A CONTRIBUTION TO THE DIAGNOSIS OF TUBEROUS SCLEROSIS

BY

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Tuberous sclerosis (epiloia) is a congenital anomaly of development with a tendency to form tumours in different tissues. Usually the ectodermal organs are involved (brain, retina, skin) but pathological changes may be found as well in the mesenchymal organs (kidneys, heart). The usual site of the disease is in the central nervous system (C.N.S.).

Tuberous sclerosis is a very rare disease according to Ross and Dickerson (quoted by Jordan, 1956); it is found in 1 in 500,000 persons, and according to Dawson (quoted by Jordan, 1956) the occurrence of cases with mental changes is 1 in 300,000. The milder cases with no mental defect have probably a similar incidence. In comparison, neurofibromatosis, which is relatively rare, is 18 times more common than tuberous sclerosis (Holt and Dickerson, 1952). It is believed that in the total population of both mental deficiency and epileptic institutions the incidence of tuberous sclerosis is 0.5% (De Lorimier, Moehring, and Hannan, 1954).

Recently those cases which present symptoms of raised intracranial pressure have attracted the attention of neuropathologists and neurosurgeons because the growth which produces the clinical picture can sometimes be removed.

In the Yugoslav medical literature we have only been able to trace three cases and all of these have been published since the war (Miowski, 1949; Smaić, 1951).

The disease was first described by Bourneville in 1880, and von Recklinghausen in 1862 gave a short description of it in recording the post-mortem findings in a boy with sclerotic foci in the brain and cardiac myomata. Pringle (1890) described skin changes and in 1911 Sherlock introduced the term "epiloia". Kufs in 1913 (quoted by Josephy, 1936) was the first to describe the familial occurrence of the disease. Most authorities now regard it as a disease transferred by a dominant factor, but cases with no familial history do occur.

Radiological changes were first observed by Marcus in 1924 (quoted by Presthus, 1953) who

first described intracranial calcification. Berkwitz and Rigler in 1935 described hydrocephalus and multiple protrusions into the ventricles of the brain. At the same time Gottlieb and Lavine (1935) described osteosclerosis, osteoporosis, and erosions of the long bones.

Pathological findings in the brain are usually represented by masses of gliomatous cells resembling a tumour. These masses are often calcified and seen in straight radiographs.

Case Reports

Case 1.—L. S. was an unmarried woman of 22, a nursery school teacher. Her early medical history was unobtainable. As far as we could ascertain no member of the family had adenoma sebaceum or other related familial disease.

Her mental and physical development as a child appeared to have been normal. School reports show that up to the age of 11 she was an excellent pupil but she had difficulty in keeping her place at about 15 years, so she had entered a training college for nursery teachers and finished that course. Before admission she worked in a village nursery school. She did not remember having had any illness except the one for which she came to our department.

Her present illness first presented at the age of about 5 years, with momentary attacks of loss of consciousness. These "fits" were very rare. After her school training she sometimes would fall from her chair during the lapses of consciousness but she does not know if there were convulsive movements. When asked about the skin changes she said that she had had them for a long time; they had recently become more prominent, but she did not know precisely how long she had had them.

This is her third course of residential treatment and investigation in a neuropsychiatric department. During her previous stays in hospital skull radiographs and air-encephalograms were done. She was diagnosed and treated as a case of schizoid psychopathy, psychomotor epilepsy, and epilepsy with dementia. During the present stay in hospital the patient had three major convulsive fits with no localizing signs.

On admission in the autumn of 1953 the clinical findings were on both cheeks a reddish-blue papular rash with a "butterfly" distribution also present but more scanty

FIG. 1

FIG. 2

round the mouth (Fig. 1). On the back (Fig. 2) and anterior aspect of thighs there were areas of skin change about 2 cm. in diameter which consisted of raised, firm, whitish patches. Several nails on each hand showed raised white longitudinal striae (Fig. 3). In the right parietal region of the scalp she had a patch of grey hair. There was a slight radial deviation of the third and fifth fingers of both hands. She had an arched palate.

