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Learning disability and epilepsy in an epidemiological sample of individuals with tuberous sclerosis complex

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ABSTRACT

Background. Intellectual impairments are a recognized feature of tuberous sclerosis complex (TSC), but the frequency and degree of intellectual impairments has not been systematically studied in large epidemiological samples using standardized measures. As such, the form of the IQ distribution (uni- or bi-modal) has not been established and the relationship between IQ and other features (e.g. epilepsy history) is poorly delineated. To address these shortcomings, we assessed the intellectual abilities of a large epidemiological sample of individuals with TSC, drawn from the 'Wessex' area of SW England and compared them with the abilities of their unaffected siblings.

Method. Standardized tests were used to estimate the abilities of 108 (56 males, 52 females, median age = 25, range = 4–75) individuals with TSC and 29 unaffected siblings (14 males, 15 females, median age = 18, range = 6–55). Seizure history was obtained from informants and medical records.

Results. Estimated IQ was bi-modally distributed: 55·5% had an IQ in the normal range; 14% had mild to severe impairments; and 30·5% had profound disability (IQ < 21). Forty-four per cent of the individuals with TSC had an IQ < 70. In the subset of normally intelligent individuals with TSC, IQ was normally distributed with a mean of 93·6. This mean was significantly lower than the mean IQ of unaffected siblings (IQ = 105·6). All individuals with learning disability had a history of seizures that usually commenced before 12 months of age and that often presented as infantile spasms. Multivariate analyses indicated that a history of seizures as well as a history of infantile spasms was predictive of the degree of intellectual impairment.

Conclusions. Intellectual abilities were bi-modally distributed in a representative sample of individuals with TSC. The likelihood of impairment was associated with a history of seizures, particularly infantile spasms. The genetic and brain basis of these findings requires further investigation.

INTRODUCTION

Tuberous sclerosis complex (TSC) is a genetic disorder with a point prevalence rate of around 1:10 000 (O'Callaghan, 1999). It is caused by a mutation of either the TSC1 gene located at chromosome 9q34 or the TSC2 gene located at chromosome 16p13 (Povey *et al.* 1994). Approximately two-thirds of mutations are sporadic and the rest are inherited in an autosomal dominant fashion. The mutations result in the formation of hamartias and hamartomas (benign tumours), which can develop anywhere in the body, but which frequently arise in the skin, eyes, heart, kidneys, lungs and brain (Gomez, 1999). The hamartias/hamartomas underlie the development of various complications such as cardiac/renal dysfunction, epilepsy, learning disability, autism and hyperactivity.

Several studies have estimated the prevalence of learning disability in TSC. Population-based

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Table 1. *Previous population-based studies looking at the rate of learning disability in TSC*

Study	*N*	Rate of learning disability (%)
Nevin & Pearce (1968)	18	(61)
Hunt & Lindenbaum (1984)	68	(65)
Wiederholt *et al.* (1985)	8	(50)
Shepherd & Stephenson (1992)	104	(56)
Gillberg *et al.* (1994)*	28	(64)
Webb *et al.* (1996)	131	(53)

* Standardized cognitive testing.

studies have reported rates ranging from 50–65% (Table 1). However, only one of the studies undertook standardized assessments of IQ (Gillberg *et al.* 1994). The others estimated the level of disability on the basis of educational history, clinical reports and literacy level. Consequently, an accurate estimate of learning disability (mental retardation) in TSC is yet to be established. Some of these studies have suggested a bimodal distribution of ability, with most individuals having either normal intelligence or a severe or profound impairment (Hunt & Lindenbaum, 1984; Shepherd & Stephenson, 1992; Webb *et al.* 1996). However, bimodality in the distribution of IQ has not yet been confirmed, even though its presence would cast light on the mechanisms that underlie intellectual impairments in TSC (see Harrison & Bolton, 1997 for a discussion). If the distribution proves to be bimodal, another research question in need of investigation is whether individuals with TSC who are normally intelligent have lower IQs than expected when compared to unaffected siblings. One small study conducted on patients who lived in 'Wessex', compared a clinical sample of seven individuals with TSC who were normally intelligent with an unaffected control group of nine individuals. A significantly greater overall rate of specific cognitive deficits was found in the individuals with TSC (Harrison *et al.* 1999).

