

Cognitive and adaptive development of patients with tuberous sclerosis complex: A retrospective, longitudinal investigation

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ABSTRACT

Objective: The aim of the work described here was to systematically analyze the developmental trajectory of patients with tuberous sclerosis complex (TSC).

Methods: A retrospective longitudinal chart review was performed, selecting patients who received multiple neuropsychological assessments. Intellectual/Developmental Quotients, Adaptive Behavior Composite scores, and clinical data were collected. On available EEGs, interictal epileptiform discharges were counted.

Results: Sixty-six (18%) patients with TSC received multiple cognitive and adaptive development assessments. The mean intelligence of this study group remained relatively stable, albeit variable. Significant decline in adaptive functioning was observed, associated with lower age at seizure onset. Patients who underwent neurosurgery prior to baseline testing showed cognitive improvement. Developmental declines were significantly associated with increased numbers of antiepileptic drugs, with a trend toward association with mutation type and interictal epileptiform discharges.

Conclusion: This study suggests that the developmental course of patients with TSC may be altered by epilepsy comorbidity and neurosurgery, underlining the need for early and effective interventions in this population.

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1. Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder that arises from germline mutations in either the TSC1 or TSC2 gene, which encode hamartin and tuberin, respectively [1]. These proteins function as tumor suppressors by forming a heterodimer complex that inhibits the mammalian target of rapamycin complex 1 (mTOR1) pathway [2,3]. Loss or dysfunction of these proteins results in growth of benign tumors called hamartomas in various organ systems, including the brain. Clinical manifestations associated with brain involvement are common and include epilepsy, cognitive impairment, and psychiatric disorders. The prevalence of cognitive impairment in TSC is estimated to be between 44 and 70% and has been associated with various epilepsy features, including early age at seizure onset, infantile spasms (IS), mixed seizure type, TSC2 mutations, and poor seizure and IS control [4–12].

In a study of infants with TSC, development was found to be slow but relatively stable, although a subset showed large variability [13].

Increased knowledge of the developmental course and the influence of epilepsy comorbidity will provide more information for patients and assist clinicians in important treatment decisions, especially now that early (preventative) treatments with mTOR inhibitors are being considered. Therefore, our primary aim was to determine if the generally stable development reported in infants with TSC is also the case for older age cohorts. Furthermore, we wanted to determine if, and which, factors influence cognitive and adaptive development in patients with TSC, exploring the effect of genetic background, age at seizure onset, neurosurgery, and autism, as well as dynamic epilepsy characteristics such as interictal epileptiform discharges (IEDs) and antiepileptic drugs (AEDs) used for treatment.

2. Methods

2.1. Study group

Charts of all patients with a definite diagnosis of TSC who were treated at the Herscot Center for TSC at Massachusetts General Hospital were reviewed. Patients who had received neuropsychological assessment (NPA) at least twice were identified and the results of the earliest and most recent NPAs (NPA1 and NPA2) were obtained.

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This study was approved by the institutional review board of Massachusetts General Hospital.

2.2. Neuropsychological assessment

Neuropsychological assessment is routinely offered as a part of clinical care for patients with TSC at the time of diagnosis and at the time of changes in their neuropsychiatric morbidity or developmental trajectory. Comprehensive NPAs are performed by an experienced neuropsychologist at the Psychology Assessment Center of Massachusetts General Hospital (M.P.) and include assessment of cognitive and adaptive functioning. For the study cohort, we gathered test scores from measures of intelligence and adaptive skills at two time points (NPA1 and NPA2). Intellectual Quotient (IQ) or Developmental Quotient (DQ) was derived from one of the following six neuropsychological measures, selected in conformity with the mandate of best clinical practice: (1) Bayley Scales of Infant Development, Second Edition (BSID-II) [14]; (2) Stanford–Binet Intelligence Scale, Fifth Edition [15]; (3) Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI) [16]; (4) Wechsler Intelligence Scale for Children, Fourth Edition (WISC) [17]; (5) Wechsler Abbreviated Intelligence Scale–Revised (WAIS-R) [18]; and (6) Differential Abilities Scales [19]. To assess adaptive functioning, the Survey Form of the Vineland Adaptive Behavior Scale [20] was used, yielding standardized scores for communication, daily living skills, socialization, and, for children less than 6 years old, motor skills, resulting in a total Adaptive Behavior Composite (ABC) score. Both IQ and ABC scores have a mean of 100 and a SD of 15. For patients with outcomes on the floor of the standardized scores, we calculated DQs (mental age/chronological age \times 100), where a DQ of 100 would be considered the mean.

