ICNC-0587  Psychosocial support for adolescents and young adults with Neurofibromatosis type 1

Background and aims

Neurofibromatosis type 1 (NF1) is a genetic disorder with a prevalence of 1 in 2,500. It is characterized by neurocutaneous symptoms and by cognitive and behavioural problems. Until now, research in NF1 has focused mainly on cognition and behaviour, predominantly in young children. Little is known about mental health of adolescents and adults with NF1 and even less about the effect of psychosocial interventions in these patients. Therefore SPOT-NF1, a study of social and psychological support for teenagers and young adults with NF1, was initiated.

SPOT-NF1 is a randomized controlled trial (RCT), aiming to test effectiveness of a disease-specific psychosocial intervention to improve quality of life by targeting societal participation, self-efficacy, and coping with a chronic disorder.

Methods

From April 2013 to June 2015, participants with NF1 aged 16 to 30 from two university hospitals in the Netherlands and Belgium, were randomly assigned to the control condition (care as usual) or to the intervention. The psychosocial intervention consisted of five group sessions and a maximum of four individual sessions, delivered by a social worker or a psychologist. At baseline and six months after randomization, questionnaires were completed to assess quality of life, self-efficacy, psychopathology, societal participation, fatigue, medical consumption, and body image.

Results and conclusions

100 participants have concluded baseline assessment. Determinants of quality of life and psychosocial problems in adolescents and young adults with NF1, such as fatigue, social support and gender, will be presented to guide future mental health care for young people with NF1.

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Sleep and behaviour difficulties in a large cohort of patients with Sturge-Weber Syndrome

Introduction

Sturge-Weber Syndrome (SWS) typically presents with port-wine stain, seizures and motor difficulties. Comorbidities such as sleep and behaviour difficulties are described but not well understood in SWS.

Methods

Case records were reviewed of 92 children with SWS presenting at a single tertiary centre between 2002-2015. Retrospective data collection included recording diagnoses of autistic spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), documentation of sleep and behaviour difficulties and scores from standardised screening questionnaires.

Results

Behavioural difficulties were reported in 46/92 children (50%). Sleep problems were encountered in 24 children (26%). Sleep and behavioural difficulties were closely linked: 21/46 children (46%) with behavioural difficulties also had sleep disturbances, compared to only 3/46 (7%; p<0.01) among those without behavioural difficulties. Diagnosis of ASD was also more frequently associated with sleep problems (50% vs 17%; p=0.002), predominantly night-waking (90% vs 30%; p=0.006). Children with ASD or behavioural difficulties were more likely to have been given sleep medication compared to those without these difficulties (45% vs 9%; p<0.001 and 33% vs 2%; p<0.001). Those who underwent epilepsy surgery had more reported sleep problems (53% vs 19%; p=0.003), possibly an expression of disease severity. There was no association between sleep and behaviour difficulties and extent of the underlying pial angioma.

Conclusions

Behavioural difficulties and sleep disturbances are frequently encountered in children with Sturge-Weber Syndrome independent of the extent of the underlying vascular abnormality. Sleep and behaviour should be routinely assessed in SWS to facilitate intervention programmes and treatment strategies as early as possible.

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ICNC-0949  Neurological phenotypes of epidermal nevus syndrome (ENS)

Introduction: Epidermal nevus syndrome (ENS) is a less known neurocutaneous syndrome (NCS). The two most frequent phenotypes are neurological: keratinocytic nevus syndrome (KNS) and linear sebaceous nevus syndrome (LSNS) (inappropriately called Schimmelpenning syndrome). Both share the same etiology: post-zygotic mosaic mutations in RAS genes, and pathogenesis of skin and multisystemic anomalies (brain, ocular, osseous, dental, renal, lymphatic, cardiovascular, etc.) : they are neurocristopathies. LSNS presents several phenotypes depending upon the level of neural crest involvement. KNS has 2 main phenotypes: Proteus syndrome and CLOVES syndrome. Heide’s syndrome triad includes congenital hemifacial hyperplasia with lipomatosis, keratinocytic or sebaceous nevus, and hemimegalencephaly. All were described since the 19th century.

Methods: We reviewed clinical, neuroimaging and, in some, neuropathological data of patients with neurological ENS, personal cases and from the literature, to classify them into different phenotypes.

Results: The most frequent phenotype, LSNS, affecting mesencephalic neural crest, was seen in 111 patients. In all phenotypes epilepsy was the most frequent neurologic manifestation. Infantile spasms often developed in infants with congenital scalp sebaceous nevi. The main cerebral dysplasia in all forms is hemimegalencephaly (HME).

Conclusion/Discussion: LSNS and KNS are a spectrum of the same entity; however, it is important to identify neurological phenotypes early (prenatally) for investigation and management. Of all NCSs they are second in frequency after tuberous sclerosis as a cause of West syndrome. Heide's syndrome corresponds to the 'neurological variant' described in 1991. Timing and extent of the mutation determines phenotype and severity. Activation of PIK3CA -AKT explains the high association with HME.

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Neurological presentation of Tuberous Sclerosis Complex in newborns

Introduction

One in 5,800 newborns present with Tuberous Sclerosis Complex (TSC), a genetically determined neurocutaneous disorder characterized by the progressive development of hamartomas in many organs. Cardiac tumors can be disclosed as early as prenatally in vast majority of TSC patients. The most frequent neurological feature of the disease is epilepsy, which usually begins at the age of 3-6 months. Subependymal giant cell astrocytomas (SEGAs) grow usually in children between 7-11 years, however, there are some case reports on very early epilepsy and SEGAs. The aim of this report was to show the neurological complications of TSC in newborns.

