Infantile Tremor Syndrome: An uncommon but treatable cause of neuroregression

BACKGROUND: Infantile tremor syndrome is characterized by acute neuroregression; tremulous involuntary movements; skin hyperpigmentation and depigmented, sparse scalp hair; often associated with lethargy, poor appetite, pallor and developmental stagnation. Affected infants are exclusively breast-fed and the syndrome is frequently triggered by intercurrent illnesses. Affected infants respond well to treatment with vitamin B12.

CASE SERIES: We describe here a 1-year-old girl who presented with developmental stagnation and near-continuous tremulous movements of the whole body for the last 1 month. She was predominantly breast-fed and her mother was vegan. Examination showed a malnourished infant with a plump face, knuckle hyperpigmentation, hypopigmented sparse hair, pallor, mild hypotonia and a coarse generalized tremor. Her haemoglobin was 10 g/dL (normal >11), MCV was 112 fl (normal 80-96), serum B12 level was 183 pg/ml (normal 211-911); thyroid profile, metabolic screening and MRI brain was normal. She was given high dose vitamin B12 intramuscular injections and nutritional supplementation. She gradually recovered over the next month but now has mild language delay. We reviewed 50 cases seen at our institute in the last 2 years. The mean age at presentation was 11.5±3.8 months (range 7-24 months). Majority of the patients had a precipitating illness. All received injection B12 therapy; only 14% required blood transfusion for severe anaemia. All patients improved and there was no mortality.

CONCLUSION: Infantile tremor syndrome is a common disorder in Indian setting, associated with prolonged breastfeeding and vegan mothers. Early recognition of this eminently treatable disorder is key to preventing long term neurodevelopmental sequelae.

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ICNC-0689  Short- and long-term outcomes of treatment with ketogenic diet in pediatric patients with pyruvate dehydrogenase complex deficiency: The Swedish experience

Background
Ketogenic diet has traditionally been used in the treatment of refractory epilepsy but has also been tested in certain neurometabolic diseases. One of these is pyruvate dehydrogenase complex (PDC) deficiency. PDC deficiency impairs the metabolism of pyruvate to acetyl-CoA that then enters the Krebs cycle, thus limiting the mitochondrial energy production. Here, we present the Swedish experience of our pediatric patients with PDC deficiency treated with ketogenic diet.

Methods
We performed a retrospective study of patients diagnosed with PDC deficiency in Sweden during 1980-2015. These patients have been diagnosed and followed-up at the two referral centers of Sweden, at the Sahlgrenska University Hospital in Gothenburg and at the Karolinska Hospital in Stockholm. In the subgroup of patients treated with ketogenic diet, we examined the short- and long-term outcomes by applying standardized methods of data collection and validation.

Results
19 patients (7 M; 12 F) were included in this study and followed-up for a median of two years. The ketogenic diet was well tolerated in all but one patients; one patient experienced an episode of acute pancreatitis and therefore discontinued the treatment. Cognitive functioning was stable or improved in the majority of patients. Attention, mood, sleep and disease exacerbations were among the areas mostly improved.

Conclusion
The ketogenic diet is a well-tolerated treatment with positive effects on patients’ disease exacerbations and neurocognitive outcomes.

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ICNC-0617  Natural history of CLN2 disease: Quantitative assessment of disease characteristics and rate of progression
CLN2 disease is an autosomal recessively inherited storage disorder caused by deficient activity of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1). The late infantile phenotype is characterized by rapid psychomotor decline and epilepsy. Early diagnosis and exact knowledge of the natural clinical course are important for evaluating experimental therapies. Aims. (1) To analyse time of onset and character of first symptoms, (2) to provide quantitative longitudinal data on motor and language function in a cohort of 58 CLN2 patients, using an established clinical rating scale (Steinfeld et al., 2002). Results. (1) Mean age at symptom onset and diagnosis were 35 and 56 months, respectively, indicating diagnosis occurred on average 21 months after onset of first symptoms, reported as seizures (70%), loss of language (57%), or motor abilities (40%). However, a systematic review of early language development in 36 patients revealed that 83% had a significant delay in language development preceding the onset of other symptoms. (2) Our cohort showed a highly homogeneous, rapid decline in motor-language summary scores from normal (score 6) to no function (score 0), which occurred over approximately 36 months with a mean rate of decline of ~2.12 units per year. This study represents the largest set of quantitative longitudinal data on the natural history of CLN2 disease to date. Delayed language acquisition frequently precedes the onset of more typical symptoms. The course of disease is highly predictable. Our data may therefore serve as valid controls for the evaluation of effects of experimental therapies.

