SHORT REPORT

Tuberous sclerosis presenting in late adult life

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A 59 year old woman presented with a three year history of left sided weakness. Magnetic resonance imaging of the brain showed a large high signal lesion occupying most of the right temporal lobe with mass effect. A probable diagnosis of low grade glioma led to temporal lobectomy. Histology revealed dysplastic cortical morphology typical of tuberous sclerosis. There were no clinical signs or family history of the disease. Ultrasound showed multiple bilateral renal angiomyolipomas, confirming the diagnosis of tuberous sclerosis. Molecular genetic analysis of peripheral white blood cells identified a novel mis-sense mutation R1409W in exon 33 of the TSC2 gene.

Tuberous sclerosis is a neurocutaneous autosomal dominant disorder with an estimated prevalence of 9/100 000 population and a varied clinical presentation.[1] Neurological presentation of tuberous sclerosis occurs typically in children with seizures and intellectual impairment. However approximately 50% of patients who fulfil the diagnostic criteria have normal intellect and 15% remain free from seizures.[2]

Genetic studies have shown that two thirds of cases do not have affected parents, and the disease results from a new dominant mutation either in the TSC1 gene on chromosome 9q34[3] or the TSC2 gene on chromosome 16p13.3,[4] with the latter accounting for an estimated 78% of cases.[5]

We present an index case of tuberous sclerosis in a 59 year old woman with a three year history of unilateral sensory and motor symptoms but no other clinical manifestations of the disease. Histology of brain tissue showed features of tuberous sclerosis including cortical dysplasia and giant multinucleated cells. Multiple bilateral renal angiomyolipomas were found on screening. The patient was shown to have a novel mutation in the TSC2 gene.

CASE REPORT

A 59 year old right handed women presented with a three year history of paraesthesiae affecting the left foot and weakness in the left hand. There were no other neurological or systemic symptoms. A hysterectomy was the only notable feature in the past medical history. There was no relevant family history of seizures or learning disability. Her children and sibling were not examined but are reported to be in good health.

General examination was unremarkable. In particular, examination of the eyes, teeth, and skin, including inspection under Wood's light, showed no abnormalities. She scored 95/100 on the Addenbrooke's cognitive examination,[6] the impairment being in visuospatial tasks. Neurological examination showed a left homonymous hemianopia and extinction, with left sided mild pyramidal weakness associated with sensory impairment, dysgraphesthesia, and astereognosis on the same side.

Haematological and biochemical profile were normal. Computed tomography of the brain revealed no calcification but a large well defined area of low density occupying most of the right temporal lobe and extending to the occipitoparietal region compatible with a low grade glioma. Magnetic resonance imaging showed a large mass occupying most of the right temporal lobe, extending into parietal, occipital, and posterior frontal regions centred mainly on the cortex and underlying white matter (fig 1). A marked mass effect with deviation of the right uncus and compression of the cerebral peduncle was apparent, with minimal oedema. There was no evidence of subcortical dysplastic nodules or periventricular tubers.

