1
HISTORICAL BACKGROUND

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DEFINITION

Tuberous sclerosis complex (TSC) is a genetically determined, variably expressed, multisystem disorder that may affect any human organ with well-circumscribed, benign, non-invasive lesions. The skin, brain, retina, heart, kidney and lung are the organs more often involved. The importance of central nervous system (CNS) involvement in TSC is emphasized by the fact that the condition has retained its name for over a century. "Tuberous sclerosis of the cerebral convolutions" is the term used by Bourneville (1880) to describe the unique and distinctive cerebral pathology he found in a patient with seizures and learning disability.* The cerebral lesion, called *cortical tuber*, is the hallmark of a protean autosomal dominant disease with variable expression in one or more organs or tissues. The different lesions are included under the term *tuberous sclerosis complex* (TSC) proposed in 1942 by the pathologist Moolten.

Derived from a single pathologic feature, namely potato-like firmness of segments of the cerebral cortex, the term tuberous sclerosis complex persists as a designation for all forms and variants of the disease. However, the majority of patients identified as having the disorder do experience symptoms referable to the CNS. Even in subjects without neurological symptoms, CNS lesions are present in all brains studied. In those rare instances in which the brain is said to be anatomically normal, an exhaustive histological research would be likely to reveal lesions. CNS abnormalities therefore remain the hallmark of TSC and underline its most common and clinically serious manifestations.

Historical contributions to the knowledge of TSC are summarized in Table 1.1.

HISTORY OF TUBEROUS SCLEROSIS COMPLEX

1. The First Descriptions

In 1835, Pierre François Rayer completed an atlas displaying skin diseases. In this atlas a young man's face dotted with small, erythematous papules with a characteristic distribution and similar appearance is shown, resembling the facial angiofibroma often observed in patients with the tuberous sclerosis complex (see Fig. 9.1, p. 138). On March 25, 1862, Friederich Daniel von Recklinghausen presented to the

* The term "learning disability" corresponds to "mental retardation" in American usage.

TABLE 1.1
Progress in understanding tuberous sclerosis complex (from Gomez 1999, modified)

Year	Authors	Findings
1835	Rayer	Illustration of facial angiofibroma in atlas
1862	Von Recklinghausen	Cardiac "myomata" in newborns
1880	Désiré-Magloire Bourneville	Cortical "tuberosities"
1885	Balzer and Ménétrier, Hallopeau and Leredde	Report "adenoma sebaceum"
1901	Pellizzi	Dysplasia, heterotopia, myelination defect
1905	Perusini, Campbell	Pathology of brain, kidney, heart, skin
1908	Vogt	Diagnostic triad
1910	Kirpicznik	Genetic condition
1913	Berg	Hereditary nature
1914	Schuster	*Forme fruste* with normal intelligence
1918	Lutenbacher	Lung involvement
1920	Van der Hoeve	Retinal phakoma
1924	Marcus	Radiographic findings
1932	Critchley and Earl	Discover white spots, report "autistic" behaviour
1967	Lagos and Gomez	38% of patients have normal intelligence
1975	Pampiglione and Pugh	Infantile spasms as the presenting seizure
1979	Gomez	New criteria for diagnosis; decline of the Vogt's triad
1984	Dulac et al.	A cluster of spasms is preceded by a focal EEG discharge
1987	McMurdo et al.	Magnetic resonance imaging (MRI) demonstrates cortical tubers
1987	Roach et al.	Number of tubers
1987	Fryer et al.	Mapping of *TSC1* to chromosome 9q34.3
1988	Curatolo and Cusmai	Localization of tubers
1990	Chiron et al.	Vigabatrin as an effective antiepileptic treatment
1992	Kandt et al.	Mapping of *TSC2* to chromosome 16p13.3
1993	The European Chromosome 16 Tuberous Sclerosis Consortium	Cloning of *TSC2*; its product is called *tuberin*
1995	Maeda et al.	Introduction of MRI with fluid-attenuated inversion recovery
1997	Van Slegtenhorst et al.	Cloning of *TSC1*; its product is called *hamartin*
1997	Bolton and Griffiths	Autism and temporal lobe
2001	Dabora et al.	Genotype–phenotype relationship

Obstetrical Society of Berlin the pathological findings in a newborn infant who had "died after taking a few breaths". The heart had several tumours protruding on the cardiac surface, while others bulged into the cardiac chambers and still others were embedded in the ventricular walls. Von Recklinghausen labelled these cardiac tumours "myomata" and added briefly that the infant's brain contained a "great number of scleroses". Von Recklinghausen's brief report contains the first description of the two pathologic lesions more often observed in newborn infants with TSC: cardiac rhabdomyomas and cortical tubers (Gomez 1999).

