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LETTER TO THE EDITOR

Re: Coexistence of Autism Spectrum Disorders Among Three Children with Tuberous Sclerosis Complex

Case reports and review of literature

رد: حدوث اضطراب طيف التوحد واضطراب التصلب الدرني في وقت واحد في ثلاثة أطفال

تقارير حالة ومراجعة الأدبيات

Sir,

I read with interest the case report by Al-Futaisi *et al*. published in the November 2016 issue of *SQUMJ* which described three children with both autism spectrum disorders (ASDs) and tuberous sclerosis complex (TSC).[1] In case one, computed tomography (CT) of the brain appeared normal. In case two, a magnetic resonance imaging (MRI) scan of the brain revealed nodular heterotopias and tubers in the brain, adjacent to the right lateral ventricle; these MRI findings, along with clinical features, confirmed a diagnosis of TSC.[1] In the third case, an MRI scan demonstrated multiple cortical and subcortical tubers and subependymal nodules in the brain, which subsequently led to the TSC diagnosis. Although the TSC diagnoses were confirmed by MRI or CT scans in all three cases, the authors stated that it was difficult to correlate MRI findings with the severity of autistic features in each patient.[1] However, I believe for the following two reasons that an in-depth evaluation of the MRI findings could help to establish that correlation.

First, the appearance of cortical tubers on an MRI represents an important feature in the diagnosis of TSC. Gallagher *et al*. identified three different types of cortical tubers: (1) type A tubers which were isointense on volumetric T1-weighted images and subtly hyperintense on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images; (2) type B tubers which were hypointense on volumetric T1-weighted images and homogeneously hyperintense on T2-weighted and FLAIR images; and (3) type C tubers which were hypointense on volumetric T1-weighted images, hyperintense on T2-weighted images and heterogeneous on FLAIR images with a hypointense central region surrounded by a hyperintense rim.[2] Accordingly, the clinical significance of the dominant tuber type was identified, with patients with type A tubers demonstrating a milder TSC phenotype.[2] Moreover, those with tubers predominantly of type C had an increased number of MRI abnormalities—such as subependymal giant cell tumours—and were more likely to have an ASD compared to patients with type A or B tubers.[2]

Second, cortical tubers vary widely in size, location and appearance.[2] Cortical tubers in the temporal lobe and insular area have been found to be associated with ASDs.[3] Moreover, the presence of cystic-like tubers on MRI scans might also offer a structural marker for ASDs in TSC.[3] On the other hand, large tubers are reportedly more likely to be associated with ASDs, even in comparison to cases with numerous smaller tubers.[4]

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Response from the Authors

Sir,

Thank you for your interest in our article. Recently, several studies have suggested an association between tuberous sclerosis complex (TSC) severity and parameters such as the genotype of the mutation, morphological and radiological features of tubers on magnetic resonance imaging (MRI) and the pathological characteristics of brain biopsies.[1–4] However, the clinical phenotype of TSC is highly variable, thus making prediction of the phenotype based on just one parameter challenging.[2] In addition, to the best of our knowledge, there are currently no published studies focusing on the accumulative effects of all known TSC parameters on its clinical phenotype.

Furthermore, the exclusive correlation of neuromorphological features to clinical phenotype may underestimate the fact that TSC is a global disorder of brain development. Conventional MRI features of brain hamartomas may represent only a small portion of brain TSC lesions, as extensive disease has been found in white matter which appears structurally normal but has abnormal microstructures as demonstrated by histopathological analysis.[5] In addition, increased axial diffusivity has been noted in major white matter tracts on diffusion tensor imaging.[6] Therefore, MRI findings alone are not a good tool for predicting the phenotype severity of TSC cases. In conclusion, according to the current available literature, predicting the clinical phenotype of TSC is not possible. More clinical and genetic data are needed from large numbers of patients to help define more valid and clinically-oriented genotype or phenotype correlations.

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