MOVEMENT DISORDERS

FP25

MOVEMENT DISORDERS IN THE NEURONAL CEROID LIPOFUSCINOSES

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Introduction: The Neuronal Ceroid Lipofuscinoses (NCLs) comprise over 10 different inherited, fatal lysosomal storage diseases of childhood. Caused by mutations in different genes, the NCLs have several features in common including vision loss, epilepsy, progressive dementia, and motor problems. Some studies suggest that NCL forms differ by type of movement disorder, but this has not been evaluated quantitatively.

Methods: The Unified Batten Disease Rating Scale was used to assess age at onset of movement disorders and type of movement disorder. The scale includes assessment of tone, bradykinesia, tremor at rest and with action, chorea, myoclonus, tics, dystonia, dysmetria, postural instability, and gait disorder. Parkinsonism was rated by adding the tone, bradykinesia, tremor at rest, postural instability, and gait scores. Annual evaluations were performed over a 12-year period. Change in symptom severity over time was determined.

Results: Evaluations were performed in 93 individuals with CLN3 mutations (Juvenile NCL) and 12 individuals with CLN2 mutations (Late Infantile NCL). The mean age at onset of motor impairment was 11.3 years in CLN3 and 3.5 years in CLN2. Parkinsonism was the predominant movement disorder in CLN3 disease whereas myoclonus and ataxia were predominant in CLN2 disease.

Conclusion: CLN2 and CLN3 manifest different types of movement disorder that localize to different systems in the brain, suggesting selective vulnerability of different neuron types in different forms of NCL. Our findings have important implications for understanding the pathobiology and for targeting therapy in the different forms of NCL.

FP26

COPROPHENOMENA ARE ASSOCIATED WITH HIGH CLINICAL IMPACT IN TOURETTE SYNDROME

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Introduction. Tourette Syndrome (TS) is defined by chronic motor and phonic tics with onset during childhood. Although the definition and diagnostic criteria do not include coprophenomena (obscene utterances or gestures), public perception of TS often includes them. The precise prevalence of coprophenomena in TS is not known, nor is it known whether coprophenomena are associated with a more severe phenotype.

Methods: We analysed cross-sectional data obtained from a large prospective 2-site sample of 177 children ages 5-17 years with TS. Key clinical features assessed included tics (Yale Global Tic Severity Scale), ADHD (Swanson, Nolan and Pelham-IV), OCD (Child Yale-Brown Obsessive-Compulsive Scale) and overall function (Children's Global Assessment Scale).

Results: 17 TS subjects (9.6%) had at least one coprophenomenon at enrolment. Subjects with coprophenomena (TS+copro) had higher YGTSS total tic score (36.9 +/- 7.5) and impairment score compared with those without coprophenomena (TS–copro) (20.3 +/- 8.6) ($p < 0.01$). YGTSS item analysis showed that TS+copro subjects had worse scores in every domain (number, frequency, intensity, complexity, interference) except phonic tic frequency. TS+copro subjects had greater hyperactive-impulsive symptoms, but no difference in inattentive-distractible or OC symptoms compared to the TS-copro group. The TS+copro group has worse overall function (median CGAS = 51) than did the TS-copro group (median CGAS = 60) ($p < 0.01$).

Conclusion: Coprophenomena are infrequent in TS, but are associated with worse overall tics, tic-related impairment, hyperactivity-impulsivity, and overall function. The presence of coprophenomena may represent a more severe phenotype in Tourette syndrome.

