EPILOIA
(Case reports with review of literature)

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Summary

From the study of the four families of adenoma sebaceum, we have found that in two families the disease was transmitted in 3 to 4 generations, though it is mentioned by some authors that the transmission through more than 2 generations is rare. Though the characteristic features (Skin lesions, mental retardation and epilepsy) of the syndrome are seen in two cases forme frustes are found in the other members of the same family. Curiously, we have found one adult member of the family (Case 13 in the Pedigree chart 1) manifesting only epilepsy without any skin lesions which is rare, whereas two of the female members in the same generation had the adenoma sebaceum with epilepsy (Case 11 in chart 1) and adenoma sebaceum (Case 10 in chart 1) respectively. This emphasizes that the three cardinal features may occur singly or in any Combination or in any degree of severity in the members of the same family.

In the above 4 cases, except for the features of epilepsy, mental retardation and adenoma sebaceum, no other skin manifestations were found.

Introduction

Epiloia refers to development dysplasia manifested by Adenoma Sebaceum, Sclerotic masses in the cerebral cortex and tumors in various organs.

Historical Review

Von Recklinghausen in 1862 gave the first description of cerebral tuberous sclerosis in a still born child with numerous rhabdomyomata of heart and noted many sclerotic areas in the brain. Two years later Virchow found similar widespread lesions in a child whose sister had died of a cerebral tumour. These lesions were regarded then as gliomas. Bournville in 1880 first coined the word Tuberous Sclerosis and was the first to give classical clinical and pathological features of the disease in an epileptic imbecile who had died of the disease[1]. He described cases of mental deficiencies associated with potato like nodules in the brain and therefore called it Tuberous sclerosis. Though the characteristic facial eruption was portrayed in colour by Rayer as long ago as 1835 with the title of 'Vegetations Vascularis', Balzer and Menetrier in 1885 gave the first account and the name of Adenoma Sebaceum to these eruptions. Sherlock in 1911 coined the word Epiloia to comprehend the syndrome of epilepsy, mental defect and adenoma sebaceum. Pringle in 1890 reported sago grains coloured solid plaques and nodules in butterfly distribution on the face. In 1910–1911 Fowler and Dickerson collected 28 cases of tuberous sclerosis, some of which were having tumors in the heart, duodenum and thyroid. The relation between the skin lesions and the cerebral tuberous sclerosis was described by Bergin in

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1913. Von Den Hoove first described characteristic retinal tumors in 1921. In 1938 Berg published a case of cystic disease of lung associated with tuberous sclerosis.

Discussion

Etiology

The etiology of Adenoma Sebaceum is still debated. Most probably it is hamartoma in nature similar to neurofibromatosis and angiomatosis. Penrose supported the possibility of virus transmission (Placenta Passive)[2]. He also believed that it is transmitted by a single dominant autosomal gene, showing great variability of expression, even within a single family. Since the effective fertility is greatly reduced, transmission through more than two generations is rare and up to 50% of the cases are the result of new mutations which are believed to arise once in 60,000 to 1,20,000 life cycles[3]. It is evidently inherited as an irregularly dominant characteristic, that is to say the gene has incomplete penetrance and variable expressivity. Accordingly, a generation or more may be skipped (Indirect inheritance), but it is never possible to be sure that some carriers do not have undetectable or unnoticed minor expressions of the disease. Alternately genetic hypothesis is that multiple genes are present which determine the extent and degree of signs than a single incompletely penetrated gene of variable expressivity[4].

This syndrome consists of epileptic fits, hypertrophic sclerosis of the brain, tumors in the kidneys, and nodules on the floor of the lateral ventricle. Very rarely, adenoma sebaceum may present itself only as a few isolated white macules showing typical configuration of a mountain ash-leaf. These macules have long been regarded as vitiligo. They are larger than one centimeter in diameter and are characteristically dull white in contrast to vitiligo spots which are pure white. These isolated macules may be the earliest visible clues to tuberous sclerosis, inasmuch as the other important skin lesions of this disease. Adenoma sebaceum does not appear until 2 to 6 years after birth.