Previous studies have shown a number of factors to be associated with the presence of learning disability in TSC. In particular, an association with epilepsy has been widely reported. For example, the majority of reports have found that individuals with TSC almost invariably have a history of seizures (Curatolo *et al.* 1991; Webb *et al.* 1991, 1996; Shepherd & Stephenson, 1992; Shepherd *et al.* 1995). Several reports have also indicated that early age at onset of epilepsy, poor control of seizures and a history of infantile spasms are associated with an increased rate of learning disability (Shepherd & Stephenson, 1992; Webb *et al.* 1996).

In addition, intellectual impairments have been found to be associated with the nature and extent of cerebral pathology. Brain abnormalities in TSC consist of subependymal nodules which line the walls of the ventricles and occur in up to 95% of patients (Kingsley *et al.* 1986), and cortical tubers which arise at the cortical grey/white matter interface. With the advent of MRI scanning it has been shown that the size, number and location of cortical tubers vary markedly from individual to individual. They are most often found in the frontal, temporal and parietal lobes (Bolton & Griffiths, 1997; Shepherd *et al.* 1995). The number of tubers is related to degree of intellectual impairment (Jambaque *et al.* 1991; Shepherd *et al.* 1995; Bolton & Griffiths, 1997).

The rate of intellectual impairment also appears to be related to genotypic status as significantly higher rates of impairment have been reported in individuals with the TSC2 mutation (Jones *et al.* 1997, 1999; Young *et al.* 1998). The differences in the severity of disorder and the degree of intellectual impairments in relation to the type of genetic mutation may reflect differences in the likelihood of 'second hit' somatic mutations at each gene locus. The 'second hits' occurs during embryogenesis and knocks out the remaining normal copy allele. As a result, clonal abnormalities in cell proliferation, migration and differentiation develop and manifest as hamartomas (e.g. subependymal nodules/cortical tubers). Alternative explanations include a fundamental difference in intracellular mechanisms or a dominant negative effect.

The question of whether there is a gender difference in the rate of learning disability in TSC has also been investigated, with conflicting results. Webb *et al.* (1996), in an earlier investigation of individuals with TSC in the Wessex region found an increased rate of learning disability in males. However, this has not been reported in other epidemiological series. In addition, Webb *et al.* (1996) found males to have higher rates of epilepsy, seizure onset in the first year, infantile spasms and poor seizure control.

The rates of learning disability have also been shown to vary with age, with higher rates of

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learning disability found in children than among adults (Sampson *et al*. 1989; Webb *et al*. 1996). These findings may reflect an age related increase in mortality in individuals with TSC and learning disability, or may also be partly due to a correlation between age and the probability of ascertainment. This could have arisen, for example, from changing diagnostic awareness of clinicians and reducing mortality rate of individuals with learning disability born during the latter part of the last century.

The main aims of this study were to accurately determine the rate and severity of learning disability in a relatively large epidemiological sample of individuals with TSC and to examine the distribution of intellectual abilities using standardized measures of intelligence and adaptive behaviour. Associations between gender, ability level, epilepsy (including age at onset of seizures and infantile spasms) were examined. These factors were then investigated for their contribution to the explanation of variance in intellectual ability. IQ scores of individuals with TSC of normal intelligence were compared to those of unaffected siblings. The population studied was originally partly ascertained by Webb *et al*. (1996) and more recently re-ascertained by O'Callaghan and colleagues 1998).

METHOD

Participants

Participants for the study were identified in a census conducted in 1998 (see O'Callaghan *et al*. 1998 for details), which found 179 patients (94 males, 85 females, median age = 26, range = 0–87) with a confirmed diagnosis of TSC in the Wessex area of SW England. The total population of Wessex at the time of the census was 3·7 million, giving a prevalence of TSC of 4·9 per 100000 (95% confidence interval 4·2 to 5·6).