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ICNC-0622  Intracerebroventricular cerliponase alfa (BMN 190) in children with CLN2 disease: Interim results from a phase 1/2, open-label, dose-escalation study

Background. CLN2 disease, a rare, inherited, pediatric-onset, neurodegenerative lysosomal storage disorder caused by TPP1 enzyme deficiency, is characterized by seizures, ataxia, rapid loss of language and motor functions, blindness and early death. Cerliponase alfa (BMN 190) is a recombinant human TPP1 enzyme. This phase 1/2, multi-center, open-label, dose-escalation study evaluated the safety, tolerability and efficacy of every other week intracerebroventricular (ICV) infusions of cerliponase alfa in children with CLN2 aged 3 - 16 years.

Design. The first nine subjects were assigned to one of three cohorts in a dose escalation period (30 mg, 100 mg, 300 mg). All subjects were subsequently administered a stable dose of cerliponase alfa (300 mg) for at least 48 weeks. Efficacy was evaluated by monitoring changes in motor and language functions using a CLN2 clinical rating scale.

Results. 24 subjects (9 male, 15 female, mean age 4.5 ± 1.2 years) enrolled in the study. All subjects had adverse events (AEs), the majority were Grade 1-2 and included pyrexia, hypersensitivity and convulsion. A total of 29 serious AEs (9 considered study drug-related), occurred in 15 subjects. There were no anaphylaxis/anaphylactoid reactions, study drug discontinuations or deaths due to AEs. In contrast to the 2.18 ± 1.07 units/year decline observed in the natural history, no net loss of function (p < 0.0001) was observed in the 13 subjects who completed at least 36 weeks of treatment.

Conclusions. Enzyme replacement therapy with ICV-administered cerliponase alfa is well-tolerated and slows the progression of functional decline in children with CLN2.

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ICNC-0698  Screening for treatable inborn errors of metabolism in 500 intellectual developmental disorder patients

Background: Intellectual developmental disorders (IDD) are characterized by significant impairment of cognitive functions, affecting 2.5% of the population worldwide with significant morbidity and associated healthcare costs. Inborn errors of metabolism (IEM) currently constitute the only group of genetic defects amenable to causal therapy. Early diagnosis prevents or minimizes brain damage. Our literature review identified 89 such treatable IEM; although evidence is limited, therapies are often effective, safe, accessible.

Methods: We translated this knowledge into the TIDE diagnostic protocol: The 1st tier comprises metabolic screening tests in blood/urine with potential to identify 62% of treatable IDs. The second tier focuses on remaining disorders, requiring ‘single test per disease’ approach. A freely available App (www.treatable-id.org) supports the protocol. The protocol was implemented during 3 years in our 3 divisions in our tertiary care centre.

Results: Treatable IEMs in > 5% of 500 IDD patients, including creatine deficiencies, amino-acidopathies, serine deficiencies, metal disorders, vitamin responsive disorders, neurotransmitter diseases, organic acidurias etc. Analysis comparing these patients to those diagnosed in our hospital between 2000-2009 revealed that the TIDE protocol reduced ‘time to diagnosis’ by 6 months (range 1-50months) as well as costs of unnecessary testing (>-$1500- per patient).

Conclusions: Our protocol for treatable forms of ID has proven effective in terms of increasing the diagnostic yield and reducing costs and diagnostic delay. Treatment effects vary from improvement of cognitive development, behavior, epilepsy, psychiatric disturbances or stabilization of disease. Overall better outcomes can be achieved via standard screening for treatable conditions in IDD patients.

