Tuberous Sclerosis in an Infant of 28 Weeks Gestational Age

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SUMMARY: A case of tuberous sclerosis diagnosed at autopsy in a neonate at 28 weeks gestation is described. This is believed to be the earliest case yet reported. The CNS lesions consist of cortical tuberosities, heterotopic white matter nodules and subependymal nodules. These nodules consist predominantly of giant astrocytes but a small undifferentiated cell component is present as well. Multiple cardiac rhabdomyomas are also present. An explanation for neuronal hypocellularity within the cortical tuberosities is suggested.

RÉSUMÉ: Nous décrivons un cas de sclérose tubéreuse diagnostiquée à l'autopsie chez un nouveau-né de 28 semaines de gestation. Nous croyons qu'il s'agit du cas le plus précoce rapporté. Les lésions du SNC incluaient des tubérosités corticales, des nodules hétérotopiques de matière blanche et des nodules subépendymaux. Ces nodules contenaient surtout des astrocytes géants, mais il existait également une composante constituée de petites cellules non différenciées. Nous notons également des rhabdomyomes cardiaques multiples. Nous proposons une explication de l'hypocellularité neuronale dans les tubérosités corticales.

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Tuberous sclerosis, so named by Desiri Bourneville in 1880, consists of the classical clinical triad of seizures, mental retardation and skin lesions. On pathologic examination the brain and heart are the organs most often involved. The central nervous system lesions typically consist of cortical tuberosities, heterotopic white matter nodules and subependymal nodules. The most typical cardiac lesions are rhabdomyomas. The presumed defect occurs very early in gestation and results in abnormal maturation and migration of stem cells in all germ layers. However, only five cases have been reported in premature infants, the earliest at 31 weeks. This case report deals with a male infant born at 28 weeks gestation with the typical CNS lesions and multiple cardiac rhabdomyomas. The well developed manifestations at this early age are consistent with a genetically determined developmental disorder of the brain beginning early in gestation.

CLINICAL HISTORY

This white, male infant was born to a 19 year old mother at 28 weeks gestation. The baby weighed 1010 gms. and measured 39 cm. from crown to heel with a head circumference of 27.5 cm. He was flaccid, with a heart rate of 80 per minute and required intubation and ventilatory support. Three hours later he was pink on 100% oxygen and had spontaneous gasping respirations. He then suffered a cardiac arrest from which he was resuscitated but he continued to have problems with hypercapnea, hypoxia, and acidosis. Despite treatment of these problems and of repeated episodes of bradycardia he died $9^1/_2$ hours after birth. The clinical diagnoses were; severe respiratory distress syndrome, germinal matrix hemorrhage and possible myocardial infarction.

Family History

The mother's obstetrical history included a previous spontaneous abortion and delivery of a male infant with the same father as the present case. This child is clinically normal except for a single depigmented spot on the left flank. The mother underwent a clinical examination, CT scan of her head and a renal ultrasound, all of which were normal. The mother's seven siblings and their children are reportedly normal. The father is normal except for several small depigmented areas in the interscapular region. His parents, a sibling and three children by other relationships are reportedly normal.

AUTOPSY FINDINGS

Postmortem examination was begun 13 hours after death. The body was well preserved. No cutaneous abnormalities were noted. Pertinent pathologic findings were confined to the brain, heart and lungs. Detailed examination of the kidneys, pancreas, spleen and lungs failed to reveal lesions typical of tuberous sclerosis. The bones, eyes and spinal cord were not examined.

Brain: The brain weighed 140 gms (normal for this gestational age is 169 ± 46 gms). Gyral development was compatible with a gestational age of 26 to 28 weeks as was the sequence of myelination (loyez) and the lamination of the cortex in both the cerebrum and cerebellum. Several firm, elevated cortical nodules were present bilaterally. These measured approximately 7 mm in diameter. Smaller nodules (candle gutterings) were also present beneath the ependyma of the lateral ventricles. No white matter abnormalities were noted grossly. No intracerebral calcification was present on gross or microscopic examination.