Out of 179 TSC patients, 108 (56 males, 52 females, median age = 25, inter-quartile range (IQR) 26, range = 4–75) agreed (or parent/guardian gave consent for patient) to undergo cognitive testing. Of the 71 patients who did not agree to a full cognitive assessment, 35 did agree to a clinical assessment and review of their medical records. Information from GPs and review of previous research records from the Webb *et al*. (1996) study provided information about the prevalence of learning disability (ability to talk, read, write and undertake self-help) and epilepsy in the remaining 36 patients. The sample who did not agree to a full cognitive assessment ($N = 71$) were compared to those who did agree to be assessed ($N = 108$) on a number of variables. The assessed sample were no different to the remainder in terms of age (non-assessed median age = 28, IQR = 27, range = 0 to 88; Mann–Whitney U test (MWU) $P = 0{\cdot}35$), gender (non-assessed sample comprised: 38 males, 33 females, Fisher's exact (FE) $P = 0{\cdot}88$), rate of learning disability (26/71 and 48/108, FE $P = 0{\cdot}35$), or rate of epilepsy (45/66, information on seizures was unavailable for five individuals out of the 71, and 85/108, FE $P = 0{\cdot}15$). In those with epilepsy there was no difference between the assessed sample and the remainder in terms of the frequency of infantile spasms (20/45 *versus* 51/85, FE $P = 0{\cdot}10$). Survival analysis (Cox's proportional hazard; age of seizure onset censored at age of assessment) confirmed that the assessed and unassessed samples did not differ significantly in terms of age of seizure onset (hazard ratio for recruitment = 1·41; $P = 0{\cdot}07$).

Twenty-nine unaffected siblings (14 males, 15 females, median age = 18, range = 6–55) also agreed to be tested. Unaffected siblings were chosen in order to control for familial influences on IQ. For example, in epidemiological studies of this kind there may be biases in recruitment relating to social class, which may lead to differences in the IQ of cases compared with the normal population. In addition, if one parent has a low IQ due to TSC, assortative mating may result in both parents having a lower IQ and IQ in their children (affected and unaffected) would be biased toward the lower end of the distribution.

Procedure

Individuals were assessed in their own home or place of residence, or at the Royal United Hospital, Bath. A full medical history was taken and a clinical examination was performed to confirm the diagnosis according to the criteria initially outlined by Gomez (1979) but subsequently modified to require two independent hamartomas to be certain of the diagnosis (O'Callaghan & Osborne, 2000). Details on seizure history, including age at onset of seizures, history of infantile spasms and number of individuals with current seizures (presence of seizures in last

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12 months) were obtained through clinical interview with patient, parent or carer and through examination of medical records. The study also sought to determine whether a case was familial or sporadic. Familial cases were those who had a parent with a confirmed diagnosis of TSC, and sporadic cases were those where both parents were examined and confirmed not to have clinical evidence of TSC.

Those agreeing to full cognitive assessment ($N=108$) received a battery of standardized tests of ability including the Vineland Adaptive Behaviour Scale (Sparrow *et al*. 1984), the Wechsler Intelligence Scale for Children (WISC-III) (Weschler, 1992) or the Weschler Adult Intelligence Scale (WAIS-R) (Weschler, 1986), and Raven's Coloured Matrices (Raven, 1965). The Vineland Scale was given to all patients, Raven's Coloured Matrices was given to those with normal intellect and mild to moderate impairment ($N=63$), and the WISC-III or WAIS-R was given to patients aged >5 years with normal intellect or mild impairment ($N=56$).

In individuals who could not be tested using the Wechsler scales, scores derived from Raven's Coloured Matrices and Vineland Adaptive Behaviour Scales were used to estimate IQ. In order to check the validity of this procedure we examined the correlation between Raven's and Vineland scores with the IQ scores obtained from the WISC-III and WAIS-R scales in those individuals that completed both sets of tests. WISC-III or WAIS-R IQ scores were significantly correlated with Raven's converted IQ scores in the group of 53 individuals who had scores on both sets of tests ($r=0{\cdot}66$, $P<0{\cdot}001$). Similarly, Vineland Adaptive Behaviour scores were significantly correlated with IQ scores from the WISC-III or WAIS-R ($r=0{\cdot}76$, $P<0{\cdot}001$) in the group of 55 individuals who had scores on both these sets of test. Using standard scores derived from one of these measures, individuals were categorised as having normal ability (standard score >69), mild (standard score = 50–69), moderate (standard score = 35–49), severe (standard score = 21–34), or profound disability (standard score <21).

