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Intracranial Lipomatous Hamartomas (Intracranial "Lipomas")

A Study of 13 Cases Including Combinations with Medulloblastoma, Colloid and Epidermoid Cysts, Angiomatosis and other Malformations

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Summary. 13 cases of intracranial lipomatous hamartomas are presented, 12 of which were incidentally found at autopsy. Only one case, verified by biopsy, showed progressive focal symptoms and lipomatous infiltration of the acoustic nerve. 5 lipomatous hamartomas were located in the cisterna ambiens region, 3 in the cerebellopontine angle, 2 in the hypothalamic and 1 in the callosal regions. 2 cases had multiple intracranial adipose tissue masses. Extracranial malformations were present in 4 cases, whereas 8 observations showed (micro)dysgenesias of brain and meningeal tissues surrounding the lipomatous hamartoma (mixed neuroglial-mesenchymal tissue, glial dystopias, aberrant nerve fibres, "hypertrophic" nerve bundles, peripheral myelin, micropolygyria, cerebellar microdysgenesias). 5 cases are described in detail: 1. Pontine lipomatous hamartoma combined with body malformations, frontobasal epidermoid cyst, tentorial osteoma and cerebellar microdysgenesias. 2. Cerebellar medulloblastoma associated with fibrolipomatous meningeal hamartoma and cerebellar micropolygyria. 3. Large lipomatous hamartoma of the callosal region encircling a colloid cyst. 4. Multiple meningeal fatty nodules associated with facial malformations, cerebellar dysgenesias and tentorial osteoma. 5. Intracranial hamartomatosis with lipo-fibro-angiomatosis of meninges, megadolichobasilaris and multiple "subependymomas". The origin of intracranial fatty tissue is discussed; intracranial lipomatous hamartoma should be regarded as a complex malformation, affecting both the cerebral ectomesenchyma and brain parenchyma, and classified as true hamartoma (tumour-like, but primarily non-neoplastic malformation). The term "lipoma", implicating a neoplastic character, should be abandoned. Links to phakomatoses are suggested.

Key words: Hamartoma — Lipoma — Malformation — Medulloblastoma — Colloid Cyst — Phakomatoses.

Introduction

Although commonly regarded as extreme rarity, intracranial "lipomas" have been reported in more than 200 cases [4]. Because of great interest in the still disputed origin of intracranial adipose tissue, most of these observations are rather well-documented, so that intracranial "lipoma" should be known as a well-defined neuropathological entity. Thus it is surprising that intracranial "lipoma" is still classified in most cases as a neoplasm, though a congenital, embryonic and malformative origin is readily acknowledged [5, 14, 46]. The study of 13 cases enables us to stress that intracranial adipose tissue masses should be regarded as a true malformation; therefore, the term "lipoma", implicating a neoplastic character, should be abandoned. These intracranial lesions fit exactly into the definition of a hamartoma which is considered as a "tumour-like, but *primarily non-neoplastic, malformation* characterised by abnormal mixture of the indigenous tissue of the part with excess of one of them" [57].

Material and Methods

13 intracranial lipomatous hamartomas were found in the files of the Neurological Institute of Vienna University. 1 instance (case 8) was found among 4290 neurosurgical biopsy specimens collected in the years 1964—1973. The remaining 12 cases represent autopsy material from various sources; 9 observations (cases 2—4, 7, 9—13) were encountered among 1956 brain sections of the years 1970—1973 (pre-selected autopsy material). Among the latter 9 cases, 4 (cases 3, 9, 10, 13) were found in 1560 consecutive autopsies of a regional neuropsychiatric centre (1968—1973).

The material was fixed in formalin. Paraffin sections were stained with hematoxylin-eosin, cresylviolet and Klüver-Barrera's method for myelin; some with van Gieson's, Bodian's Gomori's and Kanzler's stains, PAS and combined luxol fast blue-PAS [8]. Frozen sections were stained with Sudan III and Sudanblack B.

Results

The clinical and pathological findings are summarized in Table 1. The patients included 4 males and 8 females ranging in age from 21 days to 77 years (no data available in case 1).

The *clinical symptoms* covered a wide field; only in one patient (case 8) focal symptoms, indicative of a space-occupying process, were reported.

Case 8, a 26 year-old female, complained first at age 5 about facial pain and since age 10 about left-sided trigeminal neuralgia. In the following years, a dermoid cyst of the right ovary and a fibroadenoma of the left mamma were extirpated; X-rays detected an incomplete lumbosacral spina bifida. At age 18, vertiginous attacks with nausea, vomiting and nystagmus occurred. At age 22, right-sided vestibular function was lost. 2 years later, trigeminal neuralgia developed also on the right side. At age 25, the patient became deaf on the right side. Pantopaque-cisternography suggested a right-sided cerebellopontine tumour. A yellowish mass was subtotally extirpated at craniotomy. Postoperatively, the patient has been without symptoms for 10 months.

