ICNC-0168  Analysis of Chinese children with large copy number variations in early-onset epileptic encephalopathies of unknown cause

Introduction The etiologies of early-onset epileptic encephalopathies (EOEEs) are complex, and the majority are with unknown cause. Recent studies showed that copy number variations (CNVs) is an important etiology of unknown cause EOEEs. Methods We selected a cohort of 116 patients consisting of different subtypes of EOEEs, and performed single nucleotide polymorphism arrays to detect the genome-wide CNVs. Then we used fluorescence in situ hybridization, quantitative polymerase chain reaction, and CNVplex® to perform the validation and parental resource analyses. Additionally, we identified the clinical features of the patients with large CNVs. Results Seventeen of the 116 patients with EOEEs (14.66%) carried 19 large CNVs. Fourteen CNVs in 12 patients were further validated: four of the CNVs were classified as de novo, seven were maternal, and three were paternal. Follow-up of the 12 patients, ranging from 1 to 8 years, showed that five had been seizure-free for at least 9 months, five had seizures several times a month or per year. But eight patients demonstrated severe to profound developmental delay. Conclusion This is the first genomic study to detect genome-wide CNVs in a cohort with different subtypes of EOEEs in China. At least 3.4% of patients had pathogenic CNVs. For the patients, our study laid the foundation for prenatal interventions for their families. For further study, we identified several candidate genes, namely NIPA1, KCNK9, and TRAPPC9. Our summary of the clinical features and treatments of the patients with large CNVs will contribute to the understanding of each variation.

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The clinical features of epilepsy in alternating hemiplegia of childhood with ATP1A3 mutations

The Introduction Alternating hemiplegia of childhood (AHC) is a severe neurological disorder characterized by recurrent hemiplegic episodes accompanied by other paroxysmal symptoms. Epilepsy occurs in some patients. De novo mutations in ATP1A3 were identified as a genetic cause of AHC. The aim of this study is to analyze the clinical features and genotype-phenotype correlation in AHC patients with epilepsy.

Methods The clinical data were collected and analyzed. Mutations in ATP1A3 were screened by Sanger sequencing.

Results 89 AHC patients were recruited. 13 patients (14.6%) had concurrent epilepsy, including 7 males and 6 females. The age of seizure onset ranged from six hours to six years. Focal seizures were observed in 7 cases, generalized tonic-clonic seizures (GTCS) in 4 cases, both focal seizures and GTCS in 2 cases. Seven patients experienced status epilepticus during the course. Video-electroencephalography (VEEG) were abnormal in 5 patients. The background was slow in 5. Multiple focal or generalized spikes were found in two patients. Nonconvulsive status epilepticus was monitored in one patient. ATP1A3 mutations were identified in 13 patients with epilepsy. Four types of missense mutations were found, including mutation E815K in 10 patients (76.9%, 10/13). Mutation D801N, L839P, and E277K was detected in one patient respectively. In 89 AHC patients, 15 patients were found with E815K mutation, and 10 of them (66.7%) had epilepsy.

Conclusion The age of seizure onset in AHC could be as early as neonatal period. AHC patients with epilepsy often experienced status epilepticus. Patients with epilepsy were more likely to carry E815K mutation.

Keywords: alternating hemiplegia of childhood; epilepsy; ATP1A3; mutation

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Variable phenotypes in patients with GRIN2A sequence variants or deletions

Introduction: The GRIN2A gene has been associated with epilepsies ranging from benign focal childhood epilepsies to severe epileptic encephalopathies. The aim of this study was to evaluate genotypes and phenotypes in patients with GRIN2A deletions or variants. Methods: We compared genotypes and phenotypes in six newly identified patients with GRIN2A variants with those of 149 individuals with GRIN2A variants from the literature. Results: Six new patients with epilepsy, developmental and/or behavioural problems and GRIN2A deletions (n=3), missense (n=2) or splice-site variants (n=1) are presented. In 125 (84%) of the 149 individuals with GRIN2A variants previously reported, a specific epilepsy syndrome was diagnosed, most often classified as Benign Epilepsy with Centro- Temporal Spikes (BECTS; n = 44) or Landau-Kleffner syndrome/Continuous Spike-and-Waves during Slow-wave sleep (LKS/CSWS; n = 42). Problems of speech and language development (81%), cognition (68%), motor skills (50%) or behaviour (42%) were common. Missense variants were seen in 52% of the patients reported earlier, more often in individuals with BECTS (71%) compared to those with LKS/CSWS (48%). Certain missense variants in or close to the ligand-gated ion channel domain were associated with a severe phenotype, as was also observed in two of our patients with severe epilepsy and cognitive impairment. Conclusions: Patients with GRIN2A gene variants or deletions have an extremely variable phenotype without a clear genotype-phenotype correlation. Variants in or close to the ligand-gated ion channel can be associated with a severe phenotype.

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ICNC-0172  

Clinical and molecular characterisation of KCNT1-related severe early onset epilepsy

Introduction: Heterozygous mutations in KCNT1 account for approximately 50% of epilepsy of infancy with migrating focal seizures (EIMFS) cases, but are also reported in other electro-clinical phenotypes, including Ohtahara syndrome and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).

