ICNC-0535  Diagnostic approach for pediatric patients with Dystonia

Introduction. There are many possible aetiologies of dystonia of childhood and diagnostic workup is often challenging. On 2013, an international consensus proposed a new classification of dystonia looking forward to improve diagnostic strategies. The aim of this study was to review the diagnostic approach for patients with dystonia referred to a pediatric tertiary rehabilitation center using the scheme of the new classification.

Methods. Clinical features were analyzed by age at onset, body distribution, temporal pattern, coexistence of other movement disorders and other neurological or systemic manifestations. Neuroimaging, laboratory and genetic tests provided by the original health institutions were also reviewed. Results. 69 patients (37 males) were included. Ages of onset was in infancy in 63 patients (91.3%); in childhood in 5 (7.2%) and in adolescence in 1 patient (1.5%). Diagnoses were: cerebral palsy (CP) in 57 (82%), progressive encephalopathies in 8 (12%), traumatic brain injury in 2 (3%), stroke in 2 (3%). Neuroimaging were pathological in 37 (57%), normal in 18 (26%) and were not carried out in 14 (17%). Analyzing the 57 patients diagnosed with CP, 13 had no risk factors. Of these 13 patients, 5 had no neuroimaging studies done and, in the other 8, neuroimaging was normal.

Discussion. The diagnostic approach of the new classification may be useful for a more rigorous characterization of pediatric patients with dystonia. Systematic review of these patients with dystonia highlights some inconsistencies in the diagnosis of CP. Other diagnosis should be considered in unexplained CP, especially those of a treatable disorder.

Alfredo Cerisola *(1,2);Federico Baltar(1);Eugenia Chaibun(1);Ana Nunez(1,2);Rosina Rios(2);
(1)Cátedra de Neuropediatría, Facultad de Medicina, UDELAR;(2)Centro de Rehabilitación Infantil, Teletón. Montevideo, Uruguay;
ICNC-0546 Psychiatric comorbidities in children with Dystonia

Introduction
Psychiatric comorbidities have been comprehensively described in children with Tourette Syndrome (TS) however little is known about the psychiatric and behavioural problems that affect children with genetic or acquired dystonia. Improved understanding of the basal ganglia and its role in behavioural pathways imply a plausible association between paediatric dystonia and psychiatric diagnoses. We measured the prevalence of psychiatric co-morbidities in children with dystonia (5-16 years) and compared this prevalence to children with (TS) and a community cohort.

Method
We recruited children between 5 and 16 years with dystonia or TS who attended The Children’s Hospital at Westmead between 2011 and 2014. All children were screened for psychiatric comorbidity by participating in the Development and Wellbeing Assessment (DAWBA).

Results
The families of 46 patients with dystonia and 66 patients with TS completed the DAWBA. The dystonia cohort included children with dystonic cerebral palsy, tyrosine hydroxylase deficiency, 6PPTS deficiency, dopa responsive dystonia, dystonia secondary to encephalitis or vascular injury, myoclonus dystonia and dystonic tremor.
15/46 children with dystonia (32%) and 26/66 children with TS (39%) were found to have a psychiatric comorbidity.
Children with dystonia had a three-fold increase in psychiatric diagnoses compared to known community cohort rates of 9.5%. Children with TS had a four-fold increase when compared to the healthy population.

Conclusion
Children with dystonia are more than three times likely to have a co-existing diagnosis than children in a healthy population. Rates of psychiatric comorbidity are only marginally lower in dystonia than in TS.

