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Long-term neurocognitive outcome and auditory event-related potentials after complex febrile seizures in children

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ABSTRACT

Objectives: Whether prolonged or complex febrile seizures (FS) produce long-term injury to the hippocampus is a critical question concerning the neurocognitive outcome of these seizures. Long-term event-related evoked potential (ERP) recording from the scalp is a noninvasive technique reflecting the sensory and cognitive processes associated with attention tasks. This study aimed to investigate the long-term outcome of neurocognitive and attention functions and evaluated auditory event-related potentials in children who have experienced complex FS in comparison with other types of FS.

Methods: One hundred and forty-seven children aged more than 6 years who had experienced complex FS, simple single FS, simple recurrent FS, or afebrile seizures (AFS) after FS and age-matched healthy controls were enrolled. Patients were evaluated with Wechsler Intelligence Scale for Children (WISC; Chinese WISC-IV) scores, behavior test scores (Chinese version of Conners' continuous performance test, CPT II V.5), and behavior rating scales. Auditory ERPs were recorded in each patient.

Results: Patients who had experienced complex FS exhibited significantly lower full-scale intelligence quotient (FSIQ), perceptual reasoning index, and working memory index scores than did the control group but did not show significant differences in CPT scores, behavior rating scales, or ERP latencies and amplitude compared with the other groups with FS. We found a significant decrease in the FSIQ and four indices of the WISC-IV, higher behavior rating scales, a trend of increased CPT II scores, and significantly delayed P300 latency and reduced P300 amplitude in the patients with AFS after FS.

Conclusion: We conclude that there is an effect on cognitive function in children who have experienced complex FS and patients who developed AFS after FS. The results indicated that the WISC-IV is more sensitive in detecting cognitive abnormality than ERP. Cognition impairment, including perceptual reasoning and working memory defects, was identified in patients with prolonged, multiple, or focal FS. These results may have implications for the pathogenesis of complex FS. Further comprehensive psychological evaluation and educational programs are suggested.

1. Introduction

Febrile seizures (FS) affect 2%–8% of children aged between 6 months and 6 years [1]. Whether prolonged or complex FS cause long-term injury to medial temporal structures, including the hippocampus, is a critical question concerning the neurocognitive outcome of these seizures. Researchers have proposed that complex FS are a risk factor in human temporal lobe epilepsy and temporal lobe sclerosis [2,3]. Evidence from MRI studies has revealed focal hippocampal atrophy after prolonged FS in some children [4–6] and abnormal T2 signal enhancement in the limbic structures in children with FS and a rat FS model [7]. Animal studies revealed that prolonged or repeated FS cause a decrease of neuronal inhibition, deficit in spatial memory, and behavioral alteration and impairment of cAMP response element-binding protein activation in rats [8–10].

The results of studies examining the cognitive effect in children with complex FS have been inconsistent. Earlier studies have reported that children with prolonged FS exhibited significantly reduced nonverbal intelligence and abnormalities in other neuropsychological tests compared with controls and children with simple FS [11–13]. However, some published population-based studies found no increase in the risk

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of unfavorable neurodevelopmental outcome according to the Wechsler Intelligence Scales for Children (WISC-III) in patients with FS [14–16]. Facilitation of working memory function was reported in school-age children with a history of FS [17]. Nevertheless, a higher incidence of behavioral disturbances, sleep problems, and learning difficulties have been reported in children with FS [13,18]. No large series has evaluated cognitive function using WISC-IV in patients with a history of complex FS. The WISC-IV differs from the WISC-III and earlier editions in both content and structure and may yield different prospective results [19].

Event-related potential (ERP) recording from the scalp is a noninvasive technique that provides knowledge of the neural activity associated with sensory, cognitive information, attention, and decision-making processes [20,21]. The long-latency response is presumed to reflect the limbic system and multiple neocortical regions [20,21]. Event-related potential recording has been used as an electrophysiologic tool for studying the neural bases of cognitive activities and applied clinically in patients with psychopathology, neurological diseases, learning and attention disorders, dementia, memory disorders, and other cognitive deficits [21–23]. Changes in auditory ERP in children with complex FS have not been studied.

Taking together, we hypothesized that a history of prolonged or complex FS disrupts neurocognitive function and auditory long-term evoked potentials. The aims of our study were the following: (1) to investigate the long-term outcome of neurocognitive function, behavior, and attention function and (2) to evaluate auditory ERPs in children with FS after they reach 6 or more years of age.

2. Methods

2.1. Patients

A febrile seizure is defined as an event in infancy or childhood that occurs between 3 months and 5 years of age and is associated with fever but exhibits no evidence of intracranial infection or defined causes [24]. Febrile seizures are generally categorized as simple or complex [25]. Complex FS exhibit at least one of the following characteristics: seizure duration of more than 15 min, more than one seizure in 24 h, and focal features. All other FS are defined as simple. Simple recurrent FS are defined as comprising more than one simple FS.

