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Hemimegalencephaly and Focal Megalencephaly in Tuberous Sclerosis Complex

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Summary: We describe two children with complex cortical malformations as well as the typical intracranial manifestations of tuberous sclerosis complex. One child had hemimegalencephaly and the other had extensive focal megalencephaly. These cases are discussed in terms of the current concepts of cortical malformations.

Tuberous sclerosis complex (TSC) is a relatively common disorder affecting approximately one in 8000 children (1). The diagnosis is generally made on the basis of findings at clinical examination, and is often supported by a positive family history. Typical neuroradiologic features confirm the diagnosis, demonstrate the extent of the abnormality, and show unsuspected but associated disease (2). The four neuropathologic hallmarks of TSC are subependymal nodules (SEN), cortical tubers, subependymal giant cell astrocytomas, and a variety of white matter abnormalities (3). All these abnormalities have been described in terms of abnormal proliferation, migration, and organization of the neocortex. In this article we describe two children whose neuroradiologic findings showed extensive cortical malformations as well as the usual characteristics of TSC.

Case Reports

Case 1

This girl had a strong family history of TSC, with an affected mother and maternal grandfather. A maternal sibling had died at the age of 9 years with an "astrocytoma," presumed to be giant cell astrocytoma associated with TSC. The patient's seizures started at 7 weeks, but she lacked the cutaneous stigmata of TSC at that time. Left hemiplegia and severe learning disabilities became apparent. A CT study at 2 months showed a large right hemicranium, cerebral hemisphere, and lateral ventricle. Dense white matter calcification was present in the white matter of the medial frontal lobe, superior temporal lobe, and all of the occipital and parietal lobes. The cortex of the posterior half of the hemisphere was smooth and thick. Three subependymal areas of calcification were present on the left, situated at the foramen of Monro, the trigone, and the body of the lateral ventricle. MR imaging at 7 years of age (Fig 1) showed similar findings, confirming a right hemimegalencephaly and features of TSC. Pachygyria was confirmed in the posterior portion of the hemisphere, and showed some enhancement within the subjacent white matter after injection of contrast material. A hypoplastic right cerebral peduncle was noted. More extensive calcified SEN were shown on the surfaces of both ventricles, and typical cortical tubers were demonstrated: at least eight in the left hemisphere and four in the lateral part of the right frontal lobe, which was not severely affected by hemimegalencephaly. A diagnosis of hemimegalencephaly and definite TSC was made on the basis of one primary and two secondary criteria of Roach et al (4) (see Table).

Case 2

This girl was the second of nonidentical twins born after a normal pregnancy. There was no family history of TSC and the first twin was healthy. Seizures started at 3 weeks of age, but after an initial good response to anti-epileptic treatment became uncontrollable. The patient had a left hemiplegia and was moderately delayed developmentally. A CT study at 2 months showed bilateral high-attenuation lesions at the foramina of Monro and extensive calcification within the right hemisphere (Fig 2A). MR imaging at 3 years (Fig 2B and C) showed multiple, bilateral periventricular lesions that were of low signal intensity on all sequences, consistent with calcified SEN. High-signal abnormalities were present on long-TR sequences in cortical gyri of both hemispheres, typical of the hypomyelination and gliosis seen with cortical tubers. In addition, there was a large region of heavily calcified white matter extending from the ventricular surface to an area of cortex with broad, thickened gyri (pachygyria). This involved the right temporal, parietal, and posterior frontal lobes with hyperintense signal in the surrounding white matter, probably representing gliosis. The adjacent cerebrum and ventricle were larger than those on the left.

A right periinsular hemispherectomy stopped her seizures completely and produced generalized improvement in alertness and communication. Pathologic examination of the specimen revealed abnormal neurons and glia, with marked disruption of cortical architecture with gliosis and prominent calcification. Numerous balloon cells were present, but there were no mitotic figures. A diagnosis of TSC (one primary, one secondary, and one tertiary feature) and focal megalencephaly was made on the basis of a focal transmantle dysplasia and hemispheric/ventricle enlargement.