2.3. Clinical data

Clinical data were obtained from the clinic records of the consultation with the referring child neurologist (E.T.), which was always close in time before each NPA. Information was collected on gender, age, and results of genetic mutation analysis. The diagnosis of autism spectrum disorders (ASDs) was made by our affiliated psychiatrist and M.P. based on DSM-IV criteria. Epilepsy was characterized based on age at seizure onset, IS, and number of AEDs used for seizure control. Data on epilepsy surgery and subependymal giant cell tumor (SGCT) resection surgery were obtained.

2.4. Electrophysiological data

For patients who received an EEG within a year of each NPA, available records were reviewed by an experienced and blinded neurophysiologist (C.C.-S.). EEGs were obtained using a 19-channel montage with the standard 10–20 electrode placement system. For routine clinical EEGs, the entire recording was reviewed and manually scored. For longer recordings, the first 20 minutes of the wake and sleep states were reviewed and scored. Studies were screened for IEDs. Counted discharges were averaged to a value per minute. Regional scores were summed to generate a whole brain score, portraying a quantitative index of the overall interictal activity of the EEG.

2.5. Statistical analysis

Statistical analysis was performed using SPSS for Windows (Version 11.5).

To determine change in developmental outcomes, a paired *t* test was performed to compare the IQ/DQ and ABC outcomes at NPA1 and NPA2. We preferred total change in developmental outcomes over time-dependent outcomes as the latter would inappropriately imply linearity in gains or declines. Because the NPAs were performed at different time intervals, changes in IQ/DQ and ABC were calculated

and correlated with the IQ/DQ change/year and ABC change/year to justify use of the former as primary outcomes.

Because of the different sample size, predictors of changes in intelligence and adaptive functioning were examined using a general linear model for each outcome. Levene's test was included to investigate homogeneity. Gender, mutation type, and a positive history of IS were included as predictors, and age at seizure onset and age at NPA1 were defined as covariants. To evaluate the influence of changes in IEDs and number of AEDs on changes in cognitive and adaptive outcomes, Pearson correlations were performed. Missing values were excluded when determining percentages in the results. To compare changes in IQ/DQ and ABC in groups with and without a diagnosis of ASDs or a history of neurosurgery, *t* tests were performed.

In the general population with cognitive impairment, one would expect 6% to show an IQ change of more than 10 points when reevaluated with the Wechsler scale [21]. To optimize the sensitivity and relevance of our findings, we interpreted a change of at least 15 IQ/DQ points as significant. For all tests, a confidence interval (CI) of 95% was used. We interpreted associations as significant for α values ≤ 0.05 ; α values ≥ 0.05 and ≤ 0.1 were considered trends.

3. Results

3.1. Study group

Sixty-six (18%) patients with TSC in our clinic had undergone at least two NPAs, with a mean interval of 3.9 years (range: 0.5–9.3). Of these 66 patients, henceforth called the study group, all (100%) had completed multiple intelligence tests and 41 (62%) had received multiple adaptive functioning assessments. Demographic and clinical data of the study group are summarized in Table 1.

3.2. Course of cognitive and adaptive development

The mean IQ/DQ change for the total study group was -2 points, which was not significant ($P < 0.29$, CI: -1.9 to 6.3) and showed large variability, ranging from a relative decrease of 48 to an increase of 52 points, with a SD of 16.7 (see Fig. 1, left). Twenty (30%) patients had a significant IQ/DQ change of > 15 points, including 9 patients with an increase and 11 patients with a relative decline (see Table 1). Of note is that 9 of the 11 (82%) patients with a cognitive decline were male. The mean ABC change between NPAs was significant ($P < 0.0001$, CI: 3.2 – 10.4), with a mean relative decrease of 7 ABC points (see Fig. 1, right).

When the total change in IQ/DQ and ABC was divided by the time interval, the change per year was very strongly correlated with the total change (both showed correlations of 0.74, $P < 0.0001$), justifying the use of the outcome change in IQ/DQ and change in ABC as primary endpoints in our regression analysis. Age at seizure onset was shown to have a significant effect ($P < 0.002$) on the change in adaptive scores (Fig. 2) and showed a trend toward association with mutation type ($P < 0.09$) (Fig. 3).

