Abstract We report a prospective longitudinal study of cognitive development in a series of 20 clinic-referred infants with Tuberous Sclerosis. The infants were seen between the ages of 11 and 37 months and were assessed regularly at 6-month periods using a within-subjects repeated measures design. Assessment using the Mullen Scales of Early Learning, a measure of cognitive and motor showed that with the exception of one child, all children had composite developmental quotients that fell into the mentally retarded range of intellectual functioning. In general, the infants’ developmental quotients changed little between 12 and 36 months of age. Developmental progress was evident; however, with small incremental changes in raw scores for subjects over the course of the study. In three children, the developmental quotient changed by more than 20 points during the course of the study. The findings are considered in relation to the neurobiological risk factors for cognitive development in Tuberous Sclerosis.

Key words tuberculosis – mental retardation – epilepsy

Introduction

TS is a genetic disorder that is inherited in an autosomal dominant fashion in approximately one third of cases. It is a consequence of spontaneous mutation in the remainder. There are two genes that cause the condition: one on 9q34 (TSC1) and one on 16p13 (TSC2) [7, 18]. TSC1 and TSC2 are thought to be tumour suppresser genes. The birth rate of TSC is estimated to be 1 in 10,000 [27, 34].

The physical presentation of TS is very variable. TS is characterised by benign tumours that can affect most organs of the body, e.g. skin, brain, retina, kidney, lung and liver [8]. In 90% of cases there is cerebral involvement in the form of subependymal nodules or cortical tubers. Tubers are commonly found in the frontal, parietal and temporal lobes. Some patients only have a few cortical tubers while others have in excess of thirty [11]. Other cortical abnormalities include microdysgenesis, heterotopic grey matter, and lamination defects [23]. Subependymal nodules, subependymal giant cell astrocytomas [20], and abnormalities in subcortical function have been reported [2]. These structural abnormalities arise during embryogenesis and are present at birth so that cognitive development occurs in the context of brain abnormalities. These brain abnormalities give rise to epilepsy, hyperkinetic disorder, autism, specific cognitive impairment, and mental retardation.

This study aimed to identify the level and trajectory of cognitive functioning in a series of clinic referred infants with Tuberous Sclerosis. There is evidence of a bi-
modal distribution in the IQ scores in those affected with TSC [15, 30]. Joinson et al. [16] in their sample of 108 individuals found that 56% had an IQ in the normal range and 44% had an IQ below 70. The prevalence of mental retardation in TS is estimated to be between 44% and 60% [31]. Prevalence rates vary as milder cases often go undetected and the use of standardised assessments has not been common. Tuberous Sclerosis is estimated to account for 1–2% of people with mental retardation [12].

The number of tubers is associated with an increased risk of mental retardation. In general, those with more tubers are more at risk for mental retardation and tend to have more severe forms of intellectual handicap [29]. In addition, the risk of mental retardation is associated with the presence and age of onset/type of epilepsy. Eighty percent of individuals with TS develop epilepsy [8] and seizures often begin in the first two years of life. Importantly, the likelihood of infantile seizure increases as tuber count rises [29], so it is unclear to what extent the risk and severity of mental retardation is due to neuroanatomical abnormality, the effect of seizures in the developing brain or both factors [5, 22, 24]. It is noteworthy that the relationship between mental retardation and epilepsy is very strong, and that it is rare for a child with TS and mental retardation not to have a history of seizures [14].

While we recognise that variables such as attention, response time, and social communication will affect performance on standardised measures of cognition, charting the intellectual development of this group of infants is in and of itself important. Despite the significant risk of developmental disorders and mental retardation associated with Tuberous Sclerosis, we know little about the natural history of intellectual development in children with Tuberous Sclerosis. In view of the emergence of structural brain abnormalities during embryological development and the high rate of seizure disorders during infancy it might be anticipated that children with Tuberous Sclerosis would show developmental impairments at a very early age. However, the marked variability in the physical and psychopathological manifestations raise questions about the way in which the variable expression develops: is the course of intellectual development, for example, established early on or do children show significant changes in trajectory? Answers to these questions may throw light on the mechanisms involved. To date, however, there have been no prospective longitudinal studies examining intellectual development in infants with TS so there are no data to help answer these questions.

A detailed picture of the early natural history of cognitive impairments in this group of infants with Tuberous Sclerosis will help to develop and test hypotheses regarding the associations between underlying pathology (both anatomical and neurophysiological) and developmental course. The sample reported on here is representative of the young children with TS who present clinically. Families of these children come to clinic with many questions about prognosis and early intervention. The findings presented here will have implications for the planning of early interventions designed to remediate the cognitive impairments associated with Tuberous Sclerosis Complex. At present, the phenotypic heterogeneity of TS makes it difficult for families to anticipate and plan for their child’s future. By clarifying the developmental picture, we hope to make it possible to offer families more accurate advise regarding their child’s development and prognosis.

Methods

This study examined the development of young children with TS using a longitudinal repeated measures design. We aimed to 1) chart the level and stability of intellectual and motor abilities between 12 and 36 months of age and 2) identify within subject patterns of cognitive strengths and weaknesses.

Participants

Twenty infants with a diagnosis of Tuberous Sclerosis participated in the study. All were between the ages of 11 and 37 months. The sample includes 13 males and 7 females and represents a consecutive series of cases referred to the Cambridge Tuberous Sclerosis Clinic for Infants, based at the Section of Developmental Psychiatry, University of Cambridge.

Voluntary written consent was obtained from the parents of all children involved in the study. Ethics approval was obtained from the local research ethics committee.

Design

We used a longitudinal within-subjects repeated measures design. All children were assessed regularly at 6-month periods from the time they entered the study. Assessment points spanned from 11 months to 37 months, yielding a maximum of five assessments.

Because TS is a relatively rare genetic condition, we included any child ascertained under the age of 36 months regardless of their age.

Measures

The Mullen Scales of Early Learning [25] (MSEL was administered at every time point, in accordance with its