She was tested psychologically in 1951 and 1953 and impairment of intelligence was found on both occasions but with no further deterioration between these dates. The higher intellectual functions were chiefly impaired.

FIG. 3

FIG. 4

FIG. 1.—Case I showing butterfly distribution of adenoma sebaceum.

FIG. 2.—Case I showing patches of fibrous changes of the skin.

FIG. 3.—Right hand of Case I showing radial deviation of third finger and longitudinal striation of nails.

FIG. 4.—Air encephalogram of Case I showing areas of calcification with ill-defined edges. There is no protrusion into the ventricles.

Other investigations, including an E.C.G., Wassermann tests on blood and C.S.F., blood films, and complete kidney function tests, were normal. A histological report on a section of one of the skin papules showed the usual changes of adenoma sebaceum.

Skull radiographs showed multiple bilateral asymmetrical amorphous small areas of calcification with ill-defined edges (Fig. 4). In the parietal bones oval areas of denser bone structure were seen. The lamina interna of the frontal bone was thickened.

Radiographs of the extremities showed oval areas of rarefaction of the second phalanx of the left fifth finger

and the phalanges of the right fourth and fifth fingers; periosteal thickening of the first and second phalanges of the right third finger; and two areas of condensation of the left tibia about the size of a grain of rice.

Air encephalograms showed evidence of a slight internal hydrocephalus. Bilateral intracerebral calcifications in the region of the caudate nucleus and subcortical areas were present, but there was no protrusion into the ventricles.

Spinal radiographs showed that the vertebral arch of the first sacral segment was not united. Radiographs of both feet showed pes cavus.

All other radiological findings of the lungs, heart, digestive, and urinary organs, were negative.

Case 2.—This was a boy, S. N., aged 9. We were able to examine both parents, his only sibling, and a cousin, and found no abnormalities and there was no family history of any nervous disorder. The patient was well until the age of 5 when attacks of momentary loss of consciousness began. These increased in frequency till the age of 8 and then he began to suffer from major epileptiform fits. From the age of 5 he began to deteriorate mentally. His speech rapidly deteriorated so that by the age of 7 he ceased speaking altogether. Physically he developed normally.

He had treatment as a hospital in-patient for the fits when 5 years old and was discharged to continue treatment at home. At the age of 9 we admitted him to our unit on account of his restless behaviour and progressive dementia. During the previous two years the parents had noticed an acne-like rash on his face.

On admission he was a boy of 9 who was physically normally developed for his age. A reddish papular rash was present on the nose, cheeks, and chin but more thickly distributed round the nose (Fig. 5). The physical examination, including that of the nervous system, was

FIG. 5.—Case 2 showing adenoma sebaceum and its distribution on the face.

FIG. 6.—Skull radiograph of Case 2 showing small areas of calcification.

rendered very difficult by his extreme restlessness and marked dementia, but no abnormality was detected. It was impossible to establish any contact with him and his habits were dirty. There was no possibility of any psychological tests. All laboratory tests were normal, including blood and C.S.F. Wassermann reactions, an E.C.G., and urinary function tests.

Radiological investigations were only possible under narcosis. A straight skull radiograph showed bilateral multiple small areas of intracerebral calcification. The density of the shadows was not great and the edges were ill defined (Fig. 6). In the parietal region there were two small sclerotic foci surrounded by an area of osteoporosis.

Air encephalograms showed a marked degree of hydrocephalus internus and bilateral areas of calcification of the brain substance but no protrusions into the ventricles.

The left hand showed cystic changes in the body of the first phalanx of the fourth finger and periosteal thickening of the third phalanx of the third finger.

All other radiographs, including those of the lungs, heart, and urinary tract, were normal.