Levene's test and the regression model revealed no significant variance in factors included in the regression analysis and no significant predictors of changes in IQ/DQ. Gender, age at NPA1, and a positive history of IS were not significantly associated with change in ABC.

3.3. TSC mutation subgroups

Because the regression analysis hinted at an association between mutation type and adaptive development, genetic subgroups were compared (see Fig. 3). These groups had a similar mean age at NPA1. The group of patients with a TSC1 mutation showed a mean decline of 5 IQ/DQ and 2 ABC points (SD = 12 and 14, respectively). The TSC2 mutation subgroup showed a mean loss of 1 IQ/DQ and 8 ABC points (SD = 20 and 11, respectively), and the no mutation identified

Table 1

Clinical characteristics of (A) the total study cohort and the subgroups with a (B) significant relative increase or (C) significant relative decrease in cognitive outcomes.

	A Total study group (N = 66)	B Cognitive improvement (N = 9)	C Cognitive deterioration (N = 11)
Gender (male)	32 (48.5%)	3 (33%)	9 (82%)
Characteristics at NPA1			
Mean age (years)	5.8 (0.5–20)	2.8 (0.9–8.4)	3.4 (0.5–12.5)
Mean Intellectual/Development Quotient	67 (8–133)	60 (19–113)	85 (47–111)
Mean Adaptive Behavior Composite score	66 (18–132)	74 (18–132)	84 (46–114)
Mean interval between NPAs (years)	3.9 (0.5–9.3)	5.3 (2.2–7.7)	3.9 (0.9–7.2)
Result of mutation analysis			
TSC1 mutation	14 (21%)	1 (11%)	3 (27%)
TSC2 mutation	39 (59%)	7 (78%)	8 (73%)
No mutation identified	10 (15%)	1 (11%)	—
Not performed	3 (5%)	—	—
Epilepsy variables			
History of epilepsy	58 (88%)	8/9 (89%)	11/11 (100%)
History of infantile spasms	32 (48%)	4/8 (50%)	7/11 (64%)
History of intractable epilepsy	36 (55%)	4/4 (50%)	6/11 (55%)
Mean age at seizure onset (years)	1.3	1.3	0.84
Mean change in number of IEDs/min (N = 23)	1.55 (−56.3 to 23.5)	−0.42 (−4.17 to 1.51)	2.72 (−20.93 to 23.51)
Mean change in number of AEDs	0.15 (−3 to 2)	−0.25 (−3 to 2)	0.5 (−1 to 2)
Neurosurgery before NPA1	13 (20%)	3 (33%)	1 (9%)
Neurosurgery between NPAs	8 (12%)	1 (11.1%)	2 (18%)

Note. Ranges and percentages provided in parentheses. NPA, neuropsychological assessment; IEDs, interictal epileptiform discharges.

(NMI) group showed a mean loss of 2 IQ/DQ and 6 ABC points (SD = 11 and 10, respectively). There were four pairs of siblings in the study group, and identical genetic mutations were identified in three pairs. Within siblings, IQ/DQ changes were extremely variable, ranging from 13 to 69, and in all but one pair IQ/DQ increased in one sibling and declined in the other.

3.4. Subgroup with neurosurgery

Thirteen patients underwent neurosurgery *before* the first NPA, including 10 (77%) for epilepsy surgery and 3 (23%) for subependymal giant cell tumor (SGCT) resection. Over a mean interval between NPAs of 4.7 years, this group displayed a significantly different developmental trajectory, showing a gain of 7 IQ/DQ points versus a loss of 4 points for the group without a history of neurosurgery ($P < 0.02$). There were mean gains of more than 7 IQ/DQ points for the patients who had epilepsy surgery and 5 points for the patients who had SGCT surgery (Fig. 4). There was no significant difference in change in adaptive scores between these two groups ($P < 0.31$), although

the group with a positive surgery history showed a decline of 3 ABC points, which was less than the 8 ABC points of the remaining cohort. For the patients for whom two ABC measurements were available, the 7 patients who had had epilepsy surgery showed a mean loss of 5 ABC points, whereas one patient who underwent SGCT surgery had a gain of 9 ABC points.