Adenoma sebaceum represents only part of a widely disseminated tissue malformation with tumors of both ectoderm and mesoderm which may involve almost any organ in the body. In the brain there is tuberous sclerosis. These potato like nodules are gliomas and occasionally become malignant. In the retina, there may be single or multiple, flat or mulberry like tumors called phakomas. These are gliomas in nature. Other lesions may be cysts or tumors of the kidneys, including angiomas, fibromas, adenomas or combinations of these. Tumors may occur in the liver, adrenals, thyroid, ovaries and gastro-intestinal tract. Most modern writers agree that the fundamental pathology in adenoma sebaceum is an increase in immature hair follicles along with more or less fibrosis and hyperplasia of collagenous tissue and the hyperplasia of capillaries. Some consider it an angiofibromatous hamartoma[5].

Although the epiloia and neurofibromatosis have certain features in common and may co-exist, they are genetically distinct. The incidence of the syndrome in U.S.A. and Western Europe is 1 : 10,000. The forme frustes are seen and epiloia may be associated with other ectodermatosis such as neurinomas, neurofibromas, nevi, pigmented spots and like. The epiloia accounts for 0.66% of mental defectives and 0.32% of epileptics[3].

The synonyms are tuberous sclerosis, Bournville's disease, Brushfield Wyatt disease and Pringle's disease.

Pathology

The pathology of skin lesions have been grouped as under :

A. Caspary type: Hyperplasia of sebaceous glands and connective tissue.

B. Pringle type: Hyperplasia predominantly of sebaceous glands alone.

C. Darrier type: Hyperplasia of Vessels.

D. Halloapeu type: Hyperplasia of connective tissue.

E. Balazer type: Multiple benign cystic epitheliomatous forms.

The lungs may have several large and small sub-pleural cysts with septal thickening and over growth of connective tissue, muscle and blood vessels. Hamartoma and alveolar cell adenoma of lung may occur. The heart may suffer from endocardial fibroelastosis or any other cyanotic or acynotic conditions. Fibroma, lipoma and rhabdomyoma are also described. Lowenfish described the various kidney tumors[6].

The lesions in the brain consists of multiple sclerotic areas. There may also be microgyria, macrogyria, demyelination, and softening and hypermineralisation of the ganglion cells. Glioma, spongioblastoma and neuroblastoma may sometimes arise from these areas. Spinal cord may be hydrometic or may develop tumors[7].

Clinical Manifestations

The characteristic features of the syndrome are the skin lesions, mental retardation, being imbecile of low grade and epileptic, but they show very wide variations in the age of onset and in severity. Onset before the age of five with cutaneous changes and epilepsy is usual but the disease may remain latent until adolescence or adult life.

The syndrome may be divided into six grades.

I. Still birth: Severest form of the disease.

II. Severe form: Onset of convulsions and frequent epileptic attacks occur during the first week of life. A number of deaths occur during the first six months of life. Status epilepticus and intercurrent infections being the most common causes of death. It is difficult to diagnose the cause as family history is absent and adenoma sebaceum occurs after 3 years of age.

III. Classical type: Characteristic symptoms of epilepsy, cutaneous manifestations and mental retardation.

IV. Classical type (Milder form): These children develop naturally upto 9 or 10 years of age and later show manifestations of epilepsy, behaviour problems and adenoma sebaceum. They gradually become demented and may survive upto old age.

V. Abortive type: Adenoma sebaceum with epilepsy, but without mental deterioration and with visceral tumours of characteristic type without any other symptoms.

VI. Adenoma sebaceum: Only cutaneous lesions are present[1].

Skin Lesions

The skin is a literal playground of the disease which disports itself in many ways. Skin lesions are found in 60 to 70% of cases and are mainly of three types.

(A) Adenoma sebaceum of Pringle type: This may rarely be present at birth or develop in infancy but usually appears between the age of 5 to 10 years. The lesions sometimes become more extensive at puberty and then remain unchanged. Firm discrete, yellowish or telengiectetic papules 1 to

10mms in diameter extending from the nasolabial furrows to the cheeks and chin and occasionally in the ears are found. They may be numerous and conspicuous and very rarely form large cauliflower like masses.