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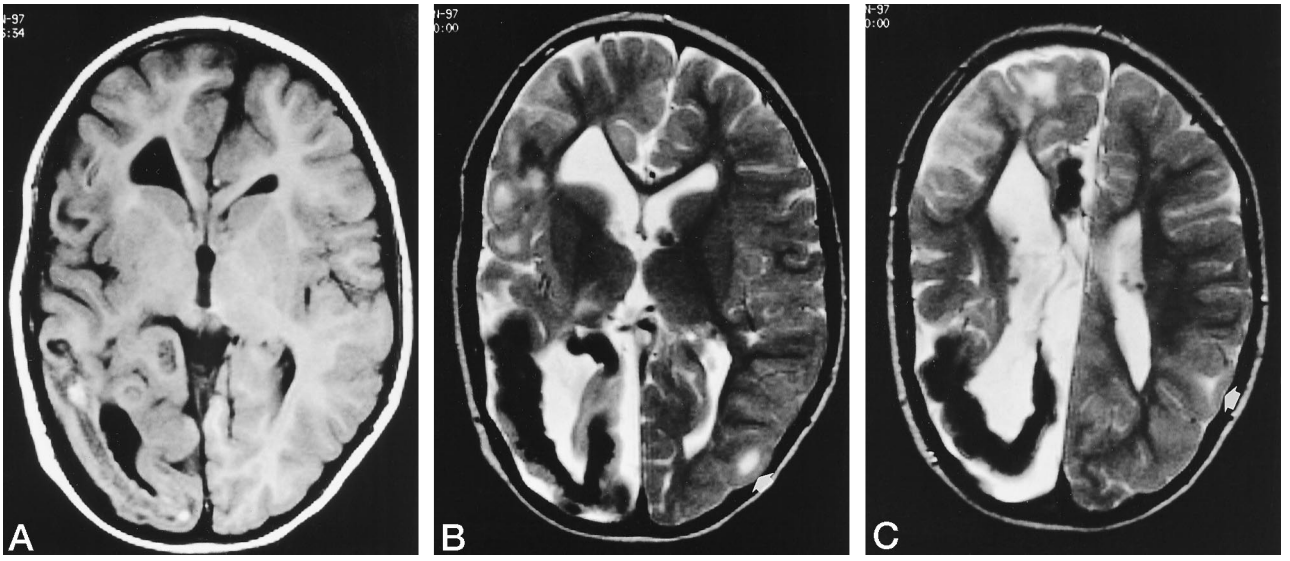

FIG 1. Case 1: hemimegalencephaly and TSC.

A–C, Axial T1-weighted (640/14/2) (*A*) and fast spin-echo T2-weighted (3500/93/1) (*B* and *C*) MR images show an enlarged right hemicranium, hemisphere, and lateral ventricle. There is signal loss in extensive portions of the right cerebral white matter on T2-weighted images due to calcification. On T1-weighted images there are some areas of high signal in the white matter, indicating microcalcification. A large area of pachygyria is present in the posterior portion of the right hemisphere. Calcified SEN are shown close to the left foramen of Monro (*B*) and in the body and trigones of the lateral ventricles (*C*). Two cortical tubers are shown in the left hemisphere (*arrows, B* and *C*) and further tubers are present in the right frontal lobe.

Diagnostic criteria for tuberous sclerosis complex

Primary features
Facial angiofibromas*
Multiple ungual fibromas*
Cortical tuber (histologically confirmed)
Subependymal nodule or giant cell astrocytoma (histologically confirmed)
Multiple calcified subependymal nodules protruding into the ventricle (radiographic evidence)
Multiple retinal astrocytomas*
Secondary features
Affected first-degree relative
Cardiac rhabdomyoma (histologic or radiologic confirmation)
Other retinal hamartoma or achromic patch*
Cerebral tubers (radiologic confirmation)
Noncalcified subependymal nodules (radiologic confirmation)
Shagreen patch*
Forehead plaque*
Pulmonary lymphangiomyomatosis (histologic confirmation)
Renal angiomyolipoma (radiologic or histologic confirmation)
Renal cysts (histologic confirmation)
Tertiary features
Hypomelanotic macules*
"Confetti" skin lesions*
Renal cysts (radiologic evidence)
Randomly distributed enamel pits in deciduous and/or permanent teeth
Hamartomatous rectal polyps (histologic confirmation)
Bone cysts (radiologic evidence)
Pulmonary lymphangiomyomatosis (radiologic evidence)
Cerebral white-matter "migration tracts" or heterotopias (radiologic evidence)
Gingival fibromas*
Hamartoma of other organs (histologic confirmation)
Infantile spasms

Note.—From Roach et al (6). Definite TSC is confirmed with either one primary feature, two secondary features, or one secondary plus two tertiary features. Probable TSC is defined by either one secondary plus one tertiary feature or by three tertiary features. Suspect TSC if either one secondary feature or two tertiary features are present.

Discussion

Our understanding of malformations of cortical development has improved because of a greater appreciation of the embryologic and genetic principles underlying those abnormalities. Advances in neuroradiology, particularly MR imaging, have also played a major role. One classification (5) of cortical malformations subdivides them into four groups: I, malformations due to abnormal neuronal and glial proliferation; II, malformations due to abnormal neuronal migration; III, malformations due to abnormal cortical organization; and IV, malformations not otherwise classified.