Eight (12%) patients from the study group underwent neurosurgery *between* NPAs (Fig. 4): five received epilepsy surgery and three underwent SGCT resection; none of these patients had prior neurosurgery. All three SGCT surgery patients showed a relative decline in IQ/DQ (range: −10 to −25) and ABC (range: −12 to −26), possibly related to postsurgical temporary obstructive hydrocephalus just before NPA2 in one patient and extreme anxiety during NPA2, which might have underestimated performance, in a second patient; for the third patient, no clear cause was evident from the medical records. The five patients who underwent epilepsy surgery between NPAs showed very variable, but no mean change in, IQ/DQ (range: −22 to +29), but a mean loss of 9 ABC points (range: −22 to −1). Age at NPA1 was very similar (4.8) for both the group with

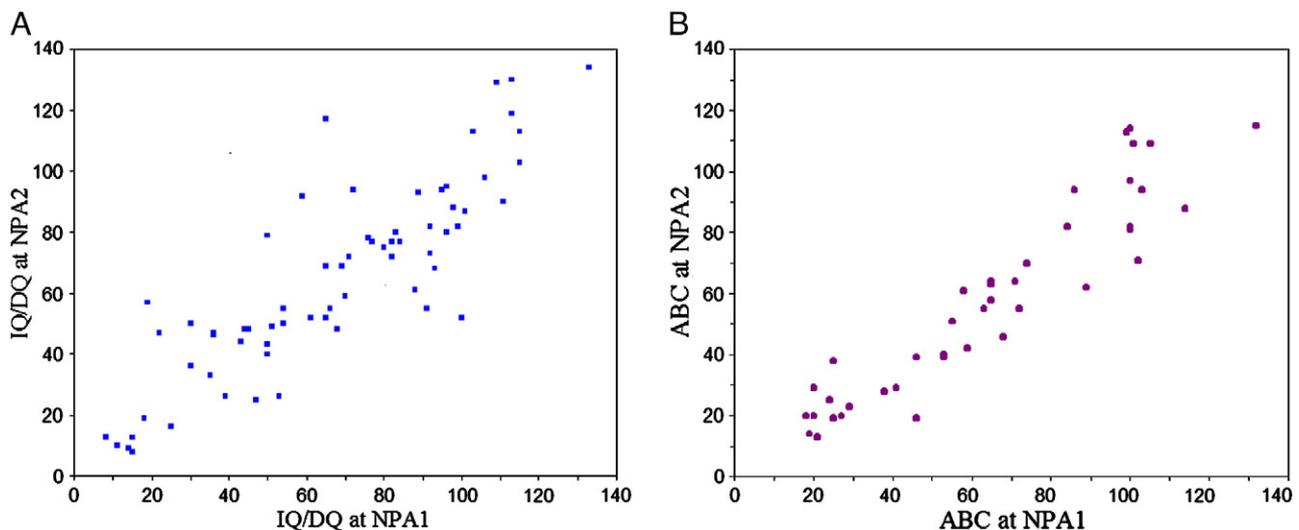


Fig. 1. Scatterplot depicting (left) intellectual outcomes and (right) adaptive functioning scores at the first and second evaluations. IQ/DQ, Intellectual/Developmental Quotient; ABC, Adaptive Behavior Composite; NPA, neuropsychological assessment.

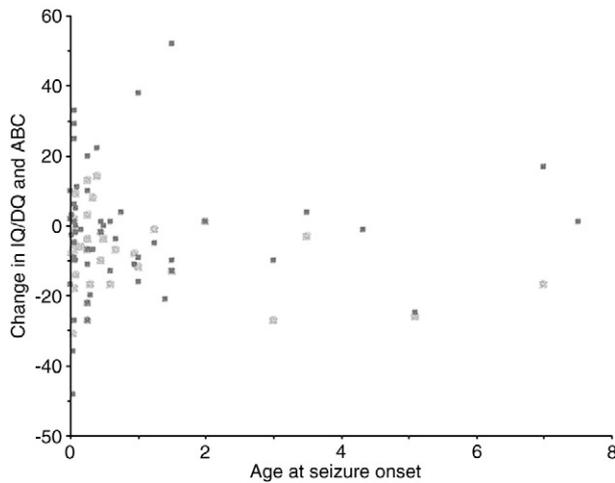


Fig. 2. Scatterplot depicting the relationship between age at first NPA and changes in intellectual (dark gray) and adaptive functioning (light gray) outcomes. IQ/DQ, intellectual/developmental quotient; ABC, Adaptive Behavior Composite.

neurosurgery at baseline and the group with recent neurosurgery, indicating that the first group was operated on at a younger age than the latter.

