Poor Mental Development in Patients With Tuberous Sclerosis Complex

Clinical Risk Factors

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Objective: To identify clinical risk factors for poor mental development among patients with tuberous sclerosis complex (TSC).

Design: Case-control analysis of a clinic population.

Setting: Specialty clinic in a hospital.

Patients: One hundred six patients with TSC consecutively seen between January 1984 and December 1995 at the Child Neurology Clinic of the Children’s Memorial Health Institute in Warsaw, Poland.

Study Variables: Seizure type, age at seizure onset, sex, and history of diphtheria, tetanus, and pertussis immunization.

Main Outcome Measure: Moderate to profound developmental delays.

Results: Seizure type (ie, infantile spasms) was the only analyzed risk factor that showed a consistent and independent association with poor mental development (adjusted odds ratio, 3.0; 95% confidence interval, 1.1-8.4; \( P = .03 \)). Age at seizure onset, which initially showed a significant association with poor mental development, was no longer significantly associated after adjustment for seizure type (adjusted odds ratio, 1.6; \( P = .43 \)). Neither sex (odds ratio, 1.1; \( P = .96 \)) nor history of diphtheria, tetanus, and pertussis immunization (odds ratio, 1.0; \( P = .80 \)) showed evidence of being a risk factor for poor mental development among patients with TSC.

Conclusions: Infantile spasms, as the type of seizure on initial examination, is a significant risk factor for poor mental development in patients with TSC. Age at time of first seizure is not an independent risk factor but reflects the early ages at which these patients are seen with infantile spasms. Neither sex nor history of diphtheria, tetanus, and pertussis immunization is a risk factor for the subsequent development of poor mental development among patients with TSC.


TUBEROUS SCLEROSIS complex (TSC) is characterized pathologically as hamartias (nongrowing local congenital anomalies), hamartomas (benign growths), and true neoplasms in various organs, such as brain, skin, kidneys, liver, and heart. The predominant neurological manifestations of TSC are seizures, mental retardation, and behavioral abnormalities, with seizures being the most common initial sign of central nervous system involvement. Poorly controlled seizures as well as certain types of seizures, eg, infantile spasms, are considered to be indicative of poor overall neurodevelopmental prognosis. Some of the other alleged risk factors include male sex and exposure to diphtheria, tetanus, and pertussis (DTP) immunizations.

Although TSC is known to be fundamentally a genetic disease (autosomal dominant inheritance and variable expressivity, with locus on chromosome 9q34 [TSC1] or 16p13.3 [TSC2] and a high spontaneous mutation rate), patient characteristics and exposures may distinguish those patients who develop moderate to profound mental retardation from those who do not. We studied the large population of patients diagnosed as having TSC and followed up by the Department of Neurology at Children’s Memorial Health Institute in Warsaw, Poland, from 1984 through 1995. The objectives of this study were to describe the clinical population and to examine the effect of various possible risk factors on neu-
MATERIALS AND METHODS

The study population consisted of 106 patients with TSC who were examined at the Child Neurology Clinic at the Children’s Memorial Health Institute in Warsaw, Poland, between January 1984 and December 1995. Most of the children were seen in the clinic in infancy or early childhood because of drug-resistant epilepsy. The patients were mainly from central Poland, although patients with diagnostic or therapeutic difficulties from other parts of the country were also admitted. Data collected on each study subject included sex, immunization history, age at onset of seizures, type of seizures, and developmental status.

The standard DTP immunization policy in Poland is that children receive their first DTP immunization during the third month of life along with oral polio immunization, their second dose 6 weeks later, and their third dose 6 weeks after that. The fourth DTP and polio immunizations are given between the ages of 1½ and 2 years, with reinforcing doses of diphtheria and tetanus vaccine in the 6th and 14th years and of polio in the 6th and 11th years of life. In addition, each child receives BCG vaccine during days 3 through 15 and again in the 7th year of life. Measles immunization (live vaccine) is given initially during the 13th to 15th month of life and again during the 8th to 9th year, and rubella is given to girls in the 13th year. Every child in Poland has his or her own “health book” in which all immunizations (dates and types of immunizations) are noted. The health books are annotated at each health service interaction and include both immunization histories and notations from regular pediatric visits. Immunization histories were obtained from these health books. Medical records and histories were reviewed to determine the reasons for delays for those patients whose immunizations were postponed.