Lorentzos, MS*(1); Heyman I(1); Baig B(1); Dossetor D(1); Marecos C(1); Waugh MC(1); Evans R(1); Burns J(1); Menezes M(1); Mohammad SS(1); Grattan-Smith P(1); Kurian MA(1); Dale RC (1)

(1) The Children’s Hospital at Westmead; The University of Sydney, South London; Maudsley NHS Foundation Trust; Great Ormond Street Hospital for Children NHS Foundation Trust, London UK
ICNC-0536  DNAJC6 mutations in childhood onset Parkinsonism-Dystonia

Early-onset parkinsonism is characterized by the development of tremor, bradykinesia, hypomimia and cogwheel rigidity in individuals usually under 20 years of age. Using autozygosity mapping and whole exome sequencing techniques, we identified homozygous nonsense DNAJC6 mutations in 6 individuals (3 families) with a complex neurological syndrome. Patients presented with childhood neurodevelopmental delay and epilepsy, and developed progressive parkinsonism-dystonia in late childhood/early adolescence, with loss of independent ambulation in mid-adolescence. Some had a favourable clinical response to L-dopa and other dopaminergic agents. Routine diagnostic testing identified low cerebrospinal fluid levels of the dopamine metabolite, homovanillic acid. Furthermore, strikingly abnormal DaTscan imaging was evident in a number of patients. DNAJC6 encodes the neuronally expressed protein auxilin, which mediates the physiological disassembly of clathrin lattices from endocytosed synaptic vesicles. Loss-of-function mutations in DNAJC6 therefore lead to impaired clathrin uncoating. Our data suggests disrupted neuronal vesicular recycling of dopamine and/or striatonigral neurodegeneration as disease mechanisms. To date, DNAJC6-related parkinsonism has only rarely been reported in the literature, and our cohort enhances understanding of the genotypic and phenotypic disease spectrum.

Elisenda Cortes-Saladelafont*(2); Esther Meyer(1); Pichet Termsarasab(3); Joanne Ng(1,4,5); Simon J.R. Heales(6,7); Simon Pope(6,7); Lorenzo Biassoni(8); Barbara Csányi(1,5); Jonathan Hill(9); Karl Rakshi(10); Helen Coutts(10); Sandeep Jayawant(11); Rosalind Jefferson(12); Deborah Hughes(13); Detelina Grozeva(14,15); F. Lucy Raymond(14,15); Christian De Goede(16); Àngels García-Cazorla(2); Toni S. Pearson (3); Manju A. Kurian(1,5)

(1)Molecular Neurosciences, Developmental Neurosciences Programme, UCL- Institute of Child Health, London, UK;

(2)Department of Paediatric Neurology, Hospital Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Spain;

(3)Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, USA;

(4)Gene Transfer Technology Group, UCL-Institute for Women’s Health, London, UK;

(5)Department of Neurology, Great Ormond Street Children’s Hospital, NHS Foundation Trust, London, UK;

(6)Clinical Chemistry, Great Ormond Street Children’s Hospital, NHS Foundation Trust, London, UK;

(7) Neurometabolic Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK;

(8) Department of Nuclear Medicine, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK;

(9) Department of Nuclear Medicine and Imaging, Lancashire Teaching Hospitals, NHS Foundation Trust, Preston, UK;
ABSTRACT BOOK PLATFORM

Thursday 5 May
Movement disorders

(10) Department of Paediatrics, East Lancashire Hospital Trust, Lancashire, UK;

(11) Department of Paediatric Neurology, John Radcliffe Hospital, Oxford, UK;

(12) Department of Paediatrics, Royal Berkshire Hospital, Reading, UK;

(13) Department of Molecular Neuroscience and Reta Lila Weston Laboratories, Institute of Neurology, Queen Square, London, UK;

(14) Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Cambridge, UK;

(15) UK10K Project, Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK;

(16) Department of Paediatric Neurology, Royal Preston Hospital, Lancashire Teaching Hospitals, NHS Foundation Trust, Preston, UK
Segawa disease; clinical heterogeneity

[Purpose] Segawa disease (SD) is an autosomal dominantly inherited dopa responsive dystonia caused by heterozygous GCH1 gene mutation. This presents the clinical heterogeneity of SD.

[Method] Seventy-eight SD cases were analyzed.

