Treatment of ARS deficiencies with specific amino acids

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Introduction
Aminoacyl-tRNA synthetases (ARS) are enzymes that attach amino acids to transfer RNAs (tRNA), which carry the amino acid to the ribosome (Fig. 1). Thus, ARS are crucial for protein translation. Recombinant cystic fibrosis ARS deficiencies are multorgan diseases with limited treatment options. Especially during periods of increased demand for protein translation, symptoms are severe. To improve prospects for these patients, we sought to develop a new treatment strategy based on the disease mechanism.

Methods
We studied patient fibroblasts to test the putative cellular mechanism of (incidentally) reduced aminoacylation to meet translational demands and develop and test amino acid treatment.

Fibroblast studies
We used fibroblasts from patients with IARS1, LARS1, FARSB and SARS1 deficiencies to study enzyme activity, the impact of fever on enzyme function. Based on severe symptoms at young age and during infections, reflecting periods of increased translation and decreased amino acid availability, we tested if patient fibroblasts were sensitive to ARS-specific amino acid concentrations.

Medical treatment
We treated four patients with IARS1, LARS1, FARSB and SARS1 deficiency with isoleucine (35-70 mg/kg/day), leucine (15-100 mg/kg/day), phenylalanine (40-100 mg/kg/day) and serine (85.7-97.5 mg/kg/day). The IARS1 and LARS1 deficient patients were additionally given protein fortification (2.5 g/kg/day). Dosages were increased during infectious episodes. Follow-up was 9 (FARB), 12 (IARS1), 12 (SARS1), and 34 months (IARS1).

Results
Aminoacylation activity of IARS, LARS, FARSB and SARS were decreased in respective patients (Fig 2, and further decreased at fever temperatures in the LARS1 and FARSB deficient patient, but not in controls (Fig 3).

Isoleucine, leucine and phenylalanine deprivation resulted in decreased patient fibroblast growth for the respective patients, which could be restored by increasing concentrations. Serine restriction did not limit proliferation for the SARS1 deficient patient fibroblasts, putting because it is a non-essential amino acid.

Medical treatment
In all patients, treatment was safe, well-tolerated, and resulted in improvements in oral feeding leading to independency from tube feeding growth, especially in height and head circumference, development, and coping with infections (Fig 5). In addition, oxygen dependency decreased and previously progressive pulmonary abnormalities stabilized in the IARS1 deficient patient, and fever function improved in the FARSB deficient patient.

Conclusion
We provide a therapeutic strategy for ARS deficiencies based on in vitro and in vivo evidence of beneficial effects of amino acid and protein supplementation (up to 22/23 years) in single patients. This affordable, accessible, and safe strategy holds the potential to improve outcomes for the expanding group of severe, often progressive, multorgan ARS deficiencies.

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