Seizure type was determined on the basis of the clinical appearance and clinical history as obtained from the parent, previous clinical reports, and clinical observations, with the use of standard clinical criteria. The diagnosis of TSC was established on the basis of the criteria of Gomez9 and the 1992 criteria of the National Tuberous Sclerosis Association.9

Developmental status was assessed with a variety of age-appropriate behavioral tests. The assessment for children younger than 30 months was based on their psychomotor performance (Brunet-Lezine Psychomotor Development Test) and mental development (Psyche Cattell Intelligence Test for Small Children). Mental development for children age 30 months or older but younger than 5 years of age was evaluated on the basis of the Termann-Merrill Mental Development Test, and mental development for children age 5 years or older was evaluated with the Wechsler Intelligence Scale for Children. Levels of mental development were separated into 6 strata ranging from normal to profound delay. The strata were based on the number of SDs below the mean for the test result, ranging from less than 1 SD below the mean to greater than 5 SDs below the mean. The classification was generally based on the International Statistical Classification of Diseases and Related Problems Ninth Revision. The upper 3 strata—normal, normal (low average), and mild delay—were classified as fair mental status. The lower 3 strata—moderate, significant, or profound delay—were classified as poor mental status. Seven children for whom formal psychometric test results were not available were assessed on the basis of the chart review.

The following coding system was used for the analysis: sex (female or male)—analyzed as male sex, or not; DTP immunization status at time of seizure onset—analyzed as whether the patient had received a DTP immunization before seizure onset, or not; seizure type—infantile spasms, generalized seizures (other than infantile spasms), partial seizures, absence seizures, or none; analyzed as infantile spasms, or not; age at onset of seizures (in months)—analyzed as before 6 months of age, or not (ie, later in life or not during the period of observation); and developmental status—fair mental status (normal average), normal (low average), and mild delay) or poor mental status (moderate, significant, or profound delay).

The prevalence rate of each variable was assessed in the study population and described as a percentage with its exact binomial 95% confidence interval (CI). For both seizure type and mental status, prevalence rates were also calculated for subgroups. Gender, DTP immunization status at time of seizure onset, age at seizure onset, and seizure type were considered to be exposure factors of interest, based on concerns previously raised in the medical literature. Mental retardation, ie, poor mental status (moderate to profound delay) was defined as the case definition or outcome of concern.

With the use of case-control analysis, the strength of association (crude odds ratio [OR]) between mental retardation (moderate to profound) and exposure to each potential risk factor was calculated. Odds ratios whose exact 95% CI excluded the value of 1.0 were considered to be statistically significant. Stratified case-control analysis was conducted for those potential risk factors that showed a statistically significant association in the crude OR analysis. This analytic strategy identified independent risk factors by controlling for the effect of other strong ORs. The results of the stratified analysis were reported as adjusted ORs, which were calculated by means of Epi Info 6.0 software (Centers for Disease Control and Prevention, Atlanta, Ga) and shown as an OR with its 95% CI. Adjusted ORs whose 95% CI excluded the value of 1.0 were considered to be statistically significant and to indicate an independent risk factor.

The age at seizure onset distributions for children with TSC with seizure onset during the first 4 months of life were compared for those with previous DTP immunization and those without it. This analysis was based on χ² analysis and comparative proportions by means of Epi Info 6.0 software and reported as the P value. A P value less than .05 was considered to be statistically significant.

RESULTS

The descriptive characteristics of the patients according to the exposures of interest are seen in Table 1. The study population consisted of 59 girls (56%) and 47 boys (44%).

rodertional status (ie, mental retardation). The possible risk factors available for analysis included sex, history of DTP immunization before seizure onset, age at time of seizure onset, and seizure type.
Twenty (19%) of the 106 patients had not had a DTP immunization before their seizure onset. Half of the patients (54/106 [51%]) had their seizure before the age of 6 months. About two thirds of the patients had infantile spasms (66/106 [62%]). Generalized seizures (other than infantile spasms) were the next most common form of seizure (24/106 [23%]), followed by partial seizures (8/106 [8%]) and absence seizures (4/106 [4%]). Only 4 (4%) of the 106 patients did not have a clinical history of seizures, 1 of whom had mild mental retardation.