3.5. Epilepsy characteristics

Among the study group, 58 (88%) patients had a positive history of epilepsy at baseline assessment and 3 (5%) developed epilepsy between NPAs. The various epilepsy variables are summarized in Table 1. The regression model showed a significant relationship between younger age at seizure onset and change in adaptive outcomes, which could not be explained by a significantly younger age at first examination ($P < 0.24$). Plotting of the data showed that greater variability of IQ/DQ and ABC changes was related to younger age at seizure onset (Fig. 2). A significant negative correlation was found between number of AEDs and cognitive change ($P < 0.02$) as well as change in adaptive functioning ($P < 0.01$). Complete information on medication use was available for 62 (94%) patients. Thirteen (21%) of these patients did not use AEDs at the time of both NPAs, including the 8 patients with no history of epilepsy. At NPA1, 14 (23%) patients used valproate, 12 (19%) lamotrigine, 9 (15%) levetiracetam, 8 (13%)

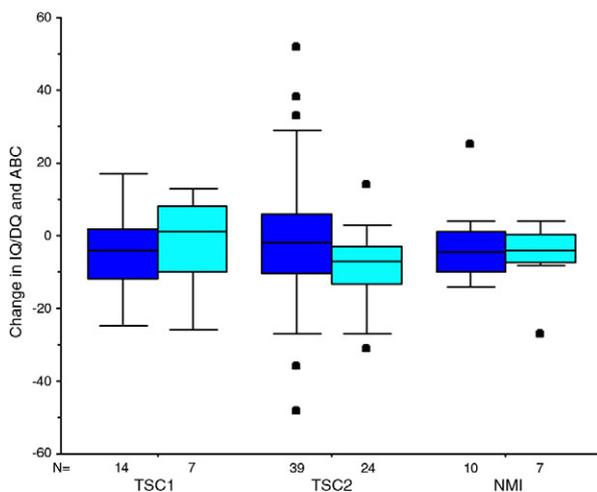


Fig. 3. Boxplot showing changes in intellectual and adaptive changes per TSC mutation type, including standard deviations and outliers. Dark blue: change in Intellectual/Developmental Quotient (IQ/DQ); light blue: change in Adaptive Behavior Composite score (ABC); NMI, cohort with no mutation identified.

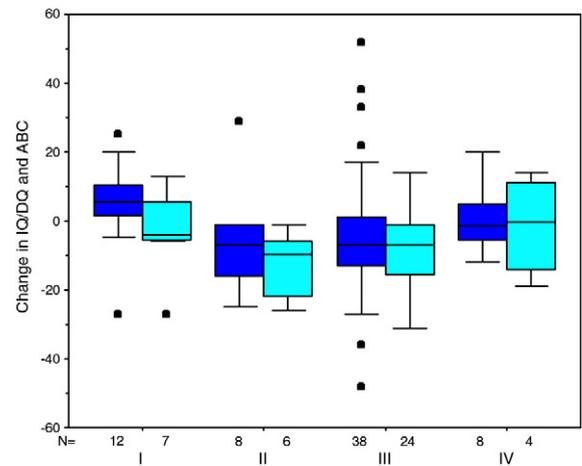


Fig. 4. Boxplot depicting changes in intellectual and adaptive functioning outcomes in subgroups I (neurosurgery before NPA1), II (neurosurgery between NPAs), III (epilepsy and no history of neurosurgery), and IV (a negative seizure history). The numbers of available intellectual and adaptive functioning outcomes for each cohort are noted underneath the x axis.

carbamazepine, 5 (8%) vigabatrin, 4 (6%) gabapentin, and 3 (5%) topiramate. At NPA2, the AED regime had been changed in 54 of the 62 patients; 7 (11%) patients started using AEDs, 5 (8%) patients ceased AED treatment, 6 (10%) used a decreased number of AEDs, and 12 (19%) used an increased number of AEDs. At NPA2, 23 (37%) patients used lamotrigine, 19 (31%) levetiracetam, 8 (13%) valproate, 6 (10%) carbamazepine, 4 (6%) gabapentin, 3 (5%) topiramate, and 3 (5%) vigabatrin.

