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Tuberous Sclerosis : Clinical Experience With 19 Cases

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Abstract

This study highlights the clinical observations on a series of 19 Indian cases of tuberous sclerosis. Males outnumbered females by a ratio of 3.75 :1. Eighteen patients were mentally retarded, and an equal number had seizures. A strong correlation was seen between the age at onset of seizures intellectual attainment in general, and language development in particular. Adenoma Sebaceum was the commonest physical feature. Eight patients had consanguineous parentage, however, the significance of this rare finding is unclear. Early diagnosis and treatment, detection of familial cases and genetic counselling are emphasised as possible means of reducing the incidence of new cases and preventing and severe disability in the existing ones.

Key words -
Tuberous Sclerosis,
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Tuberous Sclerosis (TS), also known as Bourneville's disease or epiloia, is a hereditary disorder characterised by the presence of the classical clinical triad of mental retardation, seizures and adenoma sebaceum. However, a wide range of other manifestations have been described, and any number and combination of these may be present in an individual patient. These include shagreen patches, hypopigmented macules (ash-leaf spots), hyperpigmented areas (cafe- au-lait spots), periungual / subungual / gingival fibromata, skin tags harmartomatous lesions of liver, spleen kidneys, heart, lungs, testes, thyroid, etc., cortical and subependymal gliomata, retinal phakomata, etc. It is an important cause of infantile spasms [1]. Mental retardation is not invariable and occurs in 60-70% of cases [2], [3], [4].

TS is transimitted as an autosomal dominant disorder with great variability in gene manifestation [2], [5]. However, about 80% of the cases are sporadic, representing new mutations [3]. The use of more exhaustive investigations to detect formes frustes of the disorder in the parents may yield a greater proportion of familial cases [6]. Estimates of incidence range from 1 in 20,000 to 1 in 1,50,000 in the general population [7]. Different studies have shown a varying distribution bewteen the sexes [8], [9], [10]. However, Penrose [5] states that both the sexes are equally affected. To counter an early proposition that TS does not occur in the coloured races. Case reports have been fairly common in Indian literature (reviewed by Somamsunder [11]). However, the only large series of patients is that reported by Somasunderam and

Vaidyalingam [12] comprising of 12 cases.

The present study was undertaken to analyse the clinical characteristics of a sizeable Indian series of patients with TS, and to comapre these with the findings of other major studies.

Material and Methods

This study is based on the data pertaining to 19 cases of TS seen at the National Institute of Mental Health & Neuro Sciences, Bangalore over a period of about 20 years by one of the authors(H.S.N).

Detailed history and physical findings had been recorded for each patient at the initial visit, and necessary investigations requested. Followup notes were made at each visit. The diagnosis of TS was based mainly on the presence of the classical clinical traid of the disorder. However, one patient was not mentally retarded, and another did not have epilepsy. In these instances the presence of other typical features and family history left little doubt about the diagnosis Intellectual level of the patients was assesed, wherever possible, through psychological tests. In the rest it was estimated clinically by correlating the attainment of motor, linguistic and social milestones with the chronological age.

For the purpose of this study the case files of these patients were reviewed and the available data analysed. Additional information or investigations were obtained. When necessary, for some patients who had maintained followup.

Results

There was a total of 19 cases-15 male and 4 female. Their age ranged from 8 months to 24 years at the time of the first consultation (mean: 10 years 9 months). Fourteen (73.7%) were Hindus, 4 (21.05%) Muslims, and 1 (5.26%) Christian. Seventeen patients belonged to the 4 southern states, 1 was from Maharashtra and 1 from Nepal.

All but 1 were mentally retarded to varying degrees (94.7%). Of these, 2 (10.5%) had mild, 3 (15.8%), moderate, 7 (36.8%), severe, and 6 (31.6%), profound mental retardation. Seventeen (89.5%) had epilepsy at the time of presentation. One patient had seizures starting at the age of 7 months, but they had remitted spontaneously at the age of 7 years. His brother, also a patient of TS, had never had seizures (case nos.10 and 11). In 10 (52.6%), the seizures had started before 1 year of age; in 5 (26.3%), between 1 and 3 years; and in 3 (15.8%) between 3 and 10 years. The data regarding the patients age at evaluation, age of onset of seizures, achievement of motor, linguistic milestones and toilet control and the level of mental retardation, are presented in Table 1.

Table 1 - Clinical data

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Years / Months
+=present / achieved, age uncertain
-=absent / not achieved.

The physical features are presented in Table 2. Adenoma sebaceum was seen in all the cases at the time

of presentation, except in case no. 9, who was found to develop it at the age of 6 years on followup. Shagreen patches were the next commonest finding present in 11 (57.9%) cases, followed by depigmented spots, in 10 (52.6%). However, the latter are likely to have been missed in at least some cases since examination under Wood's light was not carried out. Fundus examination for retinal phakomata and x-rays of the skull could not be carried out in many cases because they were very unco-operative. Detailed investigations to detect lesions in the heart, lungs, and kidneys were also not carried out in the absence of any specific indications. One patient (case no.2) had been operated for cerebral astrocytoma at the age of 2 years 3 months.

Table 2 - Physical Features

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Figures in parantheses indicate percentages.