Three hundred and twenty medical records of children with a clinical diagnosis of any type of FS and aged between 6 and 15 years were reviewed. One hundred and forty-seven children aged over 6 years were recruited by the investigators of the Department of Pediatrics at Cathay General Hospital and Cheng-Hsin General Hospital in Taipei, Taiwan. Patients with previous afebrile seizures (AFS), underlying brain structure pathology, neonatal seizures, CNS infection, and underlying developmental delay, mental retardation or neurological abnormality before FS were excluded. The patients were divided into groups with complex FS, simple single FS, simple recurrent FS, and AFS after FS and were age-matched with healthy controls. Informed consent was obtained from the parents or guardians of patients in accordance with the requirements of the Institutional Review Boards (IRBs) of Cathay General Hospital (CGH-CT9762) and Cheng-Hsin General Hospital (CHGH-IRB-165-98-49).

2.2. Assessment procedures

The Chinese version of the WISC-IV was administered to each patient. Five composite scores can be derived using the WISC-IV. The WISC-IV generates a full-scale intelligence quotient (FSIQ) that represents overall cognitive ability; the four other composite scores are the verbal comprehension index (VCI), perceptual reasoning index (PRI), processing speed index (PSI), and working memory index (WMI). The VCI reflects performance in three verbal subtests (Vocabulary, Similarities, and Comprehension), whereas the PRI is a composite index based on performance in three visual reasoning subtests (Block Design, Matrix Reasoning, and Picture Concepts). The WMI is based on two subtests measuring auditory working memory (Digit Span and Letter-Number Sequencing), and the PSI is based on two subtests measuring speed of thinking and motor speed (Coding and Symbol Search). All scaled scores and index scores were derived from raw scores based on Taiwanese standardization sample data [26]. Behavior tests were the Chinese version of Conners' Continuous Performance Test-II (CPT II V.5), and behavior rating scales were provided by parents [27]. For each patient, complete personal and family histories and school performance were reviewed, and detailed neurologic assessment was performed.

An auditory oddball ERP paradigm was used in examining each patient (Medtronic Keypoint V3.22; Medtronic Functional Diagnostics A/S, 2001, Denmark). The ERPs were elicited binaurally by using headphones with a typical intensity of 60 dB above the hearing threshold but were subject-dependent. A total of 200 tones were elicited. According to the paradigm, 20% were “target” (rare), the rest were “nontarget” (frequent), and the delivery sequence of frequent and rare tones was randomized. The target tones were played at 3000 Hz, whereas the nontarget tones were played at 2000 Hz. The tone was elicited at a rate of 0.7 Hz. The test was repeated twice. Instruction was provided by the technician before the test. The patients pressed a button when they heard a rare tone or counted the number of rare tones. Long-latency components (N1, P2-frequent tone and N2, P3-nonfrequent tone) from Fz, Cz, and Pz and Oz were recorded for each patient.

2.3. Statistical analysis

Mean reference values of the IQ and ERP indices (amplitude and latency) from the groups were derived in this cross-sectional study. One-way analysis of variance (ANOVA) was used to examine the differences between the group with FS and control group. The post hoc Newman–Keuls test was used when differences were found. Significant comparisons were defined as $p < 0.05$, unless otherwise indicated. All statistical analysis was performed using SPSS (Version 17.0; SPSS Inc., Chicago, IL).

3. Results

3.1. Clinical profiles

The mean age at the time of testing was 8.5 ± 1.7, 8.5 ± 1.9, 8.4 ± 1.9, 8.1 ± 1.9, and 8.6 ± 1.9 years in the control group, group with simple single FS, group with simple recurrent FS, group with complex FS, and group with AFS after FS, respectively. No significant difference in age at test or gender was present among the groups. The age at onset of FS was 2.5 ± 2.2, 2.0 ± 1.1, 1.8 ± 0.6, and 2.2 ± 1.3 years in the groups with simple single FS, simple recurrent FS, complex FS, and AFS after FS, respectively. No significant difference in age of onset was noted among the groups with FS. In the group with complex FS, seven children had prolonged FS, fourteen had multiple FS within 24 h, and five had focal features during FS. In the group with simple recurrent FS, eleven children had two FS, six had three FS, and five had three or more FS. Twenty of the 21 patients in the group with complex FS had recurrent FS. In the group with AFS, four patients had a history of simple FS, nine had recurrent FS, and seven had complex and recurrent FS. Five patients in the group with AFS were receiving antiepileptic medication, whereas 16 patients did not take any medication. No members of the group with FS were on antiepileptic drugs. Image studies (CT or MRI) were performed in 13 of the 21 patients with complex FS and in all patients with AFS; none of them showed abnormal findings.

3.2. WISV-IV performance

The Chinese WISC-IV scores were available for 101 children with a history of FS and for the controls. The mean FSIQ of the groups with complex FS (98.8 ± 13.4) and AFS after FS (91.7 ± 16.9) were significantly lower than that of the control group (111.4 ± 10.1; $p < 0.05$