Table 2 shows the distribution of mental development status by various levels of severity. Patients with TSC were classified by mental development strata and as having either fair mental development status (normal to mild delay) or poor mental development status (moderate to profound delay). The mental development status level could be assessed for 105 of the 106 patients. One patient with infantile spasms in the second month of life and a history of DTP immunization died in early infancy from the cardiac manifestations of tuberous sclerosis complex. She did not have her developmental status assessed. Forty-eight percent of the patients (50/105) were assessed to have normal mental development status, 48% (50/105) were assessed to have fair mental development status (normal to mild delay) or poor mental development (moderate to profound delay). Twenty (19%) of the 106 patients had not had a DTP immunization before their seizure onset. Half of the patients (54/106 [51%]) had their seizure before the age of 6 months. About two thirds of the patients had infantile spasms (66/106 [62%]). Generalized seizures (other than infantile spasms) were the next most common form of seizure (24/106 [23%]), followed by partial seizures (8/106 [8%]) and absence seizures (4/106 [4%]). Only 4 (4%) of the 106 patients did not have a clinical history of seizures, 1 of whom had mild mental retardation.

As the initial analysis had shown a statistically significant association for both infantile spasms and seizure onset within the first 6 months, stratified analysis was also performed for infantile spasms as a risk factor adjusted for the age at seizure onset. The odds for infantile spasms showed little change with adjustment for the age at onset and remained a statistically significant measure of the strength of association (OR, 3.0; 95% CI, 1.1-8.4; P = .03). Thus, infantile spasms were confirmed to be a risk factor for poor mental development in patients with TSC, independent of the age at seizure onset.

Table 1. Descriptive Characteristics of 106 Patients With Tuberous Sclerosis Complex According to Exposures of Interest

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) of Patients</th>
<th>95% Confidence Interval</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Female</td>
<td>59 (55.7)</td>
<td>45.7-65.3</td>
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<tr>
<td>Male</td>
<td>47 (44.3)</td>
<td>34.7-54.3</td>
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<tr>
<td>History of DTP*</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>86 (81.1)</td>
<td>72.4-88.1</td>
</tr>
<tr>
<td>No</td>
<td>20 (18.9)</td>
<td>11.9-27.6</td>
</tr>
<tr>
<td>Seizure onset at &lt;6 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>54 (50.9)</td>
<td>41.0-60.8</td>
</tr>
<tr>
<td>No</td>
<td>52 (49.1)</td>
<td>39.2-59.0</td>
</tr>
<tr>
<td>Seizure type</td>
<td></td>
<td></td>
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<tr>
<td>Infantile spasms</td>
<td>66 (62.3)</td>
<td>52.3-71.5</td>
</tr>
<tr>
<td>Generalized</td>
<td>24 (22.6)</td>
<td>15.1-31.8</td>
</tr>
<tr>
<td>Partial</td>
<td>8 (7.5)</td>
<td>3.3-14.3</td>
</tr>
<tr>
<td>Absence</td>
<td>4 (3.8)</td>
<td>1.0-9.4</td>
</tr>
<tr>
<td>None</td>
<td>4 (3.8)</td>
<td>1.0-9.4</td>
</tr>
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* DTP indicates diphtheria, tetanus, and pertussis immunization.

Table 2. Descriptive Characteristics of 106 Patients With Tuberous Sclerosis Complex According to Outcome of Interest