The Family History Interview (FHI) (Bolton *et al*. 1994; Fombonne *et al*. 1997) was used to provide a screen for a history of language difficulties, and social-communication problems in individuals of normal ability. A standardized assessment of language problems, the Clinical Evaluation of Language Fundamentals (CELF-R) (Semel *et al*. 1987), was administered to children aged five to 16 years. When behaviours suggestive of social-communication problems were reported in the FHI for a patient, the Autism Diagnostic Interview-Revised (ADI-R) (Le Couter *et al*. 1989) and Autism Diagnostic Observation Schedule (ADOS) (Lord *et al*. 1989) were administered to check for the presence of autistic disorder. Details from these assessments were used to identify individuals of normal intellect with receptive language disorder or autism spectrum disorders.

Analyses

Analyses were done using the Statistical Package for the Social Sciences (SPSS) Version 9 for Windows and STATA version 7 (Stata Corporation). In the sample of 108 individuals with TSC who agreed to a full cognitive assessment, contingency table analyses were performed to examine the associations between gender, ability level, and history of epilepsy (including a history of infantile spasms). Survival analysis was carried out in STATA (version 7) using Cox's proportional hazard model with age of seizure onset censored at age of assessment. Multivariate ordinal logistic regression (STATA 7) was used in multivariate analyses of the predictors of intellectual ability. The IQ scores of TSC patients of normal intelligence (IQ >69) were compared to those of unaffected siblings (not necessarily from the same family as the individuals with TSC). Analyses were repeated with sporadic cases alone ($N=85$) to check that ascertainment biases were not leading to a misrepresentative picture. The study was approved by the Multi-Centre Research Ethics Committee and by the Local Research Ethics Committees for each Health Authority involved.

RESULTS

Distribution of intellectual ability

In the sample of 108 individuals who received a full cognitive assessment, 55·5% ($N=60$) had normal intellectual ability (IQ >69) and 44·4% ($N=48$) had learning disability (mental retardation).

The distribution of ability level of the 108 individuals with TSC was constructed from

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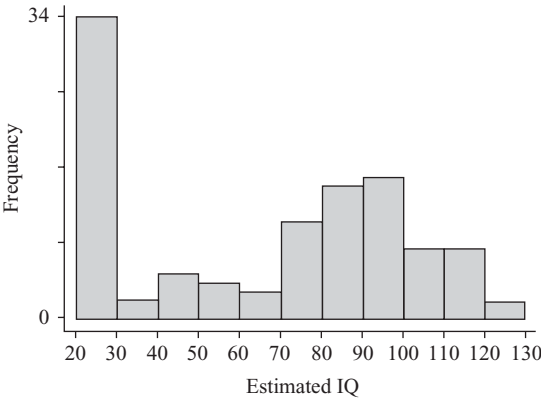


FIG. 1. Histogram illustrating the bimodal IQ distribution.

individuals' standard scores. In the distribution, the majority of standard scores were IQ scores derived from the WISC-III or WAIS-R ($N=56$, those patients aged >5 years with normal intellect or mild impairment) or Adaptive Behaviour scores derived from the Vineland scale ($N=42$, patients with severe to profound impairment). The Raven's converted IQ score was used for estimating IQ in children of normal intellect aged <6 years, and for some adult patients with mild to moderate impairment ($N=10$).

The distribution of standard scores was bimodal (see Fig. 1) with 55·5% ($N=60$) having normal ability and 30·5% ($N=33$) having profound impairment. Only 14% ($N=15$) had a non-profound (mild, moderate or severe) impairment. Individuals with profound impairment had age equivalent scores (derived from the Vineland Adaptive Behaviour Scale) ranging from 4 months to 2 years and 9 months (median Age Equivalent score = 1 year and 3 months).

Epilepsy, seizure onset and infantile spasms

In 108 individuals with TSC, 79% (85/108) had a history of seizures. Median age of seizure onset in the 85 individuals with epilepsy was 7 months with an IQR of 14 months. Of those patients with epilepsy, 60% (51/85) had a history of infantile spasms.