FP27

PEDIATRIC DYSTONIA: DBS AND DIVERSITY IN DIENCEPHALIC DYSFUNCTION

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Deep-brain stimulation (DBS) use in pediatric centers began in 2007, ten years after use in adults proved efficacious and safe in treating movement disorders. Specific challenges in using DBS to treat pediatric dystonia include careful patient selection, cooperation in intraoperative clinical assessment and pediatric adjustments to microelectrode recording. We present our experience over four years in selection, treatment success, and continuing medical management of a series of patients offered DBS for dystonia of various etiologies. After rigorous review at the Texas Children's Hospital Spasticity and Dystonia Multidisciplinary Review Committee and Baylor-wide DBS Consensus conferences, approximately 30 children have been offered DBS at our center. 12 patients with medically-intractable primary or secondary dystonia, between 6-20 years old, have undergone the procedure. Their condition results from broad underlying pathologies: 4 have primary genetic etiologies (2 pantothenate kinase deficiency, 1 DYT1, and 1 macrodeletion including 3q29), 5 have cerebral palsy (3 term HIE, 1 PVL from extreme prematurity, and 1 intrauterine stroke), and 1 patient each had stroke, necrotizing ADEM, and tardive dyskinesia after risperidone. Treatment goals individualized to presurgical function and symptoms were used to evaluate outcomes. Most have improved symptoms, reduced medications, and increased independence. Children with HIE and the one with a macrodeletion had less favourable results. 1 patient had ICH, 2 developed infection requiring implant removal, and 3 others underwent revision for improved symptom control. Despite diverse pathologies, and a moderate degree of complications in paediatric dystonias treated with DBS, this paper reviews improvement in treating static and progressive neurological diseases that would otherwise be intractable.

FP28

METHODOLOGY OF APPROACHES TO CHILDHOOD HEREDITARY ATAXIAS

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Childhood hereditary ataxias are a degenerative and extremely heterogeneous group. They are classified in various ways in the literature (1-3). While a rare group may have a possibility of treatment, specific diagnosis is especially important for genetic counseling. 196 case files suggesting cerebellar ataxia findings were selected from 30,000 patients admitted to our clinic between September 2010 and February 2013. Files included in this study were evaluated according to age, sex, clinical characteristics, patient and familial history, head circumference, cognitive capabilities and other neurological findings, labaratuvary findings and cranial imaging findings. Based on the recorded information, and undiagnosed group and the diagnosed group were established, referred to as groups I and II respectively. Group I and Group II consisted of 157 (81.1 %) and 39 (19.9 %) patients, respectively. Group II differed from group I in terms of absence of deep tendon reflexes, polyneuropathic changes at electromyelography, pathological visual evoke potential, electroretinogram and normal mental and motor development milestones before diagnosis ($p< 0.005$). In contrast, the presence of cerebellar atrophy and/or other abnormalities in MRI finding made diagnosis more difficult ($p <0.01$). Accompanying epilepsy and mental retardation did not lead to a difference between the groups. There was also no difference between the groups in terms of sex, familial history, mental retardation, vitamin B12 and E, epilepsy, basal metabolic tests, organomegaly or brain auditory evoked response (BAER) ($P>0.05$). The presence of neuropathy, VEP, ERG abnormalities, normal mental motor developmental milestones before the diagnosis and consanguinity were the factors that facilitate the diagnosis.

FP29

PLA2G6 GENE MUTATIONS CAUSE EVOLVING SPINOCEREBELLAR ATAXIA INFLUENCED BY THE GENOTYPE

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Introduction: Mutations in ***PLA2G6*** gene have variable phenotypic outcome including infantile neuroaxonal dystrophy, atypical neuroaxonal dystrophy, idiopathic neurodegeneration with brain iron accumulation (NBIA) and Karak syndrome. The cause of this phenotypic variation is so far unknown which impairs both genetic diagnosis and appropriate family counselling.

Methods: Clinical, electrophysiological, neuroimaging, histologic, biochemical and genetic characterization of 11 patients, from 6 consanguineous families, who were followed for a period of up to 17 years.

Results: Cerebellar atrophy was constant and the earliest feature of the disease preceding brain iron accumulation, leading to the provisional diagnosis of a recessive progressive ataxia in these patients. Ultrastructural characterization of patients' muscle biopsies revealed focal accumulation of granular and membranous material possibly resulting from defective membrane homeostasis caused by disrupted PLA2G6 function. Enzyme studies in one of these muscle biopsies provided evidence for a relatively low mitochondrial content. Genetic characterization of 11 patients led to the identification of six underlying ***PLA2G6*** gene mutations, five of which are novel. Importantly, by combining clinical and genetic data we have observed that while the phenotype of neurodegeneration associated with ***PLA2G6*** mutations is variable in this cohort of patients belonging to the same ethnic background, it is influenced by the genotype, considering the age at onset and the functional disability criteria.

