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Correlation of autism with temporal tubers in tuberous sclerosis complex

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Tuberous sclerosis complex (TSC) is an inherited genetic disorder commonly associated with neuropsychiatric complications like epilepsy, mental retardation, autism and other behavioral problems and constitutes about 1-4% of the autistic population. Mental retardation and seizures, particularly infantile spasms are significant risk factors for the development of autism. Patients of TSC with autism are more likely to have temporal tubers than those cases without autism. We describe clinical and neuroimaging features of two such cases of tuberous sclerosis with autism.

Key words: Autism, neuropsychiatric manifestations, tuberous sclerosis

Autism is a genetically heterogeneous neurodevelopmental disorder with onset in early childhood, characterized by impairments in communication, reciprocal social interaction and restricted and stereotyped patterns of interests and activities. The frequency of autism in tuberous sclerosis complex (TSC) ranges from 17-58% in various studies.[1-2] There is an observed association of autism and TSC, yet the mechanism underlying this association is unidentified.

Previous reports show an association between the presence of temporal lobe tubers and autism spectrum disorder in individuals with tuberous sclerosis.[3,4] We report two children with TSC and autism who had mental retardation and seizures. Their neuroimaging showed temporal tubers as previously reported. Age of seizure onset in the first three years of life and evidence of a temporal lobe electro encephalogram (EEG) focus are other independent characteristics associated with poor developmental outcome which were present in our cases. These findings extend results of previous reports showing that the association is correlated with the location of tubers in the temporal cortex.[3,4]

Case Reports

Case 1

A, six-year-old female child presented with developmental delay predominantly in the language sector and abnormal jerky movements of all limbs occurring in clusters during sleep transition. She also had seizures in the form of shouting and generalized shaking of body for a few minutes, about four to five times a day without complete loss of consciousness. Parents had noticed abnormal behavior in the form of decreased social interaction and stereotyped movements such as hand wringing and tapping on the walls. Child also had aggressiveness like biting herself and was hyperactive. These episodes were increasing in severity before she was referred to us. On examination she was found to have small head and neurocutaneous markers of adenoma sebaceum, ash leaf macules and shagreen patches. Neurological examination was normal. Developmental assessment revealed a VSMS (Vineland social maturity scale) score of 26 and intelligent quotient of 15 on developmental profile II (normal = 100) suggesting severe mental retardation. She had immediate and delayed echolalia and would talk in sentences comprising up to two words. Her score on the Childhood autism rating scale [CARS] was 38 (with five items scored 3 or higher) and thus, she was considered severely autistic. The electro encephalogram (EEG) indicated continuous epileptiform activity and generation of seizure activity from the right parieto-occipital and temporal areas. Cardiac, retinal and renal lesions were absent. Magnetic resonance imaging [Figure 1A-C] showed cortical tubers predominantly located in the right temporal lobe.

Case 2

A four-year-old male child presented with regression of milestones and hyperactivity since nine months of

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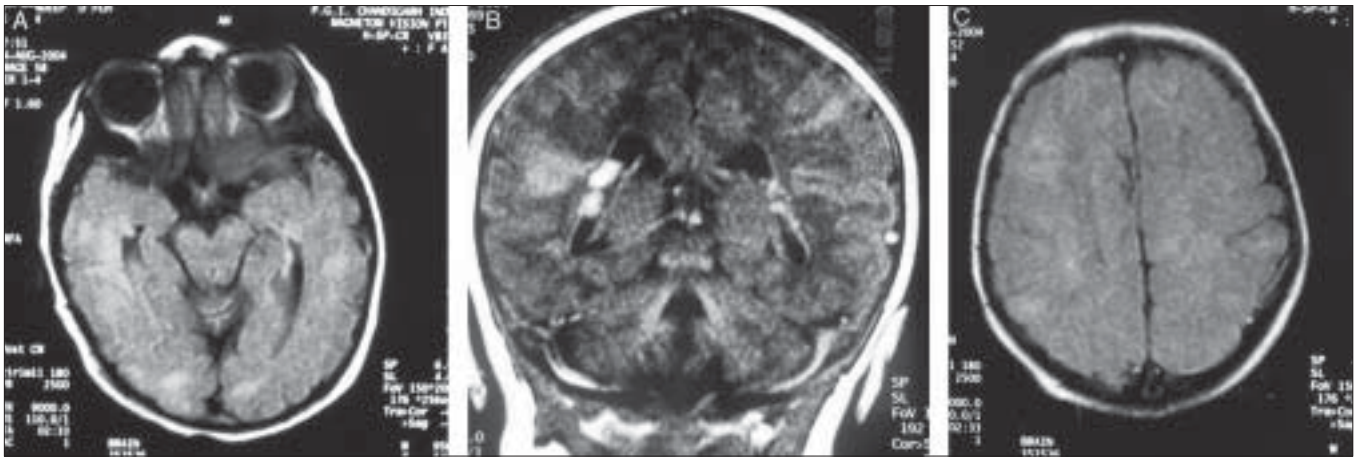