Clinical symptoms of all other patients either had no direct connection with the hamartoma (cases 2, 3, 6, 7, 9—11) or were due to associated body malformations (cases 4, 12, 13). Epileptic seizures combined with mental retardation were observed in cases 4 and 13.

Macroscopically, there was moderate (Fig. 3g) to severe internal hydrocephalus in 4 cases.

The *site* of the lipomatous hamartomas was in 5 cases the cisterna ambiens-region (quadrigeminal plate, pontine tectum and tegmentum, superior vermis—Figs. 1a, c and 2b), in 3 the cerebellopontine angle (Fig. 2c), in 2 the posterior

Fig. 1a and b. Case 2. a Adipose tissue cap above posterior tectum and superior pons. b Lipomatous extension into pontine tegmentum with surrounding "mixed" tissue. van Gieson-Elastica. ×20

Fig. 1c—g. Case 3. c Fatty tissue between superior vermis and right cerebellar hemisphere connected with dorsal cerebellar meninges. d Atrophic cerebellar cortex around dorsal part of adipose tissue. Dystopic glial bridge between pons and cerebellar white matter (lower arrow). Upper arrow shows area from where Figs. 1e and f were taken. Klüver-Barrera. ×3. e Massive collagen nerve sheathes in border area of lipomatous hamartoma. van Gieson-Elastica. ×400. f Numerous Schwann-like cells and several mast cells (arrow) in same area as Fig. 1e. Cresylviolet. ×480. g Lipomatous extension into cerebellar white matter. Two-layered transitional zone between fatty tissue (above) and normal cerebellar white matter (below). Bodian. ×55