In 1880 Bourneville gave the first detailed report of its neurological symptoms and gross cerebral pathology. In his paper, Bourneville described the pathological findings in the brains of three "idiots". Bourneville coined the term "tuberous sclerosis of the cerebral convolutions" for his third patient because its gross nodular appearance and induration resembled tubers. The patient was a 3-year-old girl admitted to *La Salpetriére* with convulsive seizures and learning disabilities. Her seizures had started in infancy and at first involved only the eyes. At the age of 2 years, they became more generalized so that both upper extremities would become "somewhat rigid and slightly rotated". Examination when she was 15 years old disclosed facial skin lesions. The patient also had many small "molluscum" lesions on the neck and a right spastic hemiplegia. Each day for several months the girl continued to have many seizures, and on May 7, 1879, she was found dead in her bed. On postmortem examination, Bourneville found that many cerebral convolutions had hard, raised, whitish areas of greater density than the surrounding cortex, and he wrote: "In one word, we are dealing with a hypertrophic sclerosis of portions of the circumvolutions." Bourneville concluded that the seizures had a focal origin and progressed to generalized attacks, and attributed their partial onset to the conspicuous sclerotic lesions in the ascending frontal and parietal convolutions of the left cerebral hemisphere.

One year later, Bourneville and Brissaud (1881) made a new clinicopathological observation. The patient was a 4-year-old boy admitted to *La Bicétre*. He had had predominantly right-sided seizures since the age of 4 months, had learned to walk at 2 years of age, and could say only one syllable at age 4. Subsequently, his seizures became more frequent and prolonged. On auscultation he had a loud cardiac murmur. Later he developed cyanosis and crepitant pulmonary rales, stopped eating and drinking, and finally died on January 6, 1880. Pathological examination of the brain disclosed sclerotic, hypertrophic convolutions. Brain cuts demonstrated ventricles normal in size, but their lateral walls were covered with many small sclerotic tumours, 2 to 5 mm in diameter. The kidneys on sectioning disclosed small yellowish-white tumours. Bourneville and Brissaud proposed that the association of the cerebral lesions and the kidney tumours was significant. In 1890, Pringle reported in much detail the same type of facial lesion on a 25-year-old woman of subnormal intelligence. He called the lesion "congenital adenoma sebaceum".

2. Clinical Phenotype

In 1908, Vogt described the association between the cerebral sclerosis of the circumvolutions reported by Bourneville and the facial adenoma sebaceum. Through Vogt's work, the syndrome consisting of seizures, learning disability and "adenoma sebaceum" was established as the classic clinical triad of features for the diagnosis of TSC. Vogt also stated that cardiac and renal tumours form part of the disease.

Noting the similarity between TSC, neurofibromatosis and von Hippel-Lindau disease in the spotty distribution of these lesions and their tendency to grow as benign tumours, in 1920, van der Hoeve developed the concept of phakomatoses, disorders characterized by the presence of circumscribed lesions or phakomas with the potential of getting larger and forming a real tumour by cellular proliferation. Van der Hoeve listed the varieties of phakomata found pathologically in patients with TSC: tumefactions in the cerebral cortex with proliferation of glia, tumours within the ventricles, heterotopical spots in the white substance, renal cysts, intestinal lipomas, thyroid adenomas, bone cysts, facial adenoma sebaceum, etc.

In 1932, Critchley and Earl reported on their observations in 29 patients with TSC. They were the first to emphasize the diagnostic value of white spots (hypomelanotic skin macules) in patients with TSC. Furthermore, they reported autistic behaviour 11 years before Kanner (1943) published his classic paper describing the paradoxical and bewildering disturbance of behaviour that he called "early infantile autism". These descriptions are quoted as an introduction to behaviour in TSC. Critchley and Earl noted that "often the family history shows no evidence of tuberous sclerosis but bears a strong psychopathic taint" (1932: 314). "The psychosis always resembles a primitive form of catatonic schizophrenia, though the exact form of the reaction varies with the level of mental development at which it occurs. . . . The depth of psychosis is independent of the degree of intellectual defect, although the two processes are so inextricably intertwined as to render impossible any accurate estimation of the part played by either in any given case. . . . All manner of bizarre attitudes and stereotyped movements occur, and these are most striking in the hands and fingers" (ibid.: 322).