The two cases described in this article are most consistent with group I. Most authorities recognize that all the pathologic features of TSC are the result of abnormal cell proliferation, migration, and organization. This is due to the abnormal differentiation of primitive giant cells, which may show either neuronal or glial characteristics and a wide spectrum in between (6). In the one case in which histologic analysis was performed (case 2), abnormal giant neuronal and glial cells were found in the region of focal megalencephaly along with balloon cells. These are the typical findings of cortical tubers, and differentiation between the two would have been difficult without the imaging findings.

Hemimegalencephaly and focal transmantle dysplasia are considered to have similar origins. Our report shows overlap in this classification, as we have described two cases of confirmed TSC, one with hemimegalencephaly and one that could be classified as focal megalencephaly (see below) or focal transmantle dysplasia.

Hemimegalencephaly is an uncommon disorder

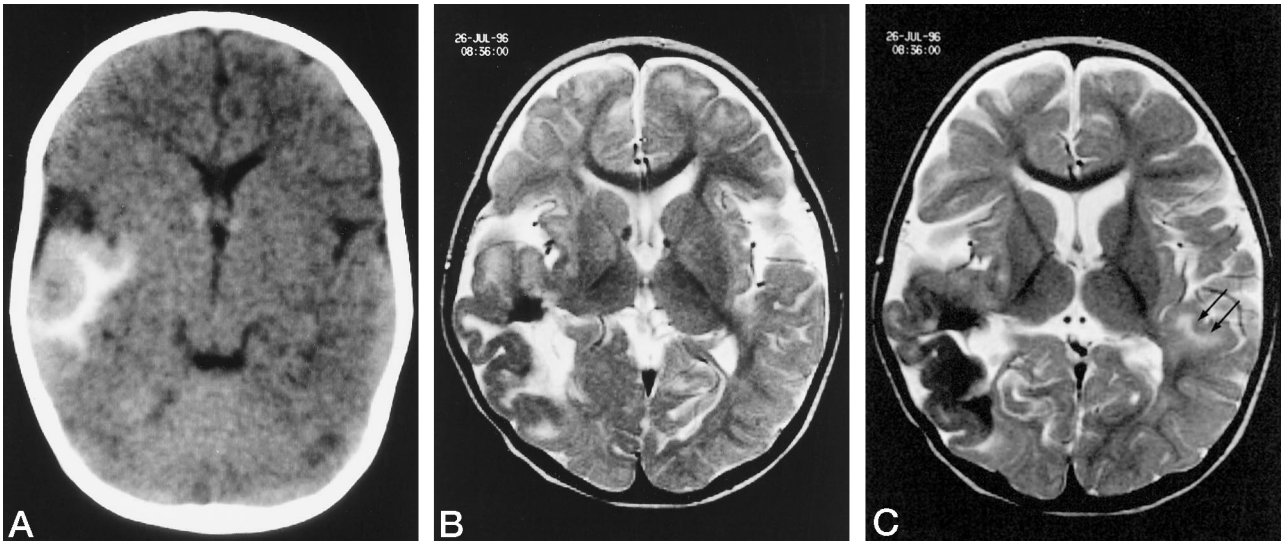

FIG 2. Case 2: TSC and focal megalencephaly.

A–C, Axial unenhanced CT scan at 2 months (*A*) shows white matter calcification and thickened cortex in the right temporal lobe. Calcified SEN are present bilaterally at the foramina of Monro. Axial fast spin-echo T2-weighted (3500/93/1) MR images (*B* and *C*) show heavily calcified white matter extending from the ventricular surface to a large area of cortex with broad, thickened gyri superficially. High-signal change in the surrounding white matter probably represents gliosis. The adjacent cerebrum and ventricle are larger than the opposite side. Multiple calcified SEN are shown close to both foramina of Monro and protruding into both lateral ventricles. Multiple cortical tubers are shown, including one in the left temporal lobe (*arrows, C*).

with pathognomonic neuroradiologic findings (7–9). Hemimegalencephaly may be isolated or occur with hemihypertrophic syndromes or phakomatoses. It is possible that hemimegalencephaly or focal megalencephaly may be misdiagnosed as tumor on imaging studies. The histologic distinction between tumor and megalencephaly can also be difficult, the appearances may be confused with low-grade glioma or as part of the ganglioglioma/gangliocytoma spectrum. In some situations, true neoplasia in hemimegalencephaly has been suspected (10). Features that may be useful in distinguishing megalencephaly from tumor are lack of mass effect, lack of edema, and no change on follow-up examinations.