Conclusion/Discussion: Testing for ***PLA2G6*** mutations is indicated in childhood-onset ataxia syndromes, if neuroimaging shows cerebellar atrophy with or without evidence of iron accumulation.

FP30

DEVELOPMENTAL STAGES OF BASAL GANGLIA REFLECTS MOVEMENT DISORDERS IN CHILDHOOD

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Introduction: In movement disorders occurring in developmental brain particular symptoms appear along with maturation of the involved neuronal systems. Among striatal pathways of the basal ganglia, the direct pathway matures earlier than the indirect pathway. As for the output pathway the descending pathway attains maturational levels by 5 years while the ascending pathway around 15 years.

Methods: The pathophysiologies of dopa-responsive dystonia (DRD) and Tourette syndrome (TS) were evaluated based on the developmental course the basal ganglia and the nigrostriatal dopamine neuron (NS-DA).

Results: Among DRD, postural type of Segawa disease (SD) caused by deficiency of tyrosine hydroxylase in the terminals of the NS-DA neuron develops postural dystonia in childhood through the direct pathway and the descending output. In action type of SD dysfunction of the DA neuron innervating to the subthalamic nucleus in the indirect pathway causes dystonic movement by disfacilitation of the descending output in late childhood and by disfacilitation of the ascending pathways focal or segmental dystonia and parkinsonism in late childhood to adulthood. TS is caused by deficiency of DA in the substantia nigra. Development of DA receptor upward regulation induces simple tics in early childhood through the direct pathway and produces complex tics and obsessive compulsive disorders in late childhood through the ascending pathways

Conclusion: Thus, to evaluate the symptoms of the movement disorders of children with correlation of the ages of the developmental courses of DA neuron and the basal ganglia makes it possible to clarify pathophysiologies of these disorders.

FP31

PHENOTYPICAL AND MOLECULAR CHARACTERIZATION OF PATIENTS WITH NEURODEGENERATION WITH BRAIN IRON ACCUMULATION (NBIA) DUE TO *PANK2* GENE MUTATIONS

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Introduction: Childhood NBIA has broad clinical and genetic heterogeneity. Pantothenate kinase-associated degeneration due to ***PANK2*** mutations account for 50% of childhood NBIA.

Methods: This retrospective study analysed patients genetically proved with ***PANK2*** mutations from a single centre.

Results: Seven patients with ***PKAN2*** mutations were diagnosed from 1995 to 2012. Four (57%) had classical presentation with mean symptoms' onset at 5.5y; three (43%) had late-onset disease with mean onset at 15.6y; two patients within the late-onset group are siblings. Interestingly, five patients (71.4%) had cognitive/behavioural issues before the extrapyramidal features. The most common movement disorder was dystonia all patients (100%). Although patients tend to have fluctuating or focal dystonia (71.4%), all of them evolved to generalized dystonia. Within the late-onset group, oromotor/tongue abnormal movements were seen in three (100%) and parkinsonism in two (66.7%). Other movement disorders noticed were myoclonus, tremor, choreoathetosis, and ballismus. Patients with classical presentation were wheelchair bound after ±2.5 y of the disease onset. In addition, they required G-tube after ±2.5 y, and died after ±5 y. In the late-onset group, two are still ambulant (66.7%) and they are all alive after ±11 y after the symptoms' onset. We found varied mutations in different exons (1, 2, 6 and 7) of the ***PANK2*** gene. The siblings share the same genotype (1231G A), previously described as one of the most common mutations. One patient had a new mutation (c.809 T C p.L270P) in homozygous. Only one patient presented with classical MRI "eye of the tiger" sign; but eventually four developed it. Substantia nigra and red nucleus were also affected.

Conclusions: Understanding the clinical course and prognosis of this rare disorder is crucial to improve health care to affected children. Although small, our study delineates clinical, genetic and radiological findings of this rare condition.