[Result] SD typically starts in childhood with leg postural dystonia. SD is clinically classified into two types; postural (P) type and action (A) type. There were 31 P-type and 47 A-type. Mean ages of onset were; P-type 6.4±3.0 years, and A-type 7.8±3.6 years, excluding three cases whose onset were 28, 35 and 58 years. P-type remains the postural dystonia throughout the course. A-type showed late onset cases, and focal or segmental dystonia. Neuropathological data of a P-type died at 90 years showed normal substantia nigra. A father of one A-type case with the same mutation started with parkinsonism at 58 years. The PET scan was not compatible with Parkinson disease at onset, but the parkinsonism progressed and the DAT scan was compatible with Parkinson disease at 72 years. GCH1 mutation was found in 60 cases (32 families), but was not found by direct sequence analysis in 18 cases, who were diagnosed by clinical and biochemical evaluations. There were no definite clinical-molecular correlation between P-type and A-type. Non-motor symptoms of SD include depression. Depression was observed more in A-type (9/47) than in P-type (3/31).

[Conclusion] Age-related specific descending and ascending output pathways in basal ganglia involving direct and indirect pathways play roles in the pathophysiology of SD, and result in the specific clinical characteristics.

Yoshiko Nomura*(1)
Neurlogical Clinic for Children, Tokyo, Japan(1)
ICNC-0553  The clinical spectrum of stereotypic movement disorders (SMD) in typically developing children and adolescents – a video and record review

Introduction: SMDs are common in typically developing children and may be misdiagnosed. Correct diagnosis prevents unnecessary investigations and treatment. Few large cohorts exist.

Methods: Review of videos and records in a pediatric movement disorders referral center.

Results: 106 typically developing children, aged 5mo-16y (5.45±3.52y, median 5.2y) were diagnosed with SMD. 51.8% were ≥5y, 10.3% were ≥10y. Prior diagnoses included tics, chorea, epilepsy, dystonia or psychogenicity. Semiology included complex motor stereotypies (CMS) (67.9%), head nodding/body rocking (14.2%), infantile self-stimulation (8.5%), shudder attacks (2.8%), and mannerisms (7.5%). SMDs started at 18±17.9mo (median 12mo, range 1mo-11y). In 72 children with CMS, limb movement included hand flapping (52.7%), posturing (48.6%), arm twirling (41.7%) and finger wiggling (37.5%). Additional CMS features included facial grimacing (63.9%), vocalization (34.7%), leg (20.8%) or eye (20.8%) movements, pacing (18.1%) or jumping (12.5%). SMD occurred with excitement (57.5%, CMS-81.9%), boredom (40.6%, CMS-27.8%) or nonspecified times (14.1%, CMS-11.1%). Episodes lasted seconds (mostly CMS) to several minutes (mostly nodding/rocking or self-stimulation). Family history noted in 19.8%/6.6%/4.7% (1st /2nd/multiple relatives), Neurodevelopmental findings (in 35.8%) included dyspraxia (20.7%), mild language (17.0%) or motor (5.7%) delay, ADHD (15.1%), nonautistic social difficulties (12.2%), sensory modulation (9.4%), anxiety (3.8%), OCD (2.8%), learning disabilities (2.8%). Of 26 children followed for 6mo-5yrs, movements persisted in 65.3%. Children tended to dislike their movements when social embarrassment ensued.

Conclusion: The spectrum of SMDs is vast and needs detailed description. Neurodevelopmental comorbidities occur. SMDs may start late, persist into adolescence and cause social embarrassment. Different presentations and prognosis relate to different SMDs.