Association of gender with ability, epilepsy, seizure onset and infantile spasms

Among the 108 individuals with TSC there was no association between gender and ability (median IQ females = 78, IQR = 74·5; median IQ males = 73·5, IQR = 73·5, MWU $P=0·49$). In addition, gender was not significantly associated with epilepsy (45/56 males, 40/52 females, $\chi^2=0·19$, $P=0·66$), age of seizure onset (median age of onset in males = 8 months IQR = 14 months; median age of onset in females = 5 months IQR = 21, hazard ratio = 1·06; $P=0·78$), or the frequency of infantile spasms (25/45 males, 26/40 females, $\chi^2=0·78$, $P=0·37$). In the group of 11 individuals who had normal intelligence following infantile spasms, there were four males (IQ 72, 77, 88, 100) and seven females (IQ 75, 77, 79, 80, 88, 98, 102). Kaplan–Meier survival plots for age to seizure onset (censored at age of assessment) in males and females are shown in Fig. 2.

Association of ability with epilepsy, seizure onset, infantile spasms

Table 2 summarizes details of IQ scores according to a history of epilepsy and infantile spasms. A history of epilepsy (MWU $P<0·001$) and infantile spasms (MWU $P<0·001$) was strongly associated with a reduction in IQ. Results also showed that all individuals with a learning disability had a history of epilepsy. The majority of individuals with learning disability had seizures that began at or before 12 months, and all but two individuals with profound impairment had a history of infantile spasms. Survival analysis (Cox's regression) confirmed that age to seizure onset (censored at age of assessment) was also strongly associated with IQ score (hazard ratio = 0·97; $P<0·0001$).

Although the mean IQ of the cognitively tested patients with normal ability and epilepsy ($N=37$, mean IQ = 91·4, S.D. = 13·7) was slightly lower than that of patients with normal ability and no epilepsy ($N=23$, mean IQ = 97, S.D = 13·7), this difference was not statistically significant ($t=-1·5$, df = 58, $P=0·13$). However, survival analysis revealed that age to seizure onset was still, albeit weakly, significantly associated with IQ in the normally intelligent subgroup (hazard ratio = 0·97; $P=0·043$).

Contribution of epilepsy, age at seizure onset and infantile spasms to the explanation of variance in IQ

An ordinal logistic regression analysis was performed with the 108 individuals with TSC to examine the contribution of presence of epilepsy, age at seizure onset, and history of infantile

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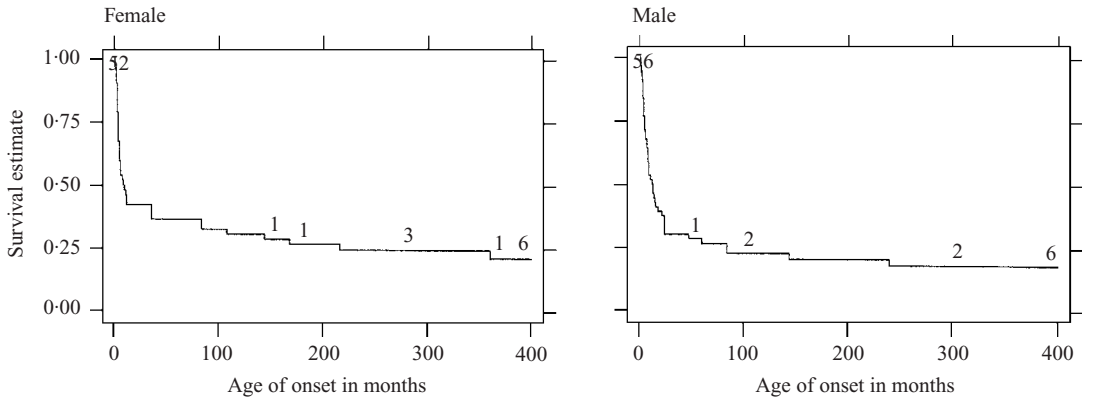


FIG. 2. Kaplan–Meier survival estimates, age of seizure onset by sex. The number of cases entered are indicated at the top of each curve and the number and age of cases lost to censoring are indicated above the plotted lines. No sex differences in age of seizure onset were found.

