEP, 0.750%) and total macular inner plexiform layer thickness (mIPL, -1.114%). In cwMS least change was in global pRNFL (0.258%), ffVEP P100 (0.425%) and mIPL (1.0724%). Greatest mean percentage change was observed in controls for 1.25% acuity (32.214%), ffVEP amplitude (-23.082%) and protan sensitivity (-19.955%); and for cwMS, 1.25% acuity (maximum improvement from 0 to 20 letters), 2.5% acuity (25.625%) and deutan sensitivity (-22.435%).

Conclusions
Our findings suggest ffVEP P100 (but not amplitude) and OCT (particularly total mIPL thickness) to be the most consistent longitudinal metrics. Assessments of visual function appear less reliable; the improvements in low contrast acuity and colour sensitivity in our participants over time may reflect a learning effect. We recommend ffVEP P100 and OCT biomarkers as potential outcome measures for paediatric clinical trials exploring remyelination and axonal health.