All eight patients without a history of epilepsy had IQ/DQ values > 65 at NPA1. This group showed average declines of 0.5 IQ/DQ and 1.5 ABC points, compared with 2.6 and 7.5 points for the group with a positive history of epilepsy, respectively (Fig. 4).

3.6. EEG analysis

For 23 patients, there were available EEGs obtained within a year of both NPAs. This EEG subgroup showed a mean increase in number of IEDs of 1.55 discharges/minute (see Table 1). The group that lost more than 15 IQ/DQ points ($N = 5$) showed an average increase of 2.7 discharges/minute at EEG2, whereas the group with a significant IQ/DQ increase ($N = 4$) showed an average IED decrease of 0.4/minute (Table 1); similar phenomena were observed for available ABC scores. When changes in IQ/DQ and ABC were correlated with changes in the number of IEDs per minute per whole brain, no significant associations were found ($P < 0.86$ and $P < 0.38$, respectively).

3.7. Subgroup diagnosed with autism spectrum disorders

Twenty-seven (41%) patients from the study group were diagnosed with an autism spectrum disorder. At time of the first evaluation, the group with ASDs had a lower mean IQ/DQ of 50 versus 79 for the group without ASDs ($P < 0.00$) and a mean ABC of 49 versus 80 ($P < 0.00$). Compared with the group without ASDs, the group with ASDs showed no significant difference in IQ/DQ or ABC score changes ($P < 0.33$ and $P < 0.28$, respectively).

4. Discussion

The current study is the largest longitudinal investigation of intellectual and adaptive development in patients with TSC to date, and identifies significant associations with neurosurgery and epilepsy characteristics. For the whole study group, mean cognition remained relatively stable, although one-third of patients showed a significant

change in cognitive performance, confirming previous observations in infants with TSC [13]. Supported by large SDs of IQ/DQ changes, this evidence suggests that the cognitive trajectory of patients with TSC can be highly variable. Cognitive decline was associated with increased numbers of AEDs, which likely reflects poor epilepsy control. Refractory epilepsy is common in patients with TSC, and epilepsy has been associated with poor cognitive outcomes [22]. Developmental decline can also occur in patients with severe and early-onset epilepsy, warranting early and aggressive treatment of seizures. However, the neurocognitive side effects of anticonvulsants could also impair function [23], striking a delicate balance for clinicians. The medication use of the study cohort shows a slight shift toward second- and third-generation AEDs in accordance with best practice, but this study type did not allow for investigation of the effects of specific AEDs on the developmental trajectory.

The significant relative decline in adaptive scores in the total study population was the most consistent finding of our study. This indicates that patients fall increasingly behind in their neurodevelopment, which is not to be confused with the term *regression*, as the latter implies loss of skills instead of slower gain. Adaptive decline was significantly related to younger age at seizure onset and increased number of AEDs, confirming the association between early seizure onset and detrimental developmental outcomes [6,24]. The observations that the patients with significant changes in developmental outcomes were relatively younger and that this variability stabilizes as age advances emphasize that infancy is a critical time when influences such as seizures can alter brain development and future outcomes in patients with TSC. The observation that patients with low baseline cognitive outcomes increased their scores and patients with relatively higher outcomes showed deterioration (Table 1) could indicate regression to the mean, which is related to large SDs, although plotting of the data showed no evidence for this statistical phenomenon (Fig. 1).

Interestingly, the subgroup who had undergone neurosurgery before the first evaluation showed a significant improvement in intellectual performance, which occurred regardless of surgery indication and could not solely be explained by a larger interval between NPAs. Whereas findings in general pediatric epilepsy surgery patients have been inconsistent [25,26], studies in epilepsy surgery patients with TSC have reported excellent long-term seizure outcomes and quality of life [27,28], confirming our observations, although referral or reporting bias should be considered. In contrast, the TSC subgroup who underwent neurosurgery *between* NPAs showed variable and little mean change in developmental outcomes. This may reflect referral bias or a pattern of initial postoperative variation followed by improvement in neurosurgical patients with TSC. The compelling observation that the three patients with a history of SGCT surgery showed intellectual improvement after neurosurgery warrants further study focusing on the neurocognitive consequences of SGCT growth.