<table>
<thead>
<tr>
<th>Mental retardation status</th>
<th>No. (%) of Patients</th>
<th>95% Confidence Interval</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>16 (15.1)</td>
<td>8.9-23.4</td>
</tr>
<tr>
<td>Low average</td>
<td>17 (16.0)</td>
<td>9.6-24.4</td>
</tr>
<tr>
<td>Mild delay</td>
<td>17 (16.0)</td>
<td>9.6-24.4</td>
</tr>
<tr>
<td>Moderate delay</td>
<td>20 (18.9)</td>
<td>11.9-27.6</td>
</tr>
<tr>
<td>Serious delay</td>
<td>20 (18.9)</td>
<td>11.9-27.6</td>
</tr>
<tr>
<td>Profound delay</td>
<td>15 (14.2)</td>
<td>8.1-22.3</td>
</tr>
<tr>
<td>Undetermined</td>
<td>1 (0.9)</td>
<td>0.02-5.1</td>
</tr>
<tr>
<td>(early death)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The patient whose mental status was undetermined because of early death was excluded from this analysis.
Half of the patients with TSC (10/20 [50%]) who had seizure onset before their first DTP immunization had no delay in their immunizations. Rather, their seizure onset occurred before the scheduled start of their DTP immunizations (Table 4). The other half (10/20 [50%]) had their immunizations postponed for various reasons. Three of these patients (3/20 [15%]) had perinatal complications that had been considered a contraindication for immunizations (ie, low Apgar scores). One patient (1/20 [5%]) had his immunizations postponed until he recovered from perinatal cardiac problems. Four other patients (4/20 [20%]) had immunizations postponed because of concurrent or recent infections in the third month (3 with respiratory tract infections and 1 with acute diarrhea).

The analysis by DTP immunization history might be confounded if patients did not get DTP immunization because they had TSC. Among the 20 patients without a history of DTP immunizations before seizure onset, only 2 may have had their immunizations postponed for reasons possibly related to TSC. One patient (1/20 [5%]), the child of a woman with TSC, had typical skin lesions of TSC observed before the onset of seizures and had not previously had a DTP immunization. Another child (1/20 [5%]) did not have DTP immunization because of early signs of developmental delay. However, her seizure onset was at age 5 years, and her TSC was not diagnosed until she was 12 years old. Analysis with these 2 cases removed from the data set did not change the nature of the analytic results.

Eighteen of the 20 infants with seizure onset before DTP immunization had seizure onset during the first 4 months of age. The distribution of age at time of seizure onset for these infants did not differ from the distribution for infants with seizure onset in the first 4 months of life and with previous DTP immunization (Table 5). Table 5 demonstrates that the proportions of patients with seizure onset in the 2 groups are similar for each of the first 4 months of life. The \( P \) value across each stratum ranged from .16 to 1.00, and the \( P \) value based on the overall \( x^2 \) distribution was .37.

Analysis has demonstrated that a clinical manifestation of infantile spasms in a child with TSC is a major determinant or predictor that the child will develop mental retardation. Seizure onset within the first 6 months of life was not an independent predictor of mental retardation. Neither sex (male vs female) nor history of DTP immunization before seizure onset was found to be a risk factor or predictor for mental retardation in children with TSC.

**COMMENT**

This study of 106 patients with TSC is one of the largest clinic-based TSC studies published. We have presented both a description of our study population and an analysis of our observations. In particular, we have focused on the factors that have been asserted to be associated with adverse
mental development in patients with TSC, ie, mental retardation. We have looked at those factors for which we generally had full information for all patients. These factors included sex, DTP immunization before the age at seizure onset, and seizure type. Other publications have reported the cortical tuber count (>7) detected by magnetic resonance imaging as a major determinant of mental retardation.10 While the cortical tuber count distribution of our few patients for whom magnetic resonance images were available (n=11) is consistent with those findings, the results (OR, 6.0) are not statistically significant and cannot be presumed to be representative.

Overall, the prevalence of mental retardation in our TSC population does not differ from that reported elsewhere. Our literature search identified 3 major types of studies reporting on TSC populations: clinic-based, population-based, and family-based. We have selected the largest and most recent studies11-13 from each of the mentioned types to compare their findings with ours. The Figure demonstrates that the prevalence of moderate to profound mental retardation across the population-based and clinic-based studies ranged between 52% and 55%. A family-based study by Webb et al13 reported a somewhat lower prevalence of neurodevelopmental abnormalities. This report was based on a study group of 26 patients with TSC born in the families who sought genetic counseling after they had more than 1 affected member. It is important to note that this study, by its design, excluded the spontaneous mutations, which account for approximately 60% of all TSC cases.