In 1967, Lagos and Gomez documented a family in which five generations were affected by TSC. These authors reviewed the clinical features of 71 individuals with TSC seen at the Mayo Clinic during a 30-year period, and reported that 38% of the 69 patients with available intelligence data had average intelligence, while 62% had learning disabilities. All the patients with learning disability had previously had seizures, while of those with average intelligence, 69% had, or had previously had, seizures. These authors were unable to find any correlation between the presence of adenoma sebaceum, retinal phakoma or intracranial calcification and the mental status (Gomez 1979). These data determined a weakening of the classic triad of Vogt and gave rise to the revision of diagnostic criteria that followed.

The relationship between West syndrome and TSC has been known for many years (Gastaut et al. 1965). The high incidence of infantile spasms (IS) in TSC has long been emphasized. Pampiglione and Pugh in 1975 reported that infantile spasms were the presenting symptoms in up to 69% of patients with TSC. Conversely TSC has been found by Curatolo and Cusmai (1987) in 11% in a series of 164 infants affected by IS who underwent CT, suggesting the existence of an important association between TSC and IS. However, in recent years important advances in the understanding of seizures associated with TSC have indicated that infants with TSC exhibit some characteristic clinical and EEG features, distinguishing these infants from those with classical West syndrome including hypsarrhythmia. In particular, Dulac et al., in 1984, stressed the fact that occasionally a particular combination of focal and generalized seizures is present and that a cluster of spasms may be preceded by a focal EEG discharge.

3. Pathological Findings

In 1905, Perusini reported a precise microscopic description of the cortical tubers, finely illustrated with ink drawings of atypical neurons, subcortical areas of hypomyelination, and subependymal nodules. He also reported the frequent association of the cerebral, renal and cardiac lesions with the "cutaneous adenomas" in TSC patients.

In 1942, Moolten proposed that the lesions of TSC belong to one of three types. In Moolten's own words, "the basic lesion is hamartial, becoming in turn tumour-like but benign (hamartoma) or truly neoplastic (hamartoblastoma)". Moolten, recognizing the complexity and "hamartial nature" of tuberous sclerosis, renamed it "the tuberous sclerosis complex". This is now the preferred name, although in a few European countries, where eponymic names of diseases are often used, it is called Bourneville disease.

Pathologically, TSC is a disorder of cell migration, proliferation and differentiation. Present evidence suggests that the CNS lesions of TSC are due to a developmental disorder of neurogenesis and neuronal migration. Two populations of neuroepithelial cells are generated by the germinal matrix in TSC. One is a population of normal neuroblasts which form normal neurons and astroglia and which migrate to the cortical plate where they form histologically normal cerebral cortex. The second is an abnormal cell population which forms primitive cells that often fail to show clear neuronal and glial differentiation. Some of these cells, named "neuroastrocytes", remain in the germinal matrix zone where they form subependymal nodules and giant cell tumours. Some neuroastrocytes show partial migration, forming heterotopias in the subcortical white matter. More differentiated cells migrate to the cortical plate where they form aggregates of dysplastic cortex, the cortical tubers. Cells in tubers share with those in subependymal nodules and giant cell tumours the frequent absence of clear neuronal and glial differentiation, showing

features of primitive stellate neurons with few dendritic spines. Tuberin and hamartin are widely expressed in human fetal tissues. This evidence suggests a critical function of these two proteins in early development and maturation of the brain. Tuberin was undetectable in subependymal giant cell astrocytomas examined in three patients, suggesting that a complete inactivation of tuberin expression is associated with tumour development. It is likely that hamartin and tuberin participate in the same pathways of cellular growth control and share a common biochemical pathway. The proteins appear to co-localize at the cellular level, and recent evidence suggests that there is a direct binding between tuberin and hamartin. These two proteins form a cytosolic complex interacting at the N-terminal ends of both proteins. This interaction is abolished by some TSC-associated mutations.

4. Imaging

In 1924, Marcus described roentgenographic intracranial calcifications as a sign of TSC. With the introduction of pneumoencephalography, the intraventricular subependymal nodules on the walls of the lateral ventricles could be demonstrated in a living patient for the first time. The image was called "candle guttering" because of its resemblance to the drippings of a burning candle. As a consequence of both these discoveries, the number of patients diagnosed increased dramatically.

Only occasionally were asymptomatic relatives of the severely affected patients recognized as having TSC, prior to the improvement of imaging methods, which began in the mid-1970s. The introduction of cranial computed tomography in 1974, followed by echocardiography, renal ultrasound and magnetic resonance imaging in 1982, provided new, reliable and non-invasive methods of diagnosis. These advances allowed new and more extensive criteria in establishing diagnosis and, as a consequence, the number of affected individuals with TSC rapidly increased.