Case 3.—A. B. was a boy of 4 years. We were able to obtain a family history for the three previous generations on both sides and no relevant illness was found. We examined and radiographed the skulls of his parents and his two siblings and there were no relevant abnormalities. His birth and his feeding in infancy was normal and he was healthy till the age of 7 months, except for some degree of rickets. At the age of 7 months he started to have frequent major epileptic fits and was admitted to a paediatric department. Air encephalography was done and he was discharged with the diagnosis of hydrocephalus, and was given anti-epileptic treatment. At 18 months he walked and started to say a few words.

FIG. 7

FIG. 9

At the age of 2 years his condition deteriorated, he stopped speaking and became almost unable to walk. His fits became very frequent and he was admitted to the children's department of another hospital. Air encephalograms were obtained again, he was seen by a neurosurgeon, and was again discharged with the diagnosis of hydrocephalus. From this time marked psychical deterioration set in. He was restless and unable to walk or talk or feed himself. At the age of 3 he was admitted to a neurosurgical department. Air encephalography was again done, and the child was discharged, after deep radiological treatment to the choroid plexuses, with a diagnosis of "mental deficiency with hydrocephalus internus". An E.E.G. showed mainly diffuse abnormalities.

At the age of 4 the child was admitted to our unit because of progressive mental deterioration and increasingly frequent epileptic fits.

On admission, for his age he was physically well

FIG. 8

FIG. 7.—Typical butterfly distribution of adenoma sebaceum in Case 3.

FIG. 8.—"Peau de chagrin" and patches of leucoderma on trunk in Case 3.

FIG. 9.—Air encephalogram in Case 3 showing "candle gutterings" marked by arrows.

developed but was hardly able to walk even when supported by two people. He could not feed himself, he had dirty habits, and he was unable to speak. It was impossible to make any contact with him. No psychological testing was possible.

Clinical investigation was very difficult because of his mental condition. He had pigeon chest deformity, rachitic teeth deformities, and bilateral pes cavus. A symmetrical rash of reddish raised papules in butterfly distribution was present on his face (Fig. 7). The skin in the lumbar region on the left side showed a patch of "peau de chagrin" about 15 cm. × 10 cm. He had also areas of leucoderma on the trunk (Fig. 8). All other medical and neurological findings were normal as far as could be ascertained.

All laboratory tests were normal including blood and C.S.F. Wassermann reactions, and E.C.G., and urinary function tests.

Radiological examinations were carried out under

narcosis. Air encephalography was carried out with 50 ml. air and showed a medium degree of hydrocephalus more marked on the left side. The basilar cisterns were partly filled but over the convexity there was practically no air. The contours of the ventricles showed protrusions into the ventricles in three places (antero-posterior position) but no calcification was shown (Fig. 9).

Straight radiographs of the skull showed no calcification, but it was thought that its absence might be due to the previous deep radiological treatment. We checked the absorption of air after the air encephalography by daily radiographs, and complete absorption did not take place till the thirteenth day. We thought that this also might be due to the effect of the previous deep radiological irradiation.

All other radiological investigations, including those of the chest, heart, urinary tract, and skeleton, were normal.

Discussion

All three of the cases described above had certain characteristics in common. (1) There was no familial or hereditary history in any of the three. (2) In all three cases the classical (Vogt) triad, *i.e.*, dementia, epilepsy, and adenoma sebaceum, was present. (3) In all three cases radiological findings aided the diagnosis. (4) All three cases had had previous hospital investigations, including air encephalography in two of them, and none of the three had been diagnosed as tuberous sclerosis which shows that this condition can be overlooked if the possibility is not borne in mind. (5) In fact all three had been suffering from tuberous sclerosis for several years before being diagnosed and this induced us to give consideration to its diagnostic criteria and the evaluation of single clinical manifestations. We therefore propose to discuss briefly the problem of diagnosis.

Clinical Diagnosis.—Tuberous sclerosis shows itself by dementia, epileptic attacks, and adenoma sebaceum. Adenoma sebaceum may be of three types—white, red, or fibrous (Aimes, 1950)—and appears between the fourth and tenth years (Holt and Dickerson, 1952), increasing during puberty. It is usually on the face in a “butterfly” distribution, but can be found on other parts of the face and anterior aspect of the neck. Other skin changes are found, *e.g.*, periangular tumours (Koenen), lipomas, fibromas, *mellusca pendula*, *peau de chagrin*. Changes may also be found in any mucous membrane, particularly hypertrophy of the lingual papillae and fibromata of the gums.