The 19 patients came from 18 families (2 were siblings). No information was available about the family of 1 patient who lived in a convent. A history of mental retardation, seizures, or adenoma sebaceum was elicited in 41.2% families involving 1 father, 1 mother, 3 siblings (excluding the 2 who were both patients), 1 maternal uncle, and 2 nephews. However, ascertainment of each individual case was not possible, and a detailed evaluation of apparently unaffected relatives may have revealed some instances of the formes frustes of TS.

There was a total of 84 children in there 18 families (average 4.7/family). The mean rank of the patient in the sibships was 3.6. In 7 families, the patient was the last born; 4 patients were the first born. The age of the father at the time of the patient's birth ranged from 26-53 years (mean 34.3 years), while that of the mother, from 17- 37 years (mean 26.19 years).One unusual finding in this study is the number of children born of a consanguineous parentage. out of the 17 for whom the data are available, 8 were born of consanguineous unions. Of these, 5 were born of a marriage between first cousins.

The follow up rate was generally poor. Two patients dropped out after the initial visit; 9 returned, irregularly, for 1 or more visits; and 3 still maintain regular follow-up. Five others received in-patient treatment due to severely disturbed behaviour. Of these, 4 went on to become chronic inmates of the hospital, and died of intercurrent problems at a mean age of 23.4 years (range 12-33 years). One has been admitted to an institution for the mentally retarded. In the group, control of seizures was difficult to achieve with antiepileptic medication. Also, the outcome for each patient in terms of intellectual development and, particularly, language attainment, seems to be related to the age at the onset of seizures. These data are presented in Tables 3 and 4 respectively.

Table 3 - Correlation between seizures and degree of MR

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Table 4 - Correlation between speech development and seizures

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N=18

Discussion

In the present series there is a clear preponderance of male patients (78.9%), who outnumber the female patients by a ratio of about 4:1. This is in contrast to some Western studies where there is an excess of females [8], [9]. The review by Somasundaram [11] also records a male: female ratio of about 3:1 among Indian patients with TS. Since no data from population surveys are available, it would be premature to attribute this finding to any real excess in the incidence of TS among males in India. Rather, it may reflect a cultural artefact which ensures a greater likelihood of male sufferers being brought to medical attention.

Despite its inclusion in the clinical triad diagnostic of TS, mental retardation is not an invariable feature of TS, as highlighted by a number of reports [4], [13], [14]. However 18 patients in this series were mentally retarded. This consistency may have been because these patients were, to some extent, selected for being mentally retarded since most of them were brought to the Mental Retardation Clinic at this institute. Secondly, with a disorder like TS which may involve multiple systems, only those cases with mental retardation, epilepsy, or behaviour disturbance are likely to come to the attention of psychiatrists. Others, particularly with formes frustes affecting isolated systems, are liable to be treated by the relevant specialists.

Although adenoma sebaceum was a universal finding in the present series, Hunt [15] in a larger series found depigmented patches to be more common. However, the frequency of some of the features may tend to vary with the awareness and perseverance with which they are sought, the investigative facilities available, and also the age at which the patient is seen, Since the assessment of physical features and investigation for asymptomatic visceral lesions were far from exhaustive in the present series, further comment on this aspect is unwarranted.

Similarly, ascertainment of familial cases was also not very reliable as detailed examination of all parents and other probable cases among the relatives could not be carried out. This may explain the anomalous finding of some distant relatives having had signs indicative of TS while the parents were apparently unaffected, and the relatively high proportion of presumed familial cases. Although Wilson and Carter [16] reported an instance of siblings suffering from TS having normal parents, the overwhelming evidence supports a dominant transmission [5], [7]. However, an interesting finding is that of patients born of a consanguineous parentage, which has been rarely reported in TS literature [7]. In this series, 8 (47.1%) out of 17 patients were born of consanguineous unions. Since the rate of consanguineous marriage is also about 40% [17] in the local population, a recessive mode of inheritance cannot be proposed based on these data. Still, as done by Penrose [5], the possibility of recessive inheritance should be kept open.

As has been suggested by Hunt [10] and earlier by Gomez [18], the profound impact of an early onset of seizures on the patient's intellectual development is evident, also from the present data. Particularly, language attainment seems to be affected even more than motor development. Out of the 9 patients who had seizures prior to 1 year of age, 5 could not speak a single meaningful word. Although motor milestones were delayed, all the patients had ultimately acquired the ability to walk unsupported. On the other hand, 8 of these patients could not speak a single word, and only 6 could speak in sentences. Since most patients were brought to the hospital long after the seizures actually started, it was not possible to type their nature at the onset accurately. However, their usual form in infancy is that of infantile spasms. Friedman and Pampiglione [19] also reported a similarly grave significance of the EEG finding of hypsarrhythmia, often manifested clinically as infantile spasms. Since early treatment

may improve the outlook in some patients, it is important not to miss the diagnosis. Also, all the children presenting with infantile spasms should be carefully investigated for other features of TS. Since these may not be striking at an early age.

Examination under ultra-violet light may be of great help in early diagnosis by detecting depigmented macules . However, an occasional case may present with involvement of another system eg., the kidneys. In such an instance, only a high degree of suspicion and awareness may lead to the detection of TS. However, a careful evaluation of all systems must be carried out in all cases periodically to detect complications early. Early treatment of seizures may improve the outlook in terms of intellectual attainment in some instances. A close examination, and if necessary, investigation of both parents is a must in all cases for genetic counselling, since this may lower the incidence of new familial cases. Genetic counselling should also be offered to patients, particularly those with normal intelligence, who are likely to have children especially since prenatal diagnosis is not yet possible.

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