The most prominent finding was the presence of collections of giant cells in the deep white matter, the subpial zone, and in the subependymal region. These resembled, but were larger than, gemistocytic astrocytes (Fig. 1). The cells contained a large central core of homogeneous eosinophilic cytoplasm which stained lightly positive with phosphotungstic acid-hematoxylin (PTAH) and glial fibril-

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lary acidic protein (GFAP), performed using standard immunohistochemical techniques. About this was a rim of more granular cytoplasm which was strongly positive with PTAH and GFAP stains. Multiple delicate processes could be seen radiating from these cells. The nuclei were large and eccentrically placed with a delicate nuclear membrane, finely dispersed chromatin and prominent nucleoli. Bi- and trinucleate forms were numerous but no mitoses were present. A single giant cell which resembled a giant neuron and stained negatively with GFAP was present (Fig. 1). The giant astrocytes were located within the germinal matrix, deep white matter and the subpial region. The germinal matrix was normal for the gestational age. It appeared to contain a dual population of cells, those with small dark nuclei and others with larger more vesicular nuclei. The cells containing the larger nuclei acquired cytoplasm as they entered the white matter and became identifiable as astrocytes.

The subependymal nodules (Fig. 2) consisted of well circumscribed collections of giant cells with a spongy background. The white matter and cortex overlying these nodules were normal.

The deep white matter nodules (Fig. 3) were less circumscribed. The giant cells appeared to arise from the germinal matrix. The large nuclei of the germinal matrix appeared to progressively acquire GFAP positive cytoplasm as they migrated. These cells formed large oval masses within the deep white matter which were more dense centrally. The nodules then thinned on their cortical aspects and the giant cells tended to become oriented along blood vessels. Scattered giant cells were visible in the overlying cortex. Giant cells then accumulated along the subpial surface overlying the nodules (Fig. 3, inset). The cortex in these regions was slightly hypocellular but otherwise normal. There was a small cell component within the giant cell nodules (Fig. 4). The small cells were either diffusely arranged as in the subependymal nodules or focally arranged

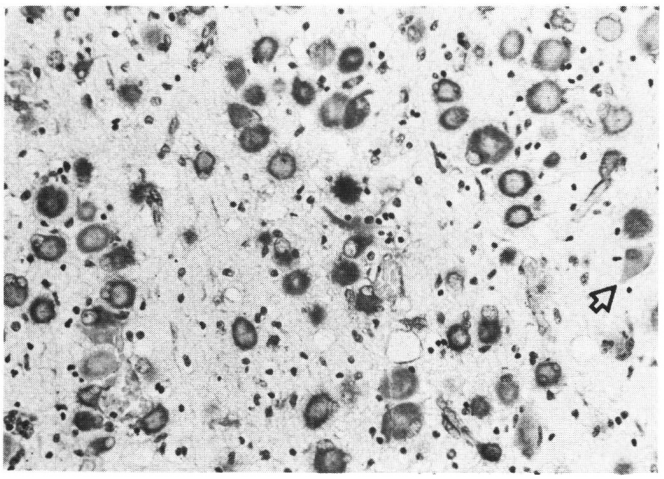

Figure 1 — Photomicrograph taken from the midperiphery of the white matter heterotopic nodule shown in figure 3. Note the GFAP negative cell resembling a giant neuron (arrow). (GFAP, original magnification x 160).

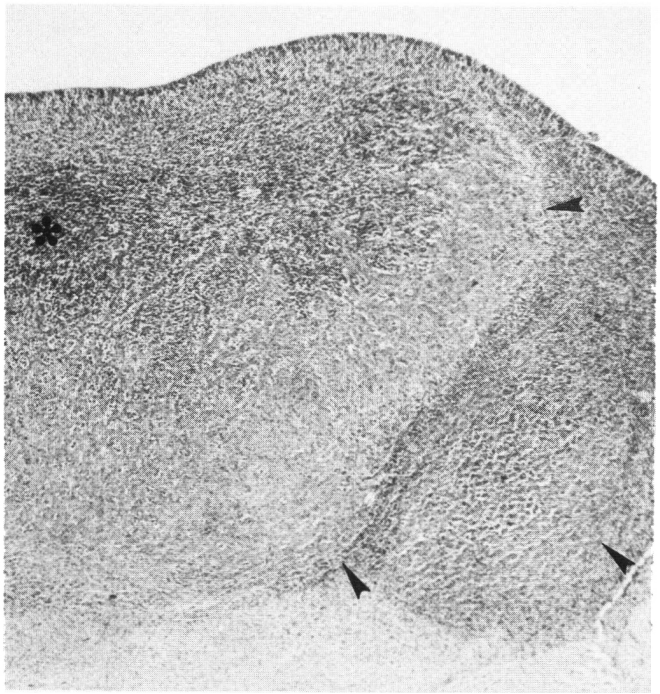

Figure 2 — Low power photomicrograph showing ependyma at the top and germinal matrix (asterix) containing two large nodules (arrows) composed of giant astrocytes with a diffuse small cell component. Elevation of the ependyma by the nodule produces the candle gutterings observed grossly. (H & E).