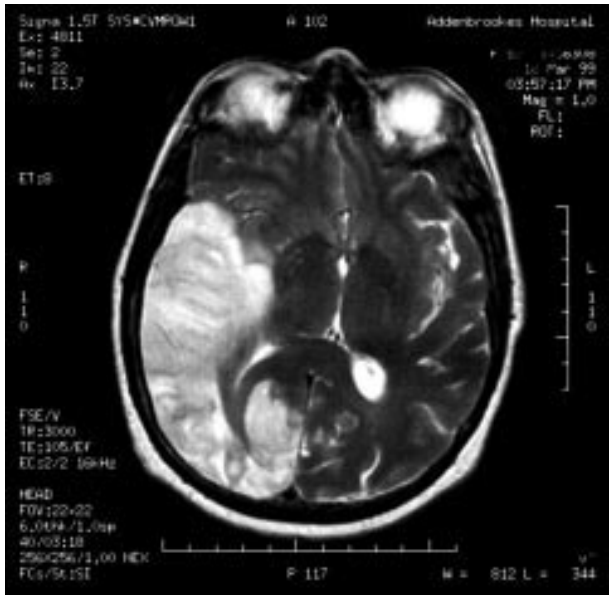

Figure 1 Brain magnetic resonance imaging showing a large well demarcated intra-axial high signal T2 weighted lesion occupying the bulk of the right temporal lobe, centred mainly on cortex and underlying white matter and sparing the temporal pole and mesial temporal structures but extending into the parietal, occipital, and posterior frontal regions.

In view of the chronicity of presentation and radiological findings the patient was started on dexamethasone and underwent surgical exploration for a presumed low grade glioma. Right temporal lobectomy was undertaken, during which the temporal lobe was found to be abnormally firm. Histological sections from the resected temporal lobe showed patchy, disrupted cortical lamination with dysmorphic neurones and giants cells, as well as gliosis. The giant cells had varying immunocytochemical characteristics (both neuronal and glial) and were frequently multinucleated and found in both the cortex and the underlying white matter (fig 2). There was no convincing evidence of a neoplastic process, with an MIB® index of zero (MIB1 antibody to Ki-67 antigen by DAKO A/S, Glostrup, Denmark). Histology was highly suggestive of tuberous sclerosis. On plain abdominal *x* ray there was calcification over the area of the right kidney, and ultrasound

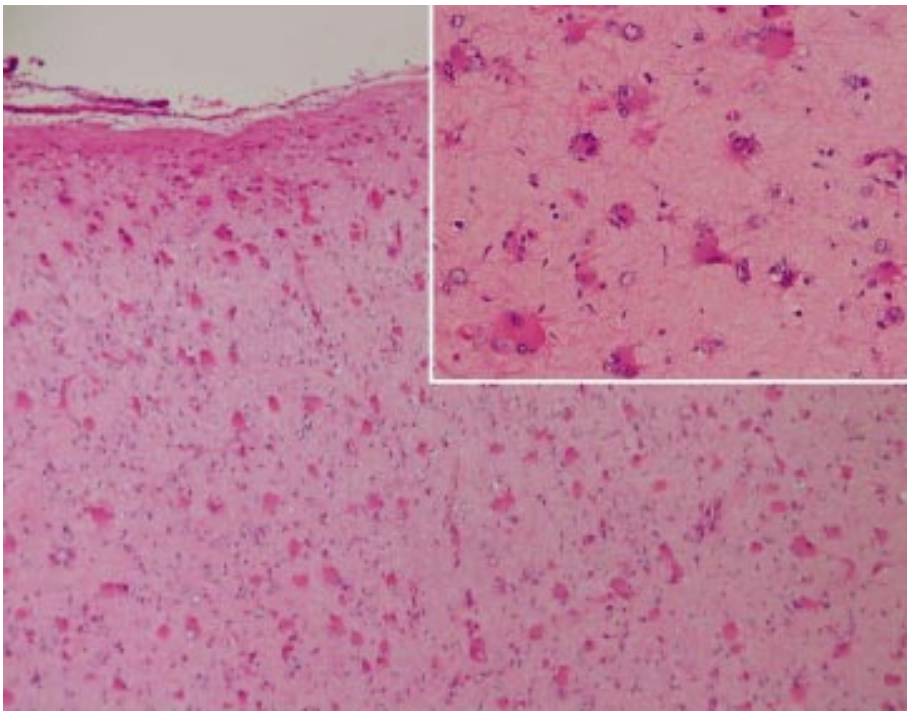

Figure 2 Micrograph demonstrating disrupted cortical lamination and gliosis. The inset shows dysmorphic neurones and giant cells upon haematoxylin and eosin stain.

showed a 12 cm cystic lesion in the mid pole of the right kidney with heavily calcified walls. There were two well defined areas of increased echogenicity of 4 mm and 7 mm diameter in the mid pole of the left kidney, having the typical appearances of angiomyolipomas.

