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

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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 onset⁴ and in particular infantile spasms⁵ are most strongly linked with cognitive impairment. In individuals with infantile spasms, specific variables including increased duration of infantile spasms

**KEYWORDS**

Tuberous sclerosis complex; Tubers; Epilepsy; Mental retardation; Autism; Infantile spasms; Bilateral; Neuropsychology

**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.

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from onset to cessation, increased time from treat-
ment 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. 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.

The goal of the present study is to characterize
the level of cognitive or adaptive functioning in a
sample of TSC individuals using standardized mea-
sures of assessment. A retrospective analysis of the
relationship between seizure status including infan-
tile 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 neuropsy-
chological assessment between July of 1993 and May
of 2003 in the context of a comprehensive neuro-
logical 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 under-
going multiple assessments, the more recent score
was examined. Subjects included 11 males and 16
females. Mean age at the time of neuropsychologi-
cal 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) was used in sub-
jects too young or too developmentally delayed to
undergo formal testing. The VABS Adaptive Behavior
Composite (ABC) standard score was derived, pro-
viding 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 Intelli-
gence (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 clin-
cal criteria.14 Information concerning seizure
onset, seizure type, and MRI findings were collected
from a review of medical records. Table 1 sum-
marizes 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 ≥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 sei-
zure 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,
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