(B) Periungual fibromata (Koenen's tumour): It appears at or after puberty as smooth, firm, flesh coloured excrescences emerging from the nail folds, 5 to 10 mms. in length and often multiple.

(C) The Shagreen patch: An irregularly thickened slightly elevated, soft plaque is usually seen in the lumbosacral region. Nevoid lesions of less distinctive types are frequent. Hard fibromatous plaques especially on the forehead and scalp, soft pedunculated fibromata around the neck and axilla and Cafe au lait pigmented spots have been found in 60% of cases. Areas of nevoid leucoderma may precede the other cutaneous signs and are of diagnostic assistance in infants with convulsions. Fibromatous tumours occaionally may be found on the gums, tongue and pharynx.

The other lesions which are recorded include Pau de chagrin spots, flat warts, pale lentigenes, hereditary palmar and planter keratosis, areas of goose flesh hypertrichosis, neoplastic lesions like lipoma, fibroma, hemangioma, Subungual fibroma, fibrolipoma, angiofibrolipoma and syringocystadenoma. Pigmented hairy and vascular nevi are found. Nevus anemicus is uncommon but highly characteristic sign, which on occasions is the only cutaneous expression of tuberous sclerosis. Pigmentary changes are frequent including Cafe au lait spots, diffuse bronzing, vitiligo and greying of the hair.

Neurological Lesions

The seizures usually appear in the first two years of life and may even occur at birth. They may be myoclonic and akinetic suggesting a subcortical origin of the seizures. Jacksonian convulsions have been described. Status epilepticus may supervene. The development is delayed and speech is retarded.[8,9]

A single large tumour will cause general and focal symptoms of intracranial neoplasms. Other neurological signs are localised paresis, contractures and muscular spasms. Epilepsy may be the only overt manifestation when tuberous sclerosis may be revealed at autopsy.[4]

Mental deficiency is present in 70% of cases and may also be progressive. Some cases have presented gross behaviour disorders although with normal intelligence. The mental impairment is usually noticed during the early years of life, varies in degree, and differs in no way from retardation from any other cause. Malignant changes occur in small proportion and are manifested by signs and symptoms of increased intracranial tension.

Ocular Lesions

They have been reported in 8 to 30% of cases. Retinal Phakomas were first described by Von Den Hoove. They are seen as white streaks along the vessels or as small rounded tumours near the disc. Other lesions may be nodular tumours, yellowish red spots, blurred pigmented spots, nevoid spots clearly outlined, Pigmentary changes identical with those of other forms of retinitis. Vitreous clouding, choroiditis, retinal artery aneurysm, catract, squint, nystagmus and myopia have been described as incidental findings.[10].

Other manifestations

The lungs may have several large and small subpleural cysts with septal thickening and overgrowth of connective tissue, muscle and blood vessels.

Hemartoma and alveolar cell adenoma of lung are also on record. The heart may suffer from endocardial fibroelastosis or any other cyanotic and acyanotic heart disease. Fibroma, lipoma, and rhabdomyoma are also described. Lowenfish described fairly high percentage of kidney tumours (81%). Teratoma, embryoma, hypernephroma have been described. Sometimes the kidney may be polycystic. Besides these the lesions of similar nature have been described in the spleen, thyroid, thymus, breast, duodenum, vagina and islet cells of pancreas. Sometimes anomalies like undescended testes, harelip, malformations of ear, hemihypertrophy, asymmetry of limbs, short little finger, simian hand and arthrogryprosis multiplex congenita may be associated with tuberous sclerosis.[11,12]