Figure 1: (A) and (B) Axial and Coronal T1 weighted MR images of first patient showing hyperintensities in the right temporal lobe suggestive of tubers. (C) T1 weighted MRI axial section showing paucity of tubers in frontal and parietal areas

life. He initially had infantile spasms and subsequently developed generalized and focal seizures. He had significant speech delay, no social interaction and stereotypic movements like repeated tapping of lips with hand. On examination he had shagreen patches and adenoma sebaceum. Neurological examination was within normal limits. His language was limited to five to six words with poor comprehension. Intelligent quotient was 27 on developmental profile II, VSMS score was 34 and CARS score revealed 44, falling in the range of severe autism. His initial EEG showed multifocal high-amplitude chaotic epileptiform activity, resembling hypsarrhythmia. The EEG done later at 3.5 years of age indicated a right temporal focus for the epilepsy which was generalized on few occasions. Ultrasound abdomen and echocardiogram were normal. Magnetic resonance imaging showed multiple subependymal tumors with bilateral temporal tubers [Figure 2A, B].

The children were treated using a multidisciplinary and comprehensive approach. Risperidone was used to control target symptoms, such as aggressiveness, obsessions, compulsive behavior and hyperactivity. Seizures were controlled with carbamazapine and topiramate. Infantile spasms in case number 2 were treated with vigabatrin resulting in significant improvement of cognition and behavior.

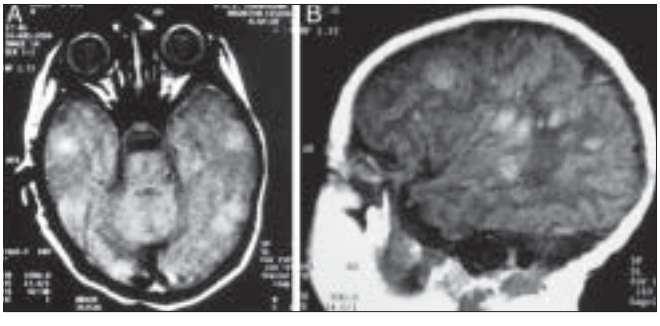

Figure 2: (A) and (B) Axial and sagittal T1 weighted MR images of second patient showing hyperintensities predominantly in the bilateral temporal lobe suggestive of tubers compared to fronto-parietal regions

Discussion

Autism and pervasive developmental disorders (PDD) are common in tuberous sclerosis. The wide range in prevalence is because of different mechanisms used for diagnosis of tuberous sclerosis and autism. Mental retardation and epilepsy are risk factors for individuals with TSC to develop autism and pervasive developmental disorder which were present in both our cases. In pooled studies incidence of autism or PDD in mental retardation (MR) and TSC is approximately 76% compared to 24% among population without MR. Among autistic populations, the frequency of TSC is 1-4% and perhaps as high as 8-14% among the subgroup of autistic individuals with a seizure.[1-3]

The pathogenesis of autism in TSC is still largely unknown and many different hypotheses have been raised. Because of the presence of easily identifiable cortical lesions in TSC, several studies of autism in TSC have attempted to correlate the behavioral disorder with the localization of cortical tubers. Curatolo and co-workers found evidence suggesting that patients with TSC and autism with early onset (before age two) presented prevalent parieto-temporal cortical lesions, while those with later onset (two to four years), had both frontal and posterior tubers.[3] Bolton and Griffiths found a very strong association between temporal lobe tubers and autism.[4] In another study, Seri and co-workers found that all the autistic patients had bilateral lesions, while none of the seven non-autistic patients had temporal lobe lesions in spite of a comparable severity of CNS involvement between the two groups. These structural features correlated with abnormalities in auditory event-related potentials (prolonged latency

and reduced amplitude in the first component of the long latency auditory response) observed only in the autistic subgroup demonstrating deficits in auditory processing and memory circuit in autistic children.[5] Both our cases had temporal tubers in accordance with these studies. In contrast to these studies Baker and co-workers found no temporal lesions in the four autistic patients identified in a series of 20 TSC patients.[6] Weber *et al.*, showed that CARS scores were low in patients of TS with cerebellar tubers. However, the limitation of this hypothesis is that it ignores the fact that there are widespread reciprocal connections between the cerebellum and cortical/subcortical structures which are also important for achieving cognitive function.[7]

An increased prevalence of autism in TSC patients presenting with infantile spasms has been reported as in our cases. There is a critical stage of brain maturation in early post-natal development in which temporal lobe epileptic discharges on the EEG can perturb the development of brain systems underlying social intelligence and possibly other cognitive skills, thereby inducing an autistic spectrum disorder.[8,9] Both the cases had significant EEG abnormalities with a temporal focus. In patients with TSC and autism, Asano *et al.* demonstrated decreased glucose metabolism in the lateral temporal cortex bilaterally, increased glucose metabolism in the deep cerebellar nuclei and augmented AMT (α-methyl-tryptophan) uptake in the caudate nuclei on PET scanning which are correlated with stereotypical behaviors and impaired social interaction, as well as communication disturbance.[10]

Thus TSC is proving to be a particularly informative model system for studying contemporary issues in behavioral neuroscience and particularly the link between brain disorders and abnormal behavior including autism.

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