On the retina one can find phakomas. In the internal organs tumours may often be found, especially in the kidneys and heart, or cystic changes, especially in the lungs. In the patient with tuberous sclerosis developmental defects, such as spina

bifida, *pubertas praecox*, congenital cardiac abnormalities, are often found.

Radiological Diagnosis.—Multiple asymmetrical areas of intracerebral calcification are seen, irregularly shaped 2 mm. to 2 cm. in size and varying in density with no defined structure. These are usually found in the region of the basal ganglia, very rarely in the cerebellum. Holt and Dickerson (1952) found intracerebral areas of calcification in 50% of their cases. Sometimes a different type of calcification situated in the vessel walls can be found (Loepp and Lorenz, 1954). On the vault can be seen osteosclerotic changes. Holt and Dickerson (1952) found them in 40% of their cases. Sometimes there is erosion of the clinoid processes, thickening of the lamina interna and rarely lamina externa, of the skull bones.

When the tumours are placed subependimally they can protrude into the ventricular space and then are seen as “candle gutterings”.

Patchy zones of osteosclerosis, periosteal thickening, and oval cysts in the long bones of the hands and feet were found by Holt and Dickerson (1952) in 66% of their cases. More rarely demineralization, osteoporosis, or erosions of bones are seen.

Multiple lung cysts with honeycomb appearance are rarely found.

Other organs occasionally show malformations, *e.g.*, kidneys, heart, spine.

There are several clinical forms of tuberous sclerosis (Stender and Zülch, 1943): (1) The classical form showing the clearly defined triad of Vogt; (2) the cases which present symptoms due only to the disease of one system (C.N.S.); (3) abortive cases which show only a single symptom of tuberous sclerosis, usually a skin manifestation; (4) Stender and Zülch described in 1943 a fourth form which shows only raised intracranial pressure caused by a single tumour in the third ventricle.

Clinical diagnosis of tuberous sclerosis is usually based on the finding of the Vogt triad and when this is absent diagnosis may be extremely difficult. Adenoma sebaceum with either epilepsy or mental deficiency is sufficient evidence to make the diagnosis.

Epilepsy with mental deficiency but without skin changes cannot be regarded as diagnostic. Skin changes without either epilepsy or mental deficiency may be simply a skin disease (Davidoff and Epstein, 1955), but if at the same time we find “candle gutterings” in an air encephalogram this is sufficient to make a diagnosis of tuberous sclerosis. “candle gutterings” in an air encephalogram even without skin changes is sufficient evidence. Retinal phakoma is a very suggestive clinical finding for the diagnosis.

In differential diagnosis one should think of the related congenital ectodermatoses, especially neurofibromatosis of von Recklinghausen. The disease described in 1949 by Rilay and Day as "central autonomous dysfunction with diminished lachrymation" mental deficiency, skin changes, and epilepsy, must also be considered (quoted by Davidoff and Epstein, 1955).

Conclusions

We believe there are cases* of tuberous sclerosis which are not recognized: the disease is easily overlooked.

In patients which show atypical dementia with epilepsy, tuberous sclerosis should be considered in the differential diagnosis. In these cases air encephalography and full radiological studies will be very helpful. The finding of phakoma of the retina in these cases would be conclusive. Air encephalography gives a conclusive picture when there are protrusions into the ventricles ("candle gutterings"). Air encephalography is very important, especially in the cases with a clinical picture of

raised intracranial pressure because it might indicate surgical treatment.

"Candle gutterings" might be shown in air encephalograms where there are no areas of intracerebral calcification as in our third case.

The severe dementia which develops shows no characteristic psychological findings.

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*The first two of our cases were written up for publication in a Yugoslav medical journal.