Although some of the literature on TSC6 reported that boys were at greater risk of learning disorder than girls, our findings did not support this observation. Our analysis found an OR of 1.1 for male sex, which was reduced to 0.7 when adjusted for seizure type. Neither OR was significantly different from 1.0.

When we specifically examined DTP immunization as a risk factor among patients with TSC, no evidence of an association was found. Immunization for DTP has been assessed as a risk factor for infantile spasms both in an ecological analysis by Melchior14 and in epidemiological analyses by Bellman et al15 and Goodman et al.16 Melchior had compared the age at onset of seizures distributions for patients with infantile spasms admitted to 1 Danish hospital from 1957 to 1967, when DTP immunization was begun at 5 months of age, with that of patients with infantile spasms admitted to 20 Danish pediatric departments from 1970 to 1975, when pertussis immunization was begun at 5 weeks of age. He reported that “there was no change in the age of onset of infantile spasms.” Bellman et al15 conducted a case-control study of infantile spasms cases in the National Childhood Encephalopathy Study and found no significant association between infantile and pertussis immunization during the 28 days before onset. They did report that some of the patients with infantile spasms appeared to have an accelerated onset of spasms. Goodman et al16 later demonstrated that this temporal shift in the onset of seizures was limited to patients who were previously normal and was not observed among those who were previously abnormal (eg, those with TSC). The US Institute of Medicine evaluated the literature on infantile spasms and DTP immunizations and concluded that there was no evidence of a causal relationship.17

It has been postulated that early seizures may lead to the disruption of brain function and ultimately result in mental retardation. In contrast, our analysis showed that the age at onset of seizures was not significantly associated with poor mental development, after the presence of infantile spasms had been controlled for. The apparent association with age at onset reflects the age distribution of patients with infantile spasms. Among our patients, infantile spasms were recorded for 85% of those with seizure onset within the first 6 months of life and for only 38% of those with seizure onset after the first 6 months of life. Among our patients with infantile seizures, the proportion who developed moderate to profound mental retardation was the same for those with onset of seizures in the first 6 months of life as it was for those with onset of seizures in the second 6 months of life. This finding is consistent with the observation of Riikonen18 that the mean age at seizure onset for patients with infantile spasms with normal IQs as adults was 6.4 months and that for patients with infantile spasms lacking normal IQs as adults was 6.1 months. It appears, therefore, that the most important single clinical finding associated with poor neurodevelopmental outcome is the presence of infantile spasms.

Goodman et al10 published a meta-analysis of the data from studies of patients with TSC from which they concluded that the cortical tuber count detected by magnetic resonance imaging was a biomarker indicating the magnitude of cerebral severity of TSC. They demonstrated that the cortical tuber count detected by magnetic resonance imaging is strongly associated with both early, poorly controlled seizures, such as infantile spasms, and moderate or greater levels of mental retardation. They found, across studies, that moderately to profoundly affected patients with TSC were 5 times more likely to have greater than 7 cortical tubers detected on magnetic resonance images than were those more mildly affected. This finding solidified the earlier observations that the cortical tuber count demonstrates the degree of cortical disruption and the relationship with clinical function.19-21 This disruption is probably the most important factor in

**Figure** Comparative prevalence of moderate to profound neurodevelopmental delay in various tuberous sclerosis study populations.
determining the severity of neurological manifestations of TSC.

CONCLUSIONS

Our analysis confirms the previously published reports that the presence of infantile spasms is strongly associated with poor (moderate to profound mental retardation) mental developmental outcome. The association between the age at onset of seizures (younger than 6 months) and moderate to profound mental retardation in patients with TSC is not an independent association but reflects the age distribution of infantile spasms. When the data were controlled for the presence of infantile spasms, there was no statistically significant association. Our study did not show any sex difference in the prevalence of moderate to profound mental retardation among patients with TSC. There was no evidence of association between previous exposure to DTP vaccine and moderate to profound mental retardation. Half of the children without previous DTP exposure had seizure onset before their scheduled DTP immunization. For infants with seizure onset in the first 4 months of life, there was no difference in the distribution of age at time of onset for those with and those without previous DTP immunization.

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REFERENCES