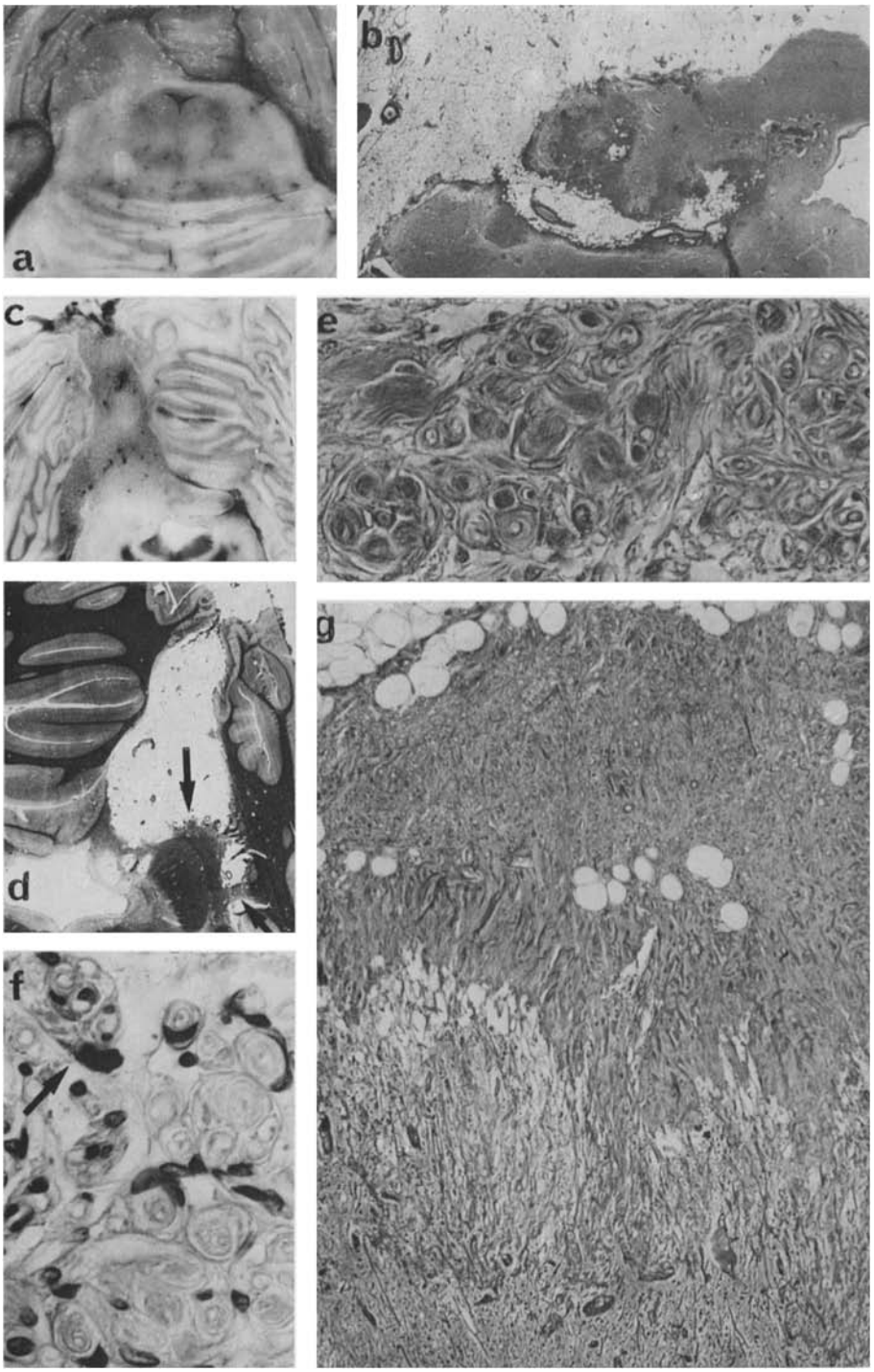

Fig. 1a—g

Table 1. Summary of clinico-pathologic findings in 13 observations of intracranial lipomatous hamartoma

Case	Age, sex	Clinical diagnosis and/or autopsy findings	Size and site	Peculiarities
1 (4775)[a]	Juvenile —	—	Pea-size; left Coll. inf. and Brach. conjunct.	"Hypertrophic" nerve bundles
2 (39-71)	38 years M	Chronic alcoholism, miliary tuberculosis, operated subdural hematoma	Bean-size; right Coll. inf. and Brach. conjunct.	Fat cells in cerebellar meninges
3 (320-71)	47 years F	Operated subdural hematoma	Olive-size; right Coll. inf. and Brach. conjunct., right paravermial cerebellum	"Hypertrophic" nerve bundles; myelin of peripheral type; glial dystopias; calcifications in brain tissue adjacent to hamartoma; atrophic cerebellar folia
4 (323-73)	8 years F	Mental retardation, epileptic seizures, microphthalmus, scoliosis, depression of sternum; Fallot's tetralogy, microcephaly, hypertelorism	Cherry-size; right pontine tectum and tegmentum	Egg-sized frontobasal epidermoid cyst; walnut-sized tentorial osteoma; "hypertrophic" nerve bundles; lipomatous distension of trochlear nerve; cerebellar microdysgenesia (Purkinje cell dystopias)
5 (4814)	$3^1/_2$ years F	Cerebral tumour	Cherry-size; angle between cerebellar folia and medulloblastoma	Small apple-sized medulloblastoma (partly desmoplastic) of superior vermis with nerve cell-containing hamartomatous plaques; tumorous infiltration of hamartoma; cerebellar micropolygyria, dysgenesia of cerebellar nuclei
6 (349)[b]	40 years F	Miliary tuberculosis, tuberculous meningitia	Olive-size; left cerebellopontine angle	Fat cells in cerebellar meninges; calcifications in adjacent brain tissue
7 (95-72)	77 years M	Cranial trauma	Olive-size; left cerebellopontine angle	"Hypertrophic" nerve bundles; "mixed tissue" plaque in pontine gray matter

8 (N 41-73)	26 years F	Spina bifida, ovarial dermoid cyst, mammary fibroadenoma; left trigeminal neuralgia since 16 years, right cerebellopontine symptoms since 4 years, asymptomatic 10 months after operation	Pea-size (?), right cerebellopontine angle	*Biopsy* case. Lipomatous infiltration of acoustic nerve
9 (389-71)	74 years F	Schizophrenia	Pea-size; hypothalamus	Ring-shaped ossification in hamartoma; glial dystopias; calcifications in adjacent brain tissue
10 (308-72)	72 years M	Senile dementia, chronic subdural hematoma	Bean-size; hypothalamus	Ring-shaped ossification in hamartoma; calcifications in adjacent brain tissue; moderate hydroceph. int.
11 (12-72)	73 years F	Apoplectic insult	Whole length of corpus callosum, dorsally and ventrally	Cherry-sized colloidal cyst ventrally of callosal splenium; moderate hydroceph. int.
12 (334-70)[c]	21 days F	Cheilo-gnatho-palato-schisis, cardiac dextroversion	a) Millet-size, adjacent to tentorial osteoma b) millet-size, inferior vermis	Osteoma of right tentorium; severe cerebellar hypoplasia with large arachnoidal cyst; nervous tissue dystopias in cerebellar meninges; severe hydroceph. int.
13 (184-72)	40 years M	Mental retardation, epileptic seizures, clubfoot, epidural hematoma	a) Multiple focal or plate-shaped in cerebellar meninges b) plum-size, around caudal medulla obl.	Intracranial hamartomatosis (multiple lipomatous hamartomas, lipo-fibro-angiomatosis of meninges, megadolichobasilaris); severe hydroceph. int.; multiple cherry-sized "subependymomas"; "hypertrophic" nerve bundles

[a] Published Krainer [30].
[b] Published Stefan [50].
[c] Case 3 of the Jellinger and Sunder-Plassmann [25]—series of connatal intracranial tumours.