FP32

AN OPEN LABEL CLINICAL PILOT STUDY OF RESVERATROL AS A TREATMENT FOR FRIEDREICH ATAXIA

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Introduction: Friedreich ataxia (FRDA) is due to a triplet repeat expansion in the ***FXN*** gene, resulting in deficiency of the mitochondrial protein frataxin. Resveratrol is a plant-derived polyphenol. It increased frataxin expression in cellular and mouse models of FRDA, and has anti-oxidant properties.

Methods: This trial evaluated the effect of two different doses of resveratrol on lymphocyte frataxin levels over a 12-week period in individuals with FRDA. Secondary aims evaluated the effect on ***FXN*** mRNA, oxidative stress markers and clinical measures of disease severity. Safety and tolerability were studied.

Results: 24 participants completed the study; 12 received low-dose resveratrol (1g daily) and 12 high-dose resveratrol (5g daily). Lymphocyte frataxin levels did not change in either dosage group [low dose group change: 0.08 pg/µg protein (95% CI -0.05, 0.21, p=0.21); high dose group change: 0.03 pg/µg protein (95% CI -0.10, 0.15, p=0.62)]. Improvement in ataxia was evident in the high-dose group (change in International Cooperative Ataxia Rating Scale, ICARS -1.9 points, 95% CI -3.1, -0.8, p=0.004) but not the low-dose group (change in ICARS -0.3 points, 95% CI -3.2, 2.6, p=0.80). Significant improvements in hearing and speech were demonstrated in the high-dose group. A significant decrease in the oxidative stress marker plasma F2-isoprostanes occurred in the high-dose group. No serious adverse events were recorded. Gastrointestinal side effects were a common, dose-related adverse event.

Conclusions: This trial provides evidence for high-dose resveratrol as a potential disease-modifying therapy for FRDA. A placebo-controlled trial is required to assess its benefits further.

FP33

MOVEMENT DISORDER PHENOMENOLOGY HELPS DIFFERENTIATE NMDAR ENCEPHALITIS FROM AUTOIMMUNE BASAL GANGLIA ENCEPHALITIS

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Introduction: Movement disorders are a dominant clinical feature of NMDAR encephalitis. They are also observed in a group of patients with autoimmune basal ganglia (BG) encephalitis that have recently been shown to be associated with antibodies to the Dopamine-2 receptor. We aimed to explore the movement disorder phenomenology in these entities.

Methods: Videos of 31 patients with NMDAR encephalitis (n=10), basal ganglia encephalitis (n=12) and Sydenham's chorea (controls, n=9) (SC) were rated by 4 movement disorder neurologists. The raters were blinded to the diagnoses. Movement disorder phenomenology was rated as primary movement disorder, other movement disorders and any additional comments were recorded. A moderator ensured blinding and consensus with use of standard terminology.

Results: Patients with SC had chorea (n=9), dystonia (n=2) and ballism (n=1). Patients with NMDAR encephalitis had stereotypy (n=8), dystonia (n=6), chorea (n=4), tonic or clonic perseveration (n=5), akinesia (n=1), tremor (n=1) and ballism (n=1). BG encephalitis patients had dystonia (n=7), akinesia (n=5), tremor (n=4) and chorea (n=3).

Conclusion: The spectrum of movement disorders in NMDAR encephalitis is wide but dominated by stereotyped movements and dystonia. BG encephalitis can be differentiated by the dominant akinesia that accompanies dystonia and sometimes chorea and tremor. Clinical differentiation of the disorders can aid diagnostic workup and management.

FP34

FAVOURABLE RESPONSE TO ACETAZOLAMIDE IN A CASE OF GLUT-1 DEFICIENCY

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Introduction: Glut 1 deficiency syndrome (GLUT1-DS) results from mutations in the SLC2A1 gene. Recently, the clinical spectrum has been broadened to include developmental delay, epilepsy and/or movement disorders. The diagnosis can be confirmed by molecular analysis and ketogenic diet remains the therapy of choice. Acetazolamide has been reported as an alternative therapy for patients with movement disorders.

Case report: An 18 month-old, previously healthy boy, presented with paroxysmal events that included eye-movements, ataxia and weakness. He had monthly episodes, each lasting from minutes to one hour. There was no positive family history and his neurodevelopment was normal.