Table 2. *Intellectual ability and epilepsy history*

Seizure history	*N*	Median IQ	Inter-quartile range	Range
Absent	23	95	20	73–120
Present	85	53	68	<20–130
No spasms	34	87·5	24	<20–130
Spasms	51	42	42	<20–102

spasms to the explanation of variance in ability. The only variables that made a significant independent contribution were a history of epilepsy ($z = -2{\cdot}1$, $P = 0{\cdot}03$) and history of infantile spasms ($z = -2{\cdot}5$, $P = 0{\cdot}01$) (LR $\chi^2 = 56{\cdot}4$, $R^2 = 0{\cdot}09$, $P < 0{\cdot}001$).

Comparison of IQ of individuals with TSC of normal ability and unaffected siblings

As the bimodal distribution of intellectual ability indicated that there was an admixture of TSC populations, we compared the IQ scores in the more able group with those of the unaffected siblings, in order to see if TSC was associated with a lower IQ within this more able subgroup. As it was not possible to determine precisely a threshold that would separate the populations, we chose to look at individuals with an IQ of >69. The distribution of IQ scores of the individuals with TSC and normal ability is shown in Fig. 3. The magnitude of skewness (0·44, S.E. = 0·31) and kurtosis (−0·37, S.E = 0·61) did not indicate any significant deviation from the normal distribution.

One unaffected sibling was found to have an IQ below the threshold for normal ability (IQ = 69), comparisons were conducted including and excluding this individual to see if there was any difference in the outcome. Mean IQ of the unaffected siblings was significantly higher with this sibling included (mean = 104·3; S.D. = 12·3; $t = -3{\cdot}5$, df = 87, $P = 0{\cdot}001$; mean difference to TSC cases = 10·7, d_s (effect size) = 0·8) or excluded ($t = -4{\cdot}1$, df = 86, $P < 0{\cdot}001$, mean difference = 12, $d_s = 0{\cdot}97$) from the analysis. Further tests were conducted to determine whether mis-specification of the threshold for partitioning the TSC population was responsible for the differences in IQ. When IQ score from just the individuals with TSC who did not suffer from epilepsy ($N = 23$, mean IQ = 97, S.D. = 13·7) were compared to IQ scores of siblings, the difference remained significant ($t = -2{\cdot}0$, df = 50, $P < 0{\cdot}05$, mean difference = 7·3, $d_s = 0{\cdot}7$). The group difference also remained significant when individuals with TSC who had current seizures ($N = 11$, presence of seizures in the last 12 months) were excluded, (TSC mean IQ = 95·3, S.D. = 14·2, $t = -3{\cdot}3$, df = 75, $P = 0{\cdot}001$, mean difference = 10·2, $d_s = 0{\cdot}8$). Lastly, when individuals with TSC who had autism spectrum disorder and/or receptive language disorder ($N = 7$) were excluded, the group difference remained (TSC mean IQ = 94·5, S.D. = 14·0, $t = -3{\cdot}7$, df = 79, $P < 0{\cdot}0001$, mean difference = 11·1, $d_s = 0{\cdot}9$).

Analyses with sporadic cases

Whether a case was familial or sporadic could be determined for 137 out of 179 individuals, with 49 familial and 88 sporadic cases. We repeated our analysis just focusing on the sporadic cases,