Methods

The group of 421 patients with TSC was reviewed in order to identify cases with seizures, SEGAs or neurological deficits present in the first month of life.

Results

In 21 patients (5.7%) epilepsy began in the first month of life. The risk factors for early presentation of epilepsy included large dysplastic lesions in the brain and birth complications. Patients with early epilepsy were more prone to intellectual disability development than general TSC population. In 10 patients (2.1%) brain MRI performed in the first month of life showed SEGAs requiring urgent treatment. The risk factors for early SEGAs included TSC2/PKD1 mutation. Surgery in this group of patients was associated with high risk of complications.

Conclusions

Neuroimaging examination and EEG should be performed in each patient with TSC suspected, including newborns. Seizures and SEGAs in this group of patients require careful workout and consideration of many risk factors while making therapeutic decisions.

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ICNC-0577  **Phenotypic variability in Tuberous Sclerosis Complex (TSC): genetic modifiers**

Tuberous sclerosis complex is caused by heterozygous mutations in the TSC1 or TSC2 genes, resulting in constitutive activation of the intracellular mTOR signaling pathway. Neurocognitive phenotypes in TSC range from profound mental retardation, intractable epilepsy, and autism, to normal cognition and only a mild behavioral phenotype. Variability in phenotype can be seen even within a single family, where all affected individuals have the same gene mutation. We hypothesize that genetic variants in genes other than TSC (belonging to an “mTOR Network”) or differential expression of genes in this network account for this phenotypic variability. Our goal is to develop a molecular profile that correlates with disease severity, and will allow early treatment of patients before onset of neurological disease.

We have studied a cohort of affected parent-child pairs. As age is a confounding factor (seizure onset, learning disability, autistic features), we have focused on parent-child pairs where the child has a severe neurocognitive phenotype and the parent is mildly affected. We used (a) whole exome sequencing to identify genetic variants in modifier genes, focusing on TSC1/TSC2/mTOR pathway genes, and (b) RNA sequencing to characterize differential expression of genes in this network. Preliminary studies in three families have identified secondary gene variants in PIK3R5 or SOS1 in two severely affected children, and a RPTOR variant in a mildly affected parent, in addition to primary TSC1 or TSC2 mutation in both parent and child. Studies in other families and the functional effect of these secondary variants on mTOR signaling will be presented.

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ICNC-0582 White matter diffusivity reflects cumulative neurological comorbidity in Tuberous Sclerosis Complex

Introduction: The effects and safety of early pre-emptive treatment with vigabatrin and inhibitors of the mechanistic target of rapamycin (mTOR) on epilepsy and neurodevelopment are being studied in Tuberous Sclerosis Complex (TSC). To justify the risk for adverse events, early selection of patients at highest risk for adverse neurological outcome is warranted in such trials. We sought to expand the use of diffusion tensor imaging (DTI) of callosal white matter as a marker for neurological outcome in TSC, and distinguish effects attributable to autism spectrum disorder (ASD), intellectual disability (ID), and epilepsy. Methods: 186 children underwent 3T MRI with 35 direction DTI: 32 TSC- (TSC, no ASD), 19 TSC+ (both TSC and ASD), 46 ASD (no TSC), and 89 HC (healthy controls). Retrospective data on cognitive function and epilepsy were collected. Results: Corrected for age, TSC+ had significantly lower fractional anisotropy (FA) and higher mean diffusivity (MD) than TSC- and HC. TSC- and ASD approached DTI values of HC (Figure 1A). ASD with ID different significantly from controls, but ASD without ID did not. TSC+ with ID had even lower FA (higher MD) and TSC- without ID approximated HC (Figure 1B). TSC+ DTI values improved when those with severe epilepsy were omitted (Figure 1C). Conclusions: Using a cross-disorder approach, this study demonstrates cumulative effects of TSC, ASD, ID and epilepsy-related variables on callosal white matter DTI metrics. In TSC, ASD was inextricably linked to ID and epilepsy, and the DTI measures reflect a total neurological disease burden rather than a specific marker for ASD.

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Sirolimus for intractable epilepsy in children with Tuberous Sclerosis Complex (RATE): a randomized controlled trial

Introduction: Tuberous Sclerosis Complex (TSC) is caused by inactivating mutations in the TSC1 or TSC2 genes. Mutations cause disinhibition of the mTOR pathway, which is involved in TSC-related epilepsy. Up to 90% of TSC patients suffer from epilepsy, and 63% are intractable to anti-epileptic drugs. Animal studies and an uncontrolled study in children suggest that mTOR inhibitors may be potent drugs for reducing seizure frequency.

Methods: We performed the first randomized clinical trial investigating the mTOR inhibitor sirolimus in intractable epilepsy in TSC patients. Eligible children were aged 3 months-12 years, had a definite clinical diagnosis of TSC and had at least one seizure per week at baseline. Participants were randomized in a cross-over design to receive add-on sirolimus treatment immediately or after six months. Total trial duration was twelve months. Primary outcome of the trial was frequency of epileptic seizures. Secondary outcomes were cognitive and motor development, and EEG abnormalities.

Results: Twenty-three children aged 1.8-10.9 years were randomized. After six months of sirolimus treatment, nine children (39%) had a seizure frequency decrease of 50% or more compared to baseline seizure frequency. Six children (26%) had such a response after six months of the control period. Cognition and behavior did not show a significant change. Adverse events occurred in all children. Five children (22%) discontinued sirolimus prematurely due to adverse events.

Discussion: This is the first randomized controlled trial showing the effect of mTOR inhibition on epileptogenesis in intractable epilepsy due to TSC. Acknowledgements: Supported by the Dutch Epilepsy Foundation.

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