Phakomatoses that have been associated with an increased frequency of hemimegalencephaly include linear nevus syndrome (11), hypomelanosis of Ito (12), neurofibromatosis type 1 (13), and Proteus syndrome (9). Less extensive forms of hemimegalencephaly, affecting only part of a hemisphere, have been called focal megalencephaly (14). MR imaging findings in a case of TSC with hemimegalencephaly have been reported previously (15). The diagnosis of TSC in that case was made by three secondary features (first-degree relative, cardiac rhabdomyoma, and noncalcified SEN). In that child, the unaffected hemisphere showed no abnormality on MR images.

The second case we describe in this report presents some problems with classification. Transmantle cortical dysplasia is defined by atypical cells, heterotopic neurons, and glia extending from the ventricular to the pial surface (5), and is a reasonable description of the findings in case 2. However, the increase in brain, along with the cortical dysplasia, leads to the classification of focal megalencephaly. A possible source of clinical confusion with TSC in the presence of seizures and hypopigmented lesions is hypomelanosis of Ito, which is associated with hemimegalencephaly (12). In addition, megalencephaly and periventricular tumors are described in linear nevus syndrome (16); however, both our cases can be classified as TSC on the basis of Roach's criteria (4).

Conclusion

We have described two cases of TSC with cortical formation abnormalities not typically found in TSC. One of the children had hemimegalencephaly and the other had focal megalencephaly. Recent classifications of cortical malformations are valuable, but our findings show that the distinctions may not be clear in some cases.

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References

1. Osborne JP, Fryer A, Webb D. **Epidemiology of tuberous sclerosis. In: Johnson W, Gomez M, eds.** *Tuberous Sclerosis and Allied Disorders. Ann N Y Acad Sci* 1991;615:125–127
2. Griffiths PD, Martland TR. **Tuberous sclerosis complex: the role of neuroradiology.** *Neuropediatrics* 1997;28:1–9
3. Griffiths PD, Bolton P, Verity C. **White matter abnormalities in tuberous sclerosis complex.** *Acta Radiol* (in press)
4. Roach ES, Smith M, Hutterlocher P, et al. **Diagnostic criteria: tuberous sclerosis complex.** *J Child Neurol* 1992;7:221–224
5. Barkovich AJ, Kuzniecky RI, Dobyns WB, Jackson GD, Becker LE, Evrard P. **A classification scheme for malformations of cortical development.** *Neuropediatrics* 1996;27:59–63
6. Braffman BH, Bilaniuk LT, Naidich TP, Altman NR, et al. **MR imaging of tuberous sclerosis: pathogenesis of this phakomatosis,**

use of gadopentetate dimeglumine and literature review. *Radiology* 1992;183:227–238
7. Barkovich AJ, Chuang SH. **Unilateral megalencephaly: correlation of MR imaging and pathologic characteristics.** *AJNR Am J Neuroradiol* 1990;11:523–531
8. Kalifa CL, Chiron C, Sellier N, et al. **Hemimegalencephaly: MR imaging in five children.** *Radiology* 1987;165:29–33
9. Griffiths PD, Welch RJ, Gardner-Medwin D, et al. **The radiological features of hemimegalencephaly.** *Neuropediatrics* 1994;25:140–144
10. Townsend JJ, Nielsen SL, Malamud N. **Unilateral megalencephaly: hamartoma or neoplasm?** *Neurology* 1975;25:448–453
11. Sarwar M, Schafer M. **Brain malformations in linear nevus sebaceous syndrome: an MR study.** *J Comput Assist Tomogr* 1988;12:338–340
12. Peserico A, Battistella PA, Bertoli P, Drigo P. **Unilateral hypomelanosis of Ito with hemimegalencephaly.** *Acta Paediatr* 1988;77:446–447
13. Cusmai R, Curatolo P, Mangano S, Cheminal R, Echenne B. **Hemimegalencephaly and neurofibromatosis.** *Neuropediatrics* 1990;21:179–182
14. Barkovich AJ. **Congenital malformations of the brain and skull. In:** *Pediatric Neuroimaging.* 2nd ed. New York: Raven; 1995:177–275
15. Maloof J, Sledz K, Hogg JF, Bodensteiner JB, Schwartz T, Schochet SS. **Unilateral megalencephaly and tuberous sclerosis: related disorders?** *J Child Neurol* 1994;9:443–446
16. Robain O, Gelot A. **Neuropathology of hemimegalencephaly.** In: Guerrini R, et al, eds. *Dysplasias of Cerebral Cortex and Epilepsy.* Philadelphia: Lippincott-Raven; 1996:89–92