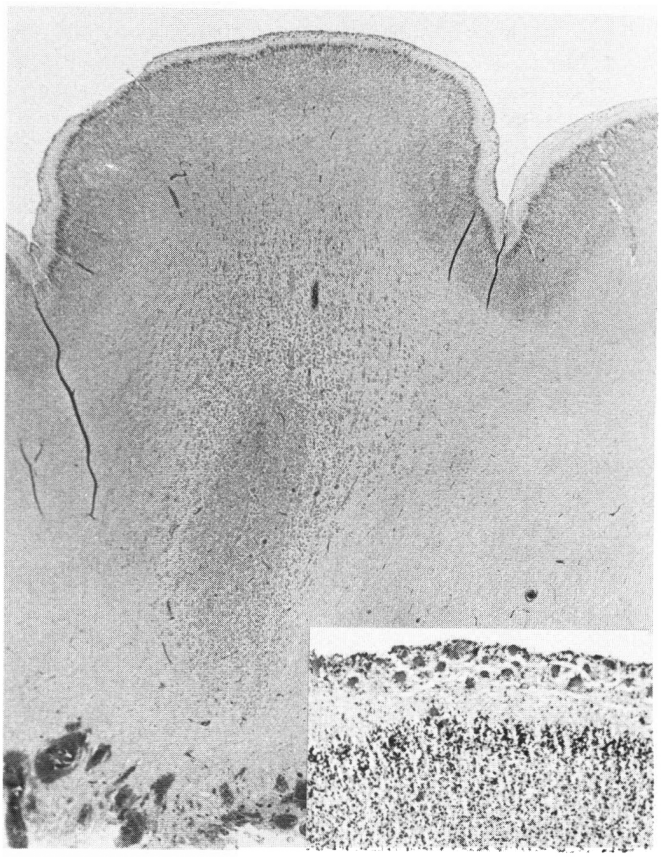

Figure 3 — Low power photomicrograph of the heterotopic white matter nodule underlying a cortical tuberosity. The centre of the nodule contained a collection of small cells. Note that the giant cell density decreases towards the cortex and then increases again in the subpial region (inset). The cortex is slightly hypocellular over the nodule. Multiple germinal matrix hemorrhages can also be seen. (H & E, inset-H & E, original magnification x 25).

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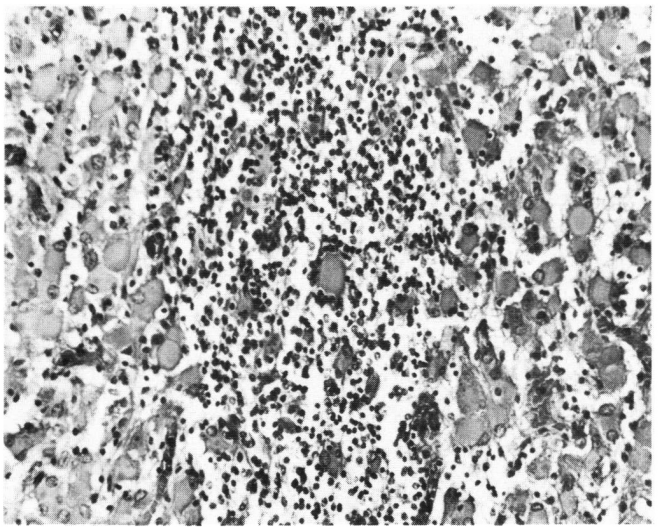

Figure 4 — Photomicrograph demonstrating the small cell component present in the centre of the deep white matter nodule shown in figure 3. (H & E, original magnification x 160).