Genomic DNA extracted from peripheral blood leucocytes was screened for mutations in the TSC1 and TSC2 genes. Individual coding exons were amplified using the polymerase chain reaction and the products analysed by conformation sensitive gel electrophoresis. The amplified product from exon 33 of the TSC2 gene gave an abnormal band. Direct sequencing of exon 33 identified the sequence change 4225 C>T predicted to give rise to the non-conservative amino acid substitution of arginine for tryptophan at codon 1409. This sequence change abolished an MspI restriction site. The presence of an abnormal fragment on MspI digestion of the amplified product of exon 33 was confirmed in the patient. There was no detectable difference in the intensity of the normal and aberrant bands to suggest somatic mosaicism for this mutation. No abnormal bands were observed with Msp1 digestion of the amplified product of exon 33 in 100 normal controls.

DISCUSSION

We describe a woman of 59 years with normal intelligence and no personal or family history of clinical manifestations of tuberous sclerosis, who presented with a neurological syndrome not typically associated with this neurocutaneous disorder which normally presents in children. Our patient fulfils the diagnostic criteria for tuberous sclerosis, with histologically confirmed cortical dysplasia, giant astrocytic-like cells, and multiple renal angiomyolipomas shown on ultrasonography.[2]

Clinical diagnosis of tuberous sclerosis is rarely difficult when the characteristic neurodevelopmental and dermatological features present in early childhood, typically with infantile spasms. Recognition is delayed in a minority until later childhood or adolescence when the manifestations are predominantly dermatological. The late adult presentation in our patient was exceptional in not presenting until late adulthood with chronic focal neurological symptoms and having cortical dysplasia and renal angiomyolipomas as the only features of the condition.

The mutation 4225 C>T found in this patient is likely to be pathogenic and in the absence of a family history of tuberous sclerosis may represent a new dominant mutation. It was the only sequence variant identified by conformation sensitive gel electrophoresis of the coding exons of the TSC1 and TSC2 genes. This screening method identifies most but not all sequence changes. This sequence variant has not been reported previously,[7] but the great diversity of mutations observed in tuberous sclerosis means that only a minority is identified in more than one family. Missense mutations account for an estimated 24% of the pathogenic mutations in TSC2.[7] In this case the neutral and hydrophobic amino acid tryptophan is substituted for the basic amino acid arginine. It is not possible to predict the functional effect of this change but the importance of arginine at this location is supported by the evolutionary conservation of this residue in the rat and mouse.

The exceptionally mild disease in this patient may simply be an example of variation in expression characteristic of tuberous sclerosis observed between affected members of the same family. A mild phenotype can also be due to somatic mosaicism where a postzygotic new dominant mutation only affects a proportion of cells and to a varying extent in different tissues.[8] However, although mosaicism was not apparent in leucocyte DNA from this patient where the dosage of normal and mutant alleles was similar, somatic mosaicism cannot be completely excluded without examining other tissues.

Conclusions

We report an unusual presentation of tuberous sclerosis manifesting in late adult life with clinical and radiological signs suggesting a cerebral hemispheric structural lesion. This provides a striking illustration of the extraordinary variation in expression of this disorder both with respect to age at presentation and severity of disease.

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NEUROLOGICAL STAMP

Nikolai Nilovich Burdenko (1876–1946)

Burdenko studied in Pavlov's laboratory after graduation, and was greatly influenced by him. He specialised in neurosurgery. In World War I, he became surgeon in chief of the Russian Army Medical Service and under his guidance and leadership, the army developed an excellent neurosurgical team. In Moscow in 1924, he founded the Soviet Neurological Institute. Burdenko also became a member of the Supreme Soviet. He has been honoured twice on stamps of Russia, most recently in 1976 on the centenary of his birth (Stanley Gibbons 745, Scott 4438).

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