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ICNC-0697  Diagnosis and discovery of treatable neurometabolic diseases via an -integrated omics approach

Background: Whole exome sequencing (WES) has transformed rare disease-gene discovery and diagnosis. Translation into disease-modifying treatments is challenging, particularly for intellectual developmental disorders (IDD). Neurometabolic diseases (NMDs) are the exception however; late in 2014, 89 were known to be responsive to causal therapy, ie targeting pathophysiology at molecular or cellular level.

Methods: To uncover the genetic basis of potentially treatable NMDs, we combined deep clinical phenotyping with WES analysis and metabolomics via an unbiased semiautomated bio-informatics pipeline, in consecutively enrolled patients with IDD and an unexplained biochemical phenotype.

Results: WES analysis was completed in 59 IDD patients (from 47 families); 8 patients were excluded due to other identified etiologies. The remaining 51 patients in 42 families were predominantly single cases born to non-consanguineous Caucasian parents. (Likely) Pathogenic variants were identified in probands of 38 families, in 43 different genes: 11 genes not previously linked to a human disease phenotype, 23 disease genes with novel patient phenotypes and 9 genes with expected phenotypes. In 5 families, complex phenotypes were explained by co-existing monogenic conditions. In 18 families the diagnosis impacted management beyond genetic counseling, including the discovery of 4 novel NMDs potentially amenable to causal therapy (e.g. NANS deficiency).

Conclusions: Our diagnostic yield and discovery rate exceeded expectation, likely due to enrichment of our cohort for new NMDs and phenotypes, semi-automated bioinformatics pipeline and close collaboration between families, clinicians and scientists. In 43%, WES diagnosis allowed for precision medicine, varying from prevention and tailored symptom management, to causal therapy

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ICNC-0661  Genetic defects of thiamine metabolism: a multicenter natural history study

Objective: To describe the natural history of inherited defects of thiamine metabolism and how vitamin replacement may improve outcome. Methods: Multicenter cross-sectional study of clinical presentation, vitamin supplementation, and outcome by means of a clinical severity score (neurological sequel, brain lesions and disability for daily living activities (DLAs)). Results: 59 patients presented between 1 month and 40 years (mean±SD) (SLC19A3 (N=51): 9.2±8 years; SLC19A25 (N=4): 19.5±5 years; TPK1 (N=4): 3.6±years) with acute encephalopathy (69%), dystonia (69%), dysarthria/anarthria (61%), dysphagia (59%), spasticity (59%), seizure (47%) and ophthalmpoplegia (23%). Identified phenotypes were: striatal necrosis and peripheral neuropathy (SLC19A25), biotin-thiamine responsive basal ganglia disease (SLC19A3, N=32), Leigh syndrome (SLC19A3, N=17; TPK1, N=4). Neuroimaging demonstrated lesions in caudate/putamen (76%), thalamus (64%), subcortical white matter (52%), cerebellum (33%) and spinal cord (21%). Flair hypointensity in dentate nuclei was seen in 2/4 TPK1-patients. Time frame from disease onset to thiamine and biotin supplementation was 7.5±857 days. On follow-up, 75% of SLC19A3-patients died in the non-treated/late-treated group, whereas early-treated patients did not suffer any decompensation. Clinical severity score was lower in early-treated (<4wk, N=19) than in late-treated patients (>4wk, N=7). Despite early treatment, SLC19A3-patients had difficulties in speech (78%), dressing/hygiene (47%), walking (47%), writing (47%), and feeding (31%). SLC25A19-patients showed a partial improvement with thiamine but encephalopathic episodes relapsed. TPK1-patients were stable on thiamine and ketogenic diet. The most frequent mutation in SLC19A3 was c.1264A>G (54%), and three novel mutations (c.157A>G, c.91T>C, and c.280T>C) were identified. All SLC25A19 patients were homozygous for c.373G>A. All TPK1 patients showed missense mutations. Conclusions: Early treatment of SLC19A3-deficient patients has a strong impact on outcome, although neurological sequel and disability are common in survival patients. Keywords: SLC19A3, SLC19A25, TPK1; Leigh syndrome; mitochondrial disease

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