Methods: We identified a cohort of 31 patients with EIMFS of unknown cause and screened for mutations in KCNT1 using a combination of direct Sanger sequencing, a multiple gene next generation sequencing panel and whole exome sequencing. Patients with other forms of early onset epilepsy in whom KCNT1 mutations were identified on our diagnostic multiple gene panel (n=2) were also included in this study. Electrophysiological assessment of mutant KCNT1 channels in a Xenopus oocyte model system and homology modelling were undertaken. Results: Mutations were identified in twelve patients, four of which are previously unreported. The majority occurred de novo, though parental mosaicism was seen in one case. Ten patients had a clinical diagnosis of EIMFS and the remaining two subjects presented with severe nocturnal frontal lobe seizures. Computational modelling analysis implicated abnormal pore function (p.Phe346Leu) and impaired tetramer formation (p.Phe502Val) as putative disease mechanisms. All evaluated KCNT1 mutations resulted in marked gain-of-function, with significantly increased channel amplitude on patch clamp testing. Two patients had a trial of quinidine without sustained clinical response. Conclusions: KCNT1 mutations cause a spectrum of severe focal epilepsies in childhood and mutations lead to gain of channel function. Currently, no clear genotype-phenotype correlations are evident. The role of targeted treatments, such as quinidine, remains yet to be elucidated.

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ABSTRACT BOOK PLATFORM

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ICNC-0152 The burden of frequent seizures on patients, parents and society in a European study of non-institutionalized children with epilepsy

Introduction

In children with epilepsy whose prolonged acute convulsive seizures (PACS) are managed in the community, each seizure may impose a burden not only on the affected child but also on parents/carers and healthcare services.

Methods

A cross-sectional study in four European countries enrolled non-institutionalized children with epilepsy (aged 3–16 years) who had experienced ≥1 PACS within the past 12 months and had currently prescribed PACS rescue medication(s). Investigators provided clinical assessments and parents/guardians completed web-based questionnaires.

Results

Enrolled children (N=286) had experienced 1–400 PACS (median, 4) in the past year. Patients were stratified post hoc into subgroups of infrequent (1–5/year, n=158), frequent (6–50/year, n=102) and very frequent (>50/year, n=26) PACS in the past year. In these subgroups, investigators reported learning disabilities in 67.3%, 89.9% and 84.6% of children, respectively; and impairment of typical day-to-day activities in 41.0%, 64.6% and 76.9%, respectively (n=156,99,26). For their most recent PACS, rescue medication was given at the seizure location to 70.6%, 78.2% and 60.9% of children with infrequent, frequent and very frequent PACS, respectively; an ambulance was called for 32.9%, 12.6% and 4.3%, respectively; and 35.7%, 14.9% and 4.3%, respectively, were admitted to hospital (n=143,87,23).

Conclusion

Among children with epilepsy and prescribed rescue medication, children who often experienced PACS were less likely to use healthcare services following a seizure, but more likely to have learning disabilities and day-to-day impairments, compared with those who seldom experienced PACS.

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ICNC-0147  Evaluation of concurrent sleep problems in children with idiopathic epilepsy

Introduction: Sleep disturbance is one of the most common behavioral problems among children with epilepsy. They adversely affect mood and quality of life in general population, thus they are expected to have particularly disruptive effects in patients with epilepsy. Aim: Study sleep patterns in children with idiopathic epilepsy. Subjects: case-control study on 100 children with idiopathic epilepsy and their age and sex matched non-epileptic siblings. Methods: Cases were subjected to history taking, examination and electroencephalogram. Sleep behavior questionnaire was used to assess sleep problems in all cases and controls. Results: Epilepsy was generalized in 78% of cases, and focal in 22%. The mean duration of illness was 1.97(±0.92) year, 55% of cases had seizures during the previous 6 months and 85% of the cases were on monotherapy. Cases had a significantly higher total sleep score and scored high than controls on all subscales of the sleep behavior questionnaire. Conclusion: Children with idiopathic epilepsy had significantly greater sleep problems which was more in those with focal seizures. Children on monotherapy suffer more from bedtime difficulties than those on polytherapy. References: • Wirrell E et al. Sleep disturbances in children with epilepsy compared with their nearest-aged siblings. Dev Med Child Neurol 2005;47:754–9. • Baxter P. Epilepsy and sleep. Dev Med Child Neurol 2005;47:723. • Batista BH et al. Evaluation of sleep habits in children with epilepsy. Epilepsy Behav 2007;11:60–4. • Cortesi F et al. Sleep problems and daytime behavior in childhood idiopathic epilepsy. Epilepsia 1999;40:1557–65.

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Fatal cerebral edema following status epilepticus in children with Dravet Syndrome

Introduction: Dravet syndrome (DS) is an infantile-onset epilepsy syndrome, characterized by febrile seizures in the first year of life, followed by developmental regression or plateau and the emergence of other seizure types. Febrile convulsive status epilepticus is a nearly universal feature of DS. Children with this disorder are also prone to sudden death, usually attributed to sudden explained death in epilepsy or multi-organ failure with refractory status epilepticus. Fatal cerebral edema following febrile status epilepticus has not previously been described in DS.

Methods: We reviewed the cases of children with DS, followed at our centre, who had died following febrile status epilepticus. We selected cases in which cause of death was secondary to massive cerebral edema.

Results: Five children with DS were identified who presented with febrile convulsive status epilepticus, developed severe brain swelling, and died. Symptoms of increased intracranial pressure became apparent between three and five days in most cases, although one child developed signs within 24 hours. When magnetic resonance imaging was performed early in the acute presentation, focal restricted diffusion was seen. Later studies demonstrated more diffuse edema and development of tonsillar and/or uncal herniation resulting in brainstem compression. Four of the children had autopsies, all of which confirmed diffuse brain edema.

Conclusions: Cerebral edema causing herniation and death is an important, previously unreported, sequela of status epilepticus in children with DS. Early interventions could potentially be life-saving if this entity is suspected and recognized in a timely manner.

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