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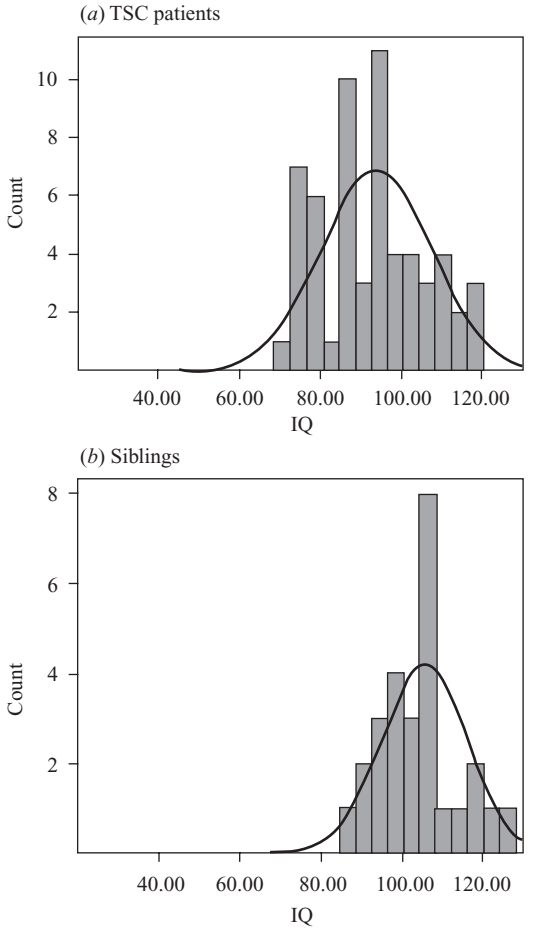


FIG. 3. Histograms of IQ scores for 60 individuals with TSC and normal ability (mean IQ = 93·6, S.D. = 13·8) and 28 unaffected siblings (mean IQ = 105·6, S.D. = 10·5).

to determine whether the overall pattern of findings was the same. These results were not significantly different to those obtained in the sample as a whole (data not shown), although the overall rate of learning disability was slightly, but not significantly, higher (50%) in the sporadic cases. However, as expected familial cases were in general more mildly affected. Thus, they had a significantly higher IQ score (MWU $P = 0{\cdot}0008$), a significantly reduced chance of developing seizures (FE $P < 0{\cdot}0001$) and a significantly later age of onset of seizures (hazard ratio = 0·38; $P < 0{\cdot}0001$). If they did develop epilepsy it less often tended to present as infantile spasms (FE $P = 0{\cdot}063$).

DISCUSSION

The prevalence of learning disability (mental retardation) in the sample of 108 individuals with TSC was 44·4%. This is a lower prevalence rate than that reported in earlier population-based studies, including that estimated in the previous ascertainment of the Wessex population (Webb *et al.* 1996). The lack of standardized cognitive testing in previous studies is one likely reason for the differing results. Only one of the earlier studies (Gillberg *et al.* 1994) employed standardized cognitive testing, but the sample size was too small ($N = 28$) to provide accurate figures on the rate of learning disability. Another possibility is that previous studies overestimated the rates of disability because they failed to identify the most mildly affected individuals. The systematic, serial and fairly exhaustive method of ascertainment employed in selecting the sample for this study (including ascertainment through GPs) is likely to have been more successful in identifying mildly affected individuals. The study by Webb *et al.* (1991) is the only study to find a lower rate of learning disability, reporting 38% in a sample including only secondarily ascertained individuals (the offspring of previously diagnosed individuals with TSC). Such a sample could be argued to represent the most complete spectrum of severity of intellectual impairments in TSC, at least in familial cases. It has been suggested that there may be a relationship between the type of mutation, the severity of TSC and the likelihood of the condition being familial. Thus, TSC1 mutations are thought to give rise to a less severe form of disorder and that more mildly affected individuals are likely to marry and have affected children. The differences in severity we observed between the sporadic and familial cases is compatible with this proposition, but it should be remembered that familial cases also include mildly affected parents that were identified after the diagnosis was established in their child and following thorough medical examination. As such ascertainment biases may also partly explain the observed differences in severity.

In keeping with the suggestive findings in previous reports, a bimodal distribution of ability was found, with most individuals falling into the normally intelligent or profoundly impaired range. This is the first study to demonstrate clearly such a distribution in a population-based