Treatment

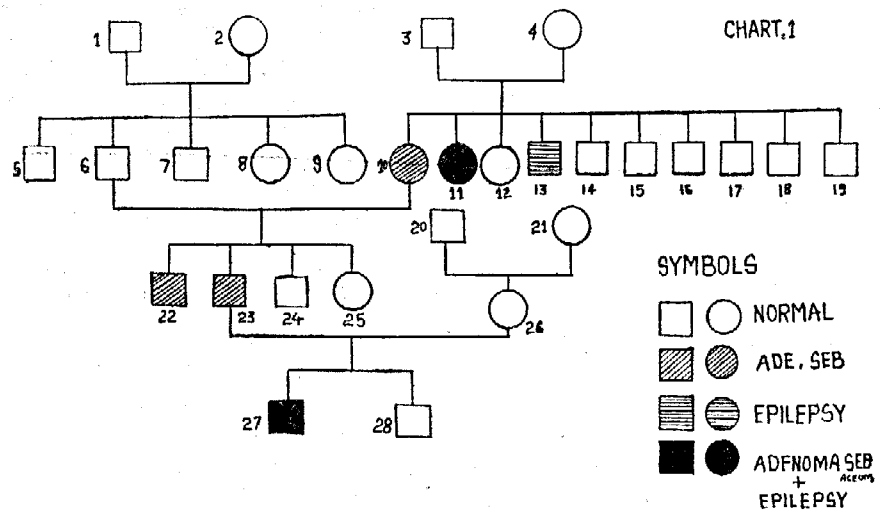
The treatment is for epilepsy and for mental retardation with appropriate measures. Neither internal remedies nor external applications have much effect on the lesions. Lesions may be removed by electrolysis, fulgurations, curettage, cauterization, scarification or excision. Much improvement may follow the use of Roentgen rays.[13]

Causes of Death

The usual causes of death in tuberous sclerosis are secondary infection, status epilepticus, increased intracranial pressure or malignant change in one of the lesions of the disease.[1]

Case Report

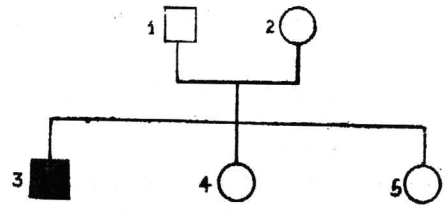
(1) A male child 5 years old (case 27 in Pedigree chart 1) was brought for consultation to the dermatology clinic. with the complaint of small multiple nodules on the face since last 2 years. On enquiry it was found that the child had delayed milestones and was having epileptic fits for the last one year. Family history revealed that the child's grandmother was also having the same type of skin lesions since her childhood, but without any epileptic fits. On examination, the child was fairly built and nourished but mentally retarded On local examination numerous firm, discrete, pigmented papules of varying sizes from 1 to 5 mms. in diameter were seen on the face of the child. Clinically systemic examination was normal. Skin lesions were confirmed by biopsy as adenoma sebaceum. The grandmother of the patient (case 10 in chart 1) was examined during the next visit. It was confirmed that the lesions were also of



similar nature. The X-ray of the skull and chest and fundoscopy were normal in both, the child and the grandmother. The pedigree showed that the child's father and uncle (Cases 23 & 22 in chart 1) had adenoma sebaceum. Further probing in the pedigree revealed that in the second generation on the paternal side, three members of the family (cases 10, 11, 13 in the chart 1) out of 10, had adenoma sebaceum, adenoma sebaceum with epilepsy, and epilepsy respectively. There were no other lesions like nevus, cafe-au-lait spots, vitiligo, periungual fibroma or Shagreen patches.

(2) A male child aged 9 years (case 3 in the pedigree chart 2) came to the out-patient department with the complaint of small nodules on the face and fore-head of 7½ years duration. The skin lesions first developed on the forehead and then around the neck and they progressed till the age of 7 years. No new lesions developed after that. The child was having epileptic fits at an interval of every three to four months from the age of two and there were no epileptic fits for the past two years.

CHART.2



The child had delayed milestones. His speech was clear. He developed left sided hemiplegia at the age of 7 years for which he was hospitalised for about 7 days. The hemiplegia slowly recovered and the child started walking gradually after the treatment. On clinical examination the child had lesions of adenoma sebaceum on the face with mental retardation, low intelligence and poor memory. Though 9 years old he was studying in the first standard, lagging behind his younger sister who was clinically free of any signs or symptoms of adenoma sebaceum. Systemic examination was normal. The fundoscopy was normal. But the X-ray of the skull showed calcification (Fig. 1.) Biopsy of the lesions confirmed the clinical diagnosis. No other family members were affected except the patient (Pedigree chart 2). Skin manifestations of any other sort were absent.