Rotstein, M.(1); Fattal-Valevski, A.(1);
(1)Tel Aviv Sourasky Medical Center, Israel;
ICNC-0558  GNAO1 – expanding a new phenotype - severe hyperkinetic movement disorder with episodic-life threatening exacerbations responsive to deep brain stimulation

Introduction: De novo GNAO1 mutations have been described in patients with epileptic encephalopathy and patients with global developmental delay and a movement disorder. 1,2,3 We report 3 patients with de novo GNAO1 mutations with a progressive hyperkinetic movement disorder with episodes of life threatening exacerbations responsive to Deep Brain Stimulation (DBS).

Methods: Three patients were identified.

Results: All three patients had a history of global delay, hypotonia and significant speech and language impairment. A background movement disorder (chorea and dystonia) was noted in all, with severe exacerbations of movements, often triggered by febrile illness. In all patients the movement disorder progressively worsened, with life threatening exacerbations requiring admission to intensive care, and was resistant to a range of medications. Investigations did not reveal a cause, and MRI was non-contributory. Each patient had DBS inserted (age 6, 11 and 13 years respectively), with an immediate improvement in the background movement disorder, and improved quality of life. At follow up (mean 11 months), all patients showed a sustained improvement. In all patients, a de novo GNAO1 mutation was found.

Conclusion/Discussion: In a subgroup of patients with GNAO1 mutations there exists a distinct syndrome: 1. Hypotonia, and global delay having a motor and language emphasis, 2. A movement disorder that shows progression over time, with severe exacerbations often related to illness, and responsive to DBS. Identification of this patient subgroup is important as DBS should be considered early given its effectiveness. 1. Nakamura K et al, Am J Hum Genet 2013; 93: 496–505. 2. Saitsu et al., European Journal of Human Genetics 2015; 24(1):129-34. 3. Kulkarni et al, J of Child Neurol 2015; Jun 9.

Waak, M.(1)*;Mohammed, S.(2);Copeland, L.(3);Sinclair, K.(1);Dale, R.(2);Silburn, P.(4);Coyne, T.(5);McGill, J.(6);O’Reagan, M.(7);Lin, J.P.(8);Symonds, J.(9);Grattan-Smith, P.(10);Malone, S.(1); (1)Lady Cilento Children’s Hospital- Brisbane, Neurosciences, Brisbane, Australia;(2)Westmead Children’s Hospital, Paediatrics & Child Health– Children’s Hospital- Westmead, Sydney, Australia;(3)Lady Cilento Children’s Hospital- Brisbane, Rehabilitation Services, Brisbane, Australia;(4)Asia-Pacific centre for Neuromodulation, Neurology, Brisbane, Australia;(5)Asia-Pacific centre for Neuromodulation, Neurology-Neurosurgery, Brisbane, Australia;(6)Lady Cilento Children’s Hospital- Brisbane, Metabolic and Neurosciences, Brisbane, Australia;(7)Glasgow Royal Infirmary for Sick Children, Neurosciences, Glasgow, United Kingdom;(8)Evelina Children’s Hospital, Neurosciences, London, United Kingdom;(9)Royal Hospital for Sick Children New South Glasgow University Hospitals, Fraser of Allander Neurosciences Unit, , United Kingdom;(10)Children's Hospital- Westmead, Neurosciences, , Australia;
ICNC-0562  **Delineation of the movement disorder spectrum in FOXG1-Related Disease**

Introduction

Patients with FOXG1 mutations present with acquired microcephaly, neurodevelopmental delay and epilepsy. Affected children frequently also manifest a movement disorder which is not well delineated to date. Methods We identified patients with FOXG1 mutations seen in tertiary movement disorder clinics or epilepsy and genetic services. In order to characterise the abnormal involuntary movements, we performed direct clinical examination or retrospectively reviewed medical records, clinical investigations, neuroimaging and available video.