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sample using standardized cognitive tests. There will inevitably have been some mis-specification of ability level in some cases, but measurement error could not account for the pronounced differences in distribution seen here. The results differ somewhat from those reported in the Swedish study of Gillberg *et al.* (1994), where there was less clear evidence of bimodality. However, the number of cases in the Swedish study was very small and this may have obscured the over-representation of profoundly impaired cases. Moreover, IQ in the Swedish study was estimated using just the Wechsler Scales, so an intellectual level below 50 could only be recorded as <50, even if they had marked impairment. This may also have partly obscured bimodality. Our findings suggest that an individual diagnosed with TSC is most likely to have either an IQ in the normal range or a profound learning disability. However, even individuals with normal ability had a lower IQ than the unaffected siblings, indicating that there is also a general shift to the left (lower IQ) in distribution of IQ in the TSC population. The identification of a bimodal distribution of this kind is important because it implies that there may be a specific set of genetic or neuro-epileptic factors that result in profound impairment in TSC. We therefore went on to investigate factors that were associated with learning disability, particularly in the profound range. First, contrary to the findings of Webb *et al.* (1996), males did not have a higher rate of learning disability in this study, and there was no gender difference in the rate of epilepsy, age at onset of seizures, or rate of infantile spasms. In addition, the current study found both males and females in the group with normal ability following infantile spasms, in contrast to Webb *et al.* (1996) who found only females in this category. Since both studies were conducted in the same part of the UK on some of the same patients, this variation may be due to sample differences or measurement error relating to the cruder estimates of IQ used in Webb *et al.*'s (1996) study. We examined the question of possible sex differences in detail, not only because of the previous findings, but also because the very limited available evidence in children with Down's syndrome suggest that sex differences in the extent of intellectual impairment may occur in autosomal conditions (Gath & Gumley, 1986; Carr, 1988). Had we found evidence for a sex difference, it would have provided evidence for a general protective effect of sex on intellectual development. We have to conclude that there is little support for this notion in these data.

The previous reports of an association between epilepsy and learning disability were again confirmed in the current study: all patients with a learning disability had a history of seizures. Seizure onset among individuals with learning disability was most likely to be at or before 12 months of age. In those with profound impairment, onset was most commonly before 5 months, and all but two of these individuals had a history of infantile spasms. These findings suggest that it is the type of seizure at onset that is associated with intellectual outcome, in particular that infantile spasms are associated with profound learning disability. A history of epilepsy and additionally, a history of infantile spasms made significant independent contributions to the variance in IQ.

Patients with TSC of normal intelligence who had a history of epilepsy were found to have a lower mean IQ (not statistically significant) than patients of normal intelligence who had never suffered from seizures. Perhaps with a greater number of patients, the difference would become significant. Interestingly, the age of seizure onset was significantly associated with IQ in this subgroup.

This is the first population-based study to reveal that individuals of normal intelligence (IQ $>$ 69) who have TSC have lower mean IQ than expected when compared to unaffected siblings. Group mean difference in IQ between individuals with TSC and normal intellect and unaffected siblings could reflect either a general decrement in IQ across all individuals, or possibly an admixture of populations. Measures of skewness and kurtosis did not suggest an admixture, but further research will be required to rule out this possibility. When subgroups of individuals with a history of epilepsy, current seizures (presence of seizures in last 12 months), and autism spectrum disorder and/or language impairments were excluded from the comparison, the difference in mean IQ between individuals with TSC and unaffected siblings remained.

Even among individuals with TSC of normal intelligence with no history of epilepsy, mean IQ was found to be lower than that of siblings. This suggests that there are other variables, apart

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from epilepsy that may play a role in determining ability level. The most likely variable would be the number (or perhaps site or size) of cerebral tubers. Previous research has shown presence of infantile spasms and age at onset to be associated with number of tubers as well as ability level (Shepherd *et al.* 1995). Neuroimaging investigations undertaken in the more able group of individuals in this study have confirmed that the number of cortical tubers is associated with IQ. However, a history of early onset spasm-like seizures was also independently associated with IQ in multivariate analyses (O'Callaghan *et al.* 2003). At this stage, therefore, it is not possible to determine whether the seizure disorder itself impairs intellectual development or whether the seizures are acting as a marker for some other unmeasured brain abnormality. Further studies are required to clarify the nature of the link between brain abnormalities, epilepsy, and ability level, and in particular, to explore the role of infantile spasms. Another important direction for future research would be to determine whether cases of TSC with learning disability are more likely to be due to TSC2 mutations as suggested by Jones *et al.* (1997).

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