McMurdo et al., in 1987, gave us the first pathologic demonstration that the signal changes on MRI corresponded with cortical tubers. At that time we believed that uncontrolled epileptic seizures were largely responsible for the learning disabilities of children with TSC. Roach et al. first reported in 1987 that children with a higher number of cortical tubers detected by MRI had poorer seizure control and more severe developmental delay. In 1988, Curatolo and Cusmai reported a topographic correspondence between EEG foci and the largest tubers detected by MRI, emphasizing the importance of cortical tubers as epileptogenic areas. In 1989, Nixon et al. demonstrated that MRI was unable to detect all the cortical tubers that can be identified pathologically. In 1990, Chiron et al. reported Vigabatrin as an effective drug treatment for infantile spasms associated with TSC. In 1995 Maeda et al. noted that fluid-attenuated inversion recovery was more sensitive than spin-echo sequences and may identify more and smaller cortical tubers than the standard T2-weighted images. Goodman et al. (1997) confirmed that the count of cortical

tubers detected by MRI is a good biomarker in predicting the severity of cerebral dysfunction.

Positron emission tomography may reveal hypometabolic regions not predicted by MRI, demonstrating that the disturbance of cerebral function may be more extensive than indicated by morphological studies alone.

The use of multimodality imaging may improve detection of epileptogenic foci in children with TSC.

5. Genetics

Since the earliest descriptions of TSC at the end of the nineteenth century, physicians and scientists have sought the underlying cause of the disease (von Recklinghausen 1862, Bourneville 1880).

TSC was first recognized as a genetic condition by Kirpicznik in 1910. He reported a family with affected individuals in three generations, and described the condition in identical and fraternal twins. Earlier studies had noted that the facial lesions of TSC, erroneously called "adenoma sebaceum", were inherited in families (Balzer and Ménétrier 1885, Pringle 1890).

The hereditary nature of TSC was first reported by Berg in 1913. Schuster (1914) confirmed it, and recognized as exceptional the patient with only the adenoma sebaceum component of the Vogt triad, that is, without learning disability. This phenotype has been named the *forme fruste* – a term derived from the French and used for any "incomplete" phenotype or to indicate reduced expression of the TSC gene (Gomez 1999).

Since then, the studies by Gunther and Penrose (1935) and Nevin and Pearce (1968) have demonstrated the dominant inheritance of TSC and its high mutation rate.

In 1951, Dickerson described three families with multiple members affected with TSC, and reviewed the literature concerning all that was known about familial cases.

Until the late 1980s, very little real progress was made toward uncovering the molecular basis of tuberous sclerosis. Fortunately, progress in the field of molecular genetics dramatically improved the ability to study this complex genetic disease.

The first report of genetic linkage analysis identifying a probable TSC gene on chromosome 9q34 appeared in 1987. This gene was denoted *TSC1* (van Slegtenhorst et al. 1997). Subsequent studies indicated that not all TSC families demonstrated linkage to the 9q34 region (indicating that there probably were other TSC genes).

Later, chromosome 16p13 was identified as the site of a second TSC locus denoted *TSC2* (Kandt et al. 1992, The European Chromosome 16 Tuberous Sclerosis Consortium 1993).

TSC results from mutations in *TSC1*, the gene on chromosome 9q34, and *TSC2*, the gene on chromosome 16p13. Frequent loss of heterozygosity for alleles in 16p13.3 and rare loss in 9q34 have been found in hamartomas from TSC patients,

indicating that a second somatic mutation may be required to produce the TSC phenotype at the cellular level. These findings are consistent with *TSC1* and *TSC2* acting as growth suppressor genes. The *TSC2* gene maps to the gene-rich region of 16p13.3, approximately 2.25 Mb from the telomere and immediately adjacent to the *PKD1* gene. The 5.5 kb transcript spans an estimated 43 kb of the genomic sequence and comprises 42 known exons, of which 41 are coding, and encodes an 1807 aminoacid protein called tuberin. The *TSC1* gene consists of 23 exons of which the last 21 contain coding sequence. The *TSC1* protein, which is called hamartin, consists of 1164 aminoacids.

In a comprehensive neurological and molecular diagnostic evaluation, Dabora et al. (2001) reported that children with *TSC2* mutations tend to have more severe neurological manifestations than children with *TSC1* mutations, with a much higher rate of infantile spasms and learning disability, suggesting that the neurological outcome may be related to the TSC mutation itself.

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