Results: Neurological examination revealed no abnormalities in between episodes. Biochemical and metabolic tests revealed normal results. Brain MRI and electroencephalogram were normal. The cerebrospinal fluid showed mild hypoglycorrachia (39 mg/dl), with a 0, 49 CSF-to-blood glucose ratio. Molecular studies identified a missense heterozygote mutation C. 119G>A (p.R400H) in the SLC2A1 gene. Oral acetazolamide was started, resulting in immediate and complete disappearance of the attacks. He has currently been symptom free for 12 months.

Conclusion: Glut 1 deficiency syndrome should be suspected in the presence of paroxysmal movement disorders and ataxia, even in the absence of epilepsy. Milder phenotypes, especially those characterized by movement disorders can be associated with CSF-to-blood glucose ratios up to 0, 4. Acetazolamide could be an alternative therapy for patients with mild forms of Glut 1 deficiency syndrome with movement disorders.

FP35

ATP1A3 MUTATIONS AND GENOTYPE-PHENOTYPE CORRELATION OF ALTERNATING HEMIPLEGIA OF CHILDHOOD IN CHINESE PATIENTS

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Introduction: Alternating hemiplegia of childhood (AHC) is a rare and severe neurological disorder. It is characterized by paroxysmal abnormal ocular movements, dystonia, alternating hemiplegia, and psychomotor developmental delay. Some AHC patients associate with epilepsy. ATP1A3 was recently identified as the causative gene of AHC. Here we report the first genetic study of AHC in Chinese cohort.

Methods: Fifty-two Chinese patients with AHC were recruited in this study. Genomic DNA was extracted from peripheral blood samples. Mutations of ATP1A3 were analysed using PCR amplification and DNA sequencing.

Results: ATP1A3 mutations were detected in 95.8% of typical AHC patients. At least 91.1% were de novo. Four atypical AHC patients of late onset were also mutation-positive, suggesting the need for testing ATP1A3 mutations in atypical cases. Totally, 12 novel missense mutations (T370N, G706R, T771N, T771I, S772R, L802P, D805H, M806K, P808L, I810N, L839P and G938R) were identified in our study. Genotype-phenotype correlation analysis showed that patients with quadriplegia were more likely to carry D801N and less likely to carry E815K mutation, whereas patients with epilepsy were more likely to carry E815K mutation. Forty-two patients were treated with Flunarizine. 29 (69%) of whom showed reduced severity, duration, or frequency of hemiplegic attacks. We found no correlation between treatment effects and the three mutation hotpots (D801N, E815K and G947R).

Conclusions: ATP1A3 is also the major pathogenic gene of AHC in Chinese patients. Most mutations are de novo. Some novel mutations have been found in Chinese patients. Mutation E815K is correlated with the phenotype of epilepsy.

FP36

CLINICAL AND GENETIC ANALYSIS OF EIGHT IDIOPATHIC CASES OF PAROXYSMAL DYSKINESIA

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Aim: To analyse and investigate the clinical features, genes and therapy of paroxysmal kinesigenic dyskinesia (PKD), paroxysmal nonkinesigenic dyskinesia (PNKD) and paroxysmal exercise-induced dyskinesia (PED).

Method: The phenotypes of eight sporadic cases of paroxysmal kinesigenic dyskinesia (PKD) were analysed. Genomic DNA was extracted from peripheral blood lymphocytes of five patients. The coding regions and flanking introns of the PRRT2, MR1 and SLC2A1 genes were screening for mutations using PCR and direct DNA sequencing or array-based Comparative Genomic Hybridization (aCGH). The clinical manifestations, clinical courses, investigations, treatments and outcomes of paroxysmal kinesigenic dyskinesia patients were analysed.

Results: In eight PD patients there were four PKD patients, two PNKD patients and two PED patients. No mutations were identified in five PD patients. Two PKD patients who had tried oxcarbazepine had a favourable response and one responded well to clonazepam. A case of PNKD responded well to clonazepam. A case of PED responded well to ketogenic diet.

Conclusion: This study reported evidence of both clinical and genetic heterogeneity in PD. The choice of specific treatment should be based on different phenotype