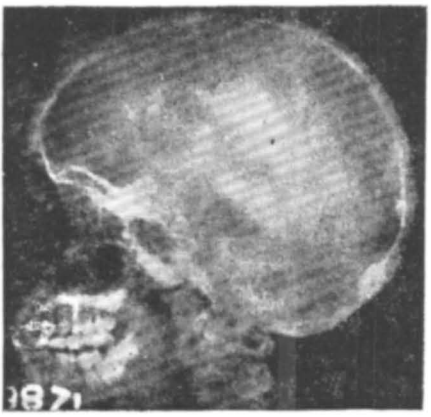


Fig. 1

Lateral view of skull showing calcification

(3) A male child aged 7 years (Fig 2 and case 10 in Pedigree chart 3) was brought for consultation for similar type of skin lesions of 4 years duration and for epileptic fits of 3½ years duration. Except for the lesions of adenoma

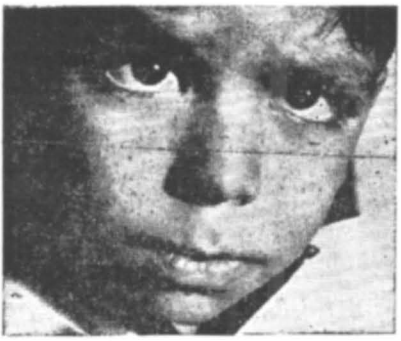
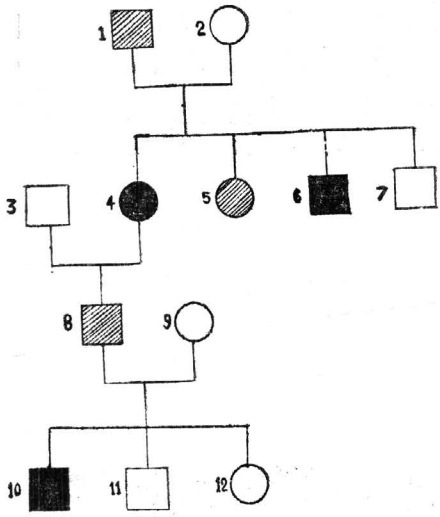


Fig. 2

Picture showing papulonodules of adenoma sebaceum on the face

sebaceum no other visible skin lesions were present. Systemic examination was normal clinically. Biopsy of the lesions confirmed our diagnosis. The father of the child (No. 8 in the Pedigree chart 3) had adenoma sebaceum and three more members in the same family were affected in the previous generation (Nos. 4, 5, 6 in the chart 3) having epiloia, adenoma sebaceum and epiloia respectively. Further tracing revealed that the paternal great grandfather of the child (No. 10 in chart 3) also had adenoma sebaceum.

CHART.3

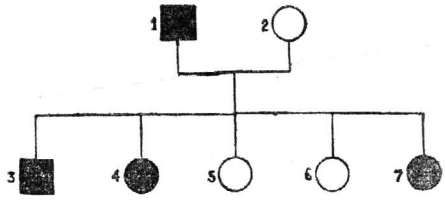


(4) A female aged 30 years (Fig 3 and case 4 in the Pedigree chart 4) was escorting a patient and was caught by a keen observing eye. On questioning about the lesions on her face, she said, "Oh ! that is since my childhood and it is not that only I have it, but my father, younger sister and elder brother have them too." (Cases 1, 3 and 7 showed as affected members in the family in the Pedigree chart 4). On further interrogation the patient revealed that she was having epileptic fits and first fit was

Fig. 3

Picture showing papulonodules of adenoma sebaceum on the face

CHART-4



noticed when she was $3\frac{1}{2}$ years old. Presently the fits are continuing intermittently without any definite interval and as per her story her father was also having fits occasionally. Her intelligence was in accordance with her age. Systemic examination did not reveal any abnormalities clinically. There was no evidence of shagreen patches, periungual fibroma, cafe-au-lait spots or nevus. Fundus examination revealed no abnormality. The cardiogram, X-ray chest and skull were normal. Biopsy of the skin lesions showed excessive mature sebaceous glands. (Fig 4)

Fig. 4

Photomicrograph (Low power) showing the histopathology of adenoma sebaceum

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