Results

28 patients with FOXG1 mutations were identified, with full characterisation of motor phenotypes in 25. A wide variety of early-onset (< 1 year of life) movement disorders were identified in all patients, with choreo-athetosis (22/25), orofacial dyskinesias (20/25) and dystonia (19/25) most commonly present. Abnormal involuntary movements were severe, disabling and progressive with time in many cases but status dystonicus was not reported. 4 patients with missense mutations achieved independent ambulation, spoken language and were normocephalic, presenting with a significantly milder phenotype than that previously reported in patients with classical FOXG1 disorder. Hyperkinetic involuntary movements were a major clinical feature in these patients. Of the symptomatic treatments targeted to involuntary movements, most did not emerge as clearly beneficial, although levodopa and tetrabenazine were beneficial in 4/9 and 2/3 cases, respectively.

Conclusion

Abnormal involuntary movements are a major feature of FOXG1 disorder. Our study delineates the spectrum of movement disorders associated with FOXG1 mutations, also confirming an expanding clinical phenotype. Symptomatic treatment may be considered for severe or disabling cases.

Papandreou*, A.(1)*;2; Schneider*, R.B.(3); Augustine, E.F.(3,4); Ng, J.(1,5); Mankad, K.(6); Esther Meyer(1); Amy McTague(1); Adeline Ngoh(1); Cheryl Hemingway(2); Robert Robinson(2); Sophia M Varadkar(2); Maria Kinali(7); Vincenzo Salpietro(7); Peggy O’Driscol(8); Nigel Basheer(9); Richard I Webster(10,11); Shekeeb S Mohammad(1,12); Shpresa Pula(13); Marian McGowan(14); Natalie Trump(15); Lucy Jenkins(15); Frances Elmslie(16); Richard H Scott(17); Jane A Hurst(17); Belen Perez-Duenas(1,18,19); Alex Paciorkowski(3,20); Manju A Kurian(1,2);
(1)University College London- Institute of Child Health, Developmental Neurosciences Programme, Molecular Neurosciences, London, UK; (2)Department of Neurology, Great Ormond Street Hospital for children NHS Foundation Trust, London, UK; (3)Department of Neurology, University of Rochester Medical Center, Rochester, NY; (4)University of Rochester Medical Center, Center for Human Experimental Therapeutics; (5)University College London- Institute for Women’s Health, Gene Transfer Technology Group; (6)Great Ormond Street Hospital for children NHS Foundation Trust, Department of Neuroradiology, London, UK; (7)Department of Paediatric Neurology, Chelsea and Westminster NHS Foundation Trust, London, UK; (8)Department of Paediatrics, Chelsea and Westminster NHS Foundation Trust, London, UK; (9)Department of Perinatal Neurology, Hammersmith Hospital, London, UK; (10)Institute for Neuroscience and Muscle Research, The Children’s Hospital at Westmead, Sydney, Australia; (11)The Children’s Hospital at Westmead- Sydney- Australia, Department of Neurology, Australia; (12)The Children’s Hospital at Westmead- Sydney- Australia, Neuroimmunology Group-Institute for Neuroscience and Muscle Research, Australia; (13)St. George’s Healthcare NHS Trust, Child Development Centre, London, United Kingdom; (14)St. George’s Healthcare NHS Trust- London- UK, Child Development Centre, London, UK; (15)Department of Molecular Genetics, North East Thames Regional Genetics Services, Great Ormond Street Hospital for children NHS Foundation Trust,
ABSTRACT BOOK PLATFORM

Thursday 5 May
Movement disorders

London;(16)South West Thames Regional Genetics Service, St. George's Healthcare NHS Trust, London, UK;(17)Department of Clinical Genetics, Great Ormond Street Hospital for children NHS Foundation Trust, London, UK;(18)Hospital Sant Joan de Déu- Universitat de Barcelona- Spain, Department of Child Neurology, , Spain;(19)Hospital Sant Joan de Déu- Universitat de Barcelona- Spain, Centre for Biomedical Research in Rare Diseases CIBERER-ISCIII, , Spain;(20)University of Rochester Medical Center- Rochester- NY- USA, Departments of Pediatrics and Biomedical Genetics,