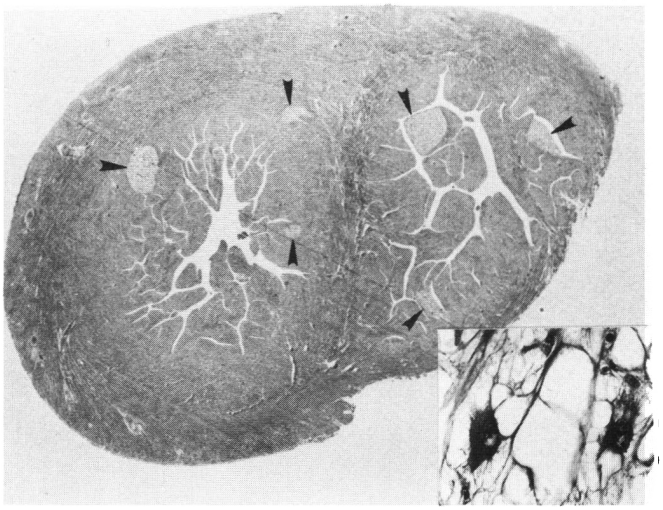

Figure 5 — Low power photomicrograph of a section of the heart showing multiple rhabdomyomas (arrows) in the walls of both ventricles. A higher power view (inset) shows the typical cells comprising the rhabdomyomas (H & E, inset - H & E, original magnification x 400).

as was seen centrally in the deep white matter lesions. These cells were identical to the small cells of the germinal matrix. The nuclei were darkly staining and round to oval in shape, and the very scant cytoplasm appeared to be GFAP negative.

The organization of the brain stem and cerebellum was unaltered, by contrast with the disorder of neuronal migration in the cerebral cortex. The hippocampus was felt to be normally developed for this gestational age.

Multiple germinal matrix hemorrhages of recent duration were also present. These did not appear to be related to the subependymal nodules. No further abnormalities in the remainder of the brain were detected.

Heart: The heart weighed 5 gms and revealed multiple small pale regions in the myocardium (Fig. 5). These were typical of rhabdomyoma. None were large enough to compromise blood flow. They were well circumscribed nodules containing greatly enlarged myocardial fibres exhibiting a central nucleus with radiating cytoplasmic strands (spider cells) (Fig. 5, inset). These were separated from each other by large vacuoles.

Lungs: The right and left lungs weighed 15 and 12 gms respectively. Alveolar ducts were lined by homogeneous eosinophilic hyaline membranes and there was marked alveolar collapse. A few scattered bronchioles contained material with the appearance of meconium. There were scattered focal hemorrhages in the air spaces and interstitial tissue.

DISCUSSION

The presence of the central nervous system lesions described above in association with cardiac rhabdomyomata establishes a firm diagnosis of the tuberous sclerosis complex. This would appear to be a random case although a more thorough investigation of the paternal family would be desirable. To the best of our knowledge this is the earliest case of tuberous sclerosis yet reported. Recent reviews of tuberous sclerosis in newborns (Thibault and Maneulidis, 1970, Ostor and Fortune, 1978) summarized 21 cases, of which 4 were diagnosed in premature infants. An additional case in an infant at 31 weeks gestation has been reported (Probst and Ohnacker, 1977). The addition of the present case brings to 6 the number reported in premature infants.

The collections of giant cells at this gestational age consist almost solely of astrocytes as demonstrated by GFAP and PTAH positivity, the presence of processes and their tendency to perivascular arrangement. The glial precursors within the germinal matrix appear normal as do the astrocytes in other areas of the brain. However, the glial precursors immediately beneath the white matter nodules progressively acquire cytoplasm and fibrillary protein in an unrestrained manner. This suggests an abnormality of maturation within the primary germ cells. Probst and Ohnacker (1977) found ultrastructural features of both astrocytes and ependymal cells in the giant cells of their case at 31 weeks gestation, also suggesting a disturbance of differentiation of the primitive glioblast.

It is interesting to speculate on the small cell component of the nodules and the overlying cortical hypocellularity. These small cells may be neuronal precursors destined for the overlying cortex which have been unable to migrate normally, possibly because of the lack of the glial framework normally present at this stage of development. The absence of giant neuronal forms may be a manifestation of the gestational age and they may appear as maturation and further migration occurs.

Gliosis and disorganization of the overlying cortex, changes which are frequently observed in tuberous sclerosis, were not present in this case, suggesting that they develop at a later age and are not an inherent part of the primary developmental disorder, but a reactive event.

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