Although theoretically IEDs may influence cognitive performance, there are few investigations of this clinically relevant issue [29]. Interestingly, we found that the frequency of IEDs was increased on available EEGs of patients who manifested significant cognitive decline, and that it was decreased in the group with relative improvement, although this was not significant. The epilepsy phenotype of TSC is relatively severe and the effect of seizures may overshadow potential cognitive effects of IEDs. As the EEG study sample was relatively small, future research should provide more information on the effect of interictal discharges on cognition to guide clinicians in the decision on treating this phenomenon.

Although cognitive deficits in TSC are related to altered signaling caused by the genetic mutation, change in IEDs was extremely variable within siblings affected by the same genetic mutation, suggesting that there is no genetic predetermination for developmental gain or decline. Effects of the relatively more severe seizures and psychiatric manifestations in patients affected by TSC, TSC2 mutations in particular [30], may override inherent cognitive abilities. This is reflected by the variability in outcomes in the TSC2 cohort which

could not solely be explained by young age at NPA. Interestingly, the NMI cohort showed the most stable developmental trajectory, reflecting the previously reported milder neurological phenotype of patients with NMI [31].

Notably, a remarkably large proportion of men showed cognitive and adaptive decline versus women (9:2), a phenomenon previously shown in males with other autosomal dominant syndromes [32], although the small subgroup limited our statistical inferences.

In patients with autism, declines and variability in adaptive behavior scores have been shown across all ages [33], more so than in individuals with learning disabilities without autism [34]. In this population, the subgroup with ASDs did not manifest a significantly different course in intellectual or adaptive outcomes. This could be due to the low baseline cognitive and adaptive functioning of this cohort, or a potential nuanced difference may be obscured by the effect of the relatively severe epilepsy type found in patients with TSC.

There are several limitations inherent to this type of study. Although previously seizure frequency has been suggested to be of importance in cognitive development in children with TSC-related epilepsy [35], this variable was difficult to determine retrospectively. Part of the variability in the cognitive outcomes could be caused by interscale validity variability, especially at young age. However, the use of multiple cognitive measures was inherent to the inclusion of different age groups and similar to other longitudinal studies on cognitive development [36]. Applying a rigorous cutoff of 15 IEDs and finding a similar proportion of patients (29%) showing significant change on the Vineland Scale, which is used across all age groups and the predictive quality of which has been validated [20], support our findings. Furthermore, our regression analyses showed no significant effect of age at evaluation on change in developmental outcomes. Because of the exploratory nature of this study, our effort to address multiple variables of influence on the developmental trajectory may have diminished statistical power and prospective studies should confirm our findings.

Although patients with TSC are routinely offered neuropsychological assessment at the time of diagnosis, most patients do not receive neuropsychological assessment multiple times unless this is clinically indicated. Hence, this cohort represents a relatively small proportion of our large clinic population and may be biased toward the more severe end of the neuropsychiatric spectrum of TSC as a result of referral bias. This is reflected by the relatively large proportion of pediatric and neurosurgical patients. However, the relatively higher IQ/DQs and stable development that was observed in patients not affected by epilepsy is likely to be an authentic reflection of development in the TSC population with milder neurological involvement. Although the investigated patients did not have equal time intervals between NPAs, the observation that the change in IQ/DQ correlated significantly with the IQ/DQ change per year suggests this method is applicable. The average test–retest interval of 4 years allows sufficient time for factors such as physical, psychological, and environmental changes to affect an individual's intellectual ability. The retrospective nature of our study and the large number of variables did not allow for comparisons between subdomains of cognitive and adaptive development.

Low intellectual quotient and adaptive skills are defining features of intellectual disability. Our findings of variable cognitive outcomes and relative decline in adaptive scores confirm the need for repeated routine neuropsychological assessments in patients with TSC [37] and multiple assessments in case of neurosurgery or changes in neuropsychiatric morbidity. The association between epilepsy variables and developmental outcomes suggests that early diagnosis and treatment of epilepsy may prevent these encephalopathic effects and improve developmental outcomes in patients with TSC.

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