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Mental retardation and relation to seizure and tuber burden in tuberous sclerosis complex

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Summary In patients with tuberous sclerosis complex (TSC), the high rates of mental retardation are associated with cortical tubers, seizure activity, and genetic factors. The goal of the study was to investigate the relationship between bilateral cortical tubers and seizure variables and mental retardation in individuals with TSC. The records of 27 patients with TSC (age 6 months to 33 years) undergoing neuropsychological assessment and the following clinical variables were examined: bilateral versus non-bilateral cortical tubers, the age of seizure onset, and presence of infantile spasms. Results were statistically analyzed. Bilateral cortical tubers ($p = 0.02$) and early age of seizure onset ($p = 0.04$) were significantly related to impaired cognitive functioning. Only one of the seven patients with normal cognitive functioning had bilateral tubers, whereas 13/21 patients with intellectual impairment had bilateral tubers. Patients with normal cognitive functioning experienced a mean age of seizure onset after 6 years. A trend was observed between infantile spasms and cognitive functioning ($p = 0.06$); the lack of statistical significance likely reflects the small sample size. Neither age nor gender was related to cognitive status. Further investigation incorporating additional neuroimaging factors, antiepileptic treatment effects, and genetic variables, is needed.

Introduction

Tuberous sclerosis complex (TSC) is a multisystem disorder associated with high rates of mental retardation and autism, often attributed to cortical tubers and seizure activity. A greater number of tubers is usually found in individuals with cognitive impairment.[1,2] Low intelligence quotient (IQ) has been correlated with the number of lobes affected.[3] In individuals with seizures, an earlier age of seizure onset[4] and in particular infantile spasms[1,5] are most strongly linked with cognitive impairment. In individuals with infantile spasms, specific variables including increased duration of infantile spasms

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from onset to cessation, increased time from treatment initiation to cessation, and control of seizures other than infantile spasms after infantile spasm resolution have been found to have a significant relationship with intellectual outcome.[6] Genetic factors contribute to outcomes; the TSC1 mutation and unidentifiable mutations have been associated with lesser degree of intellectual and behavioral compromise characterized by higher intellectual functioning and better seizure control than the TSC2 mutation.[7–9]

The goal of the present study is to characterize the level of cognitive or adaptive functioning in a sample of TSC individuals using standardized measures of assessment. A retrospective analysis of the relationship between seizure status including infantile spasms and age at seizure onset, tuber burden, and cognitive status was conducted.

Methods

Subjects

Subjects were patients seen at the tertiary care NYU Tuberous Sclerosis and Epilepsy Centers. The sample consisted of 27 individuals referred for neuropsychological assessment between July of 1993 and May of 2003 in the context of a comprehensive neurological and medical evaluation. All subjects whose neuropsychological data contained a Full Scale IQ or a Vineland Adaptive Behavior Composite standard score, and in whom an MRI scan of the brain was undertaken were included. In those subjects undergoing multiple assessments, the more recent score was examined. Subjects included 11 males and 16 females. Mean age at the time of neuropsychological assessment was 9 years (S.D., 8.4 years; range, 6 months to 33 years). Approval for the study was obtained from the institutional review board.

Neuropsychological assessment

The Vineland Adaptive Behavior Scales Interview Edition Expanded Form (VABS)[10] was used in subjects too young or too developmentally delayed to undergo formal testing. The VABS Adaptive Behavior Composite (ABC) standard score was derived, providing an overall estimate of adaptive functioning. In subjects able to undergo formal testing, the Wechsler Adult Intelligence Scale — Third Edition (WAIS-III),[11] Wechsler Abbreviated Scale of Intelligence (WASI)[12] or the Wechsler Intelligence Scale for Children — Third Edition (WISC-III)[13] were used. Both the VABS ABC and Wechsler FSIQ have a mean of 100 and a standard deviation of 15.

Neurological variables

A diagnosis of TSC was made using established clinical criteria.[14] Information concerning seizure onset, seizure type, and MRI findings were collected from a review of medical records. Table 1 summarizes demographic and clinical information.

Data analysis

Subjects were divided into three groups according to standard scores obtained on the VABS ABC or the relevant Wechsler Full Scale IQ. Scores $\geq$80 were designated as ''normal.'' Scores within the range of 60—79 were classified as ''mildly impaired.'' Those below 60 were termed ''significantly impaired.'' Subjects were also divided into two groups: those having bilateral cortical tubers and those with other findings. The percentage of subjects with bilateral cortical tubers was calculated for the sample as a whole and for each of the three cognitive groups. The mean age at seizure onset in months and the percentage of subjects with infantile spasms were calculated for the sample as a whole and for each of the three cognitive groups.

Several analyses were undertaken for the group as a whole. Chi-square analyses were performed using cognitive status and gender, cognitive status and history of infantile spasms, and cognitive status and MRI findings (bilateral tubers versus findings indicating the absence of bilateral tubers). Point-biserial correlation was computed between level of cognitive status and age at seizure onset (rank ordered). A Pearson correlation coefficient was calculated using age and cognitive status as the two variables. Level of significance was set at 0.05. All analyses were conducted using the Statistic Package for the Social Sciences (SPSS).

Results

Seven subjects (26%) obtained test scores within the ''normal'' range, seven (26%) fell in the ''mildly impaired'' range, and 13 (48%) were ''significantly impaired.'' Sixteen subjects obtained a score lower than 70 (see Table 1), a range representative of mental retardation according to the Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition-Text Revision (DSM-IV-TR).[15]

Seizures were present in 25 of the 27 individuals, with the mean age of seizure onset at 22 months (range, $<$1 month to 17 years). Mean age at seizure onset in the cognitively normal group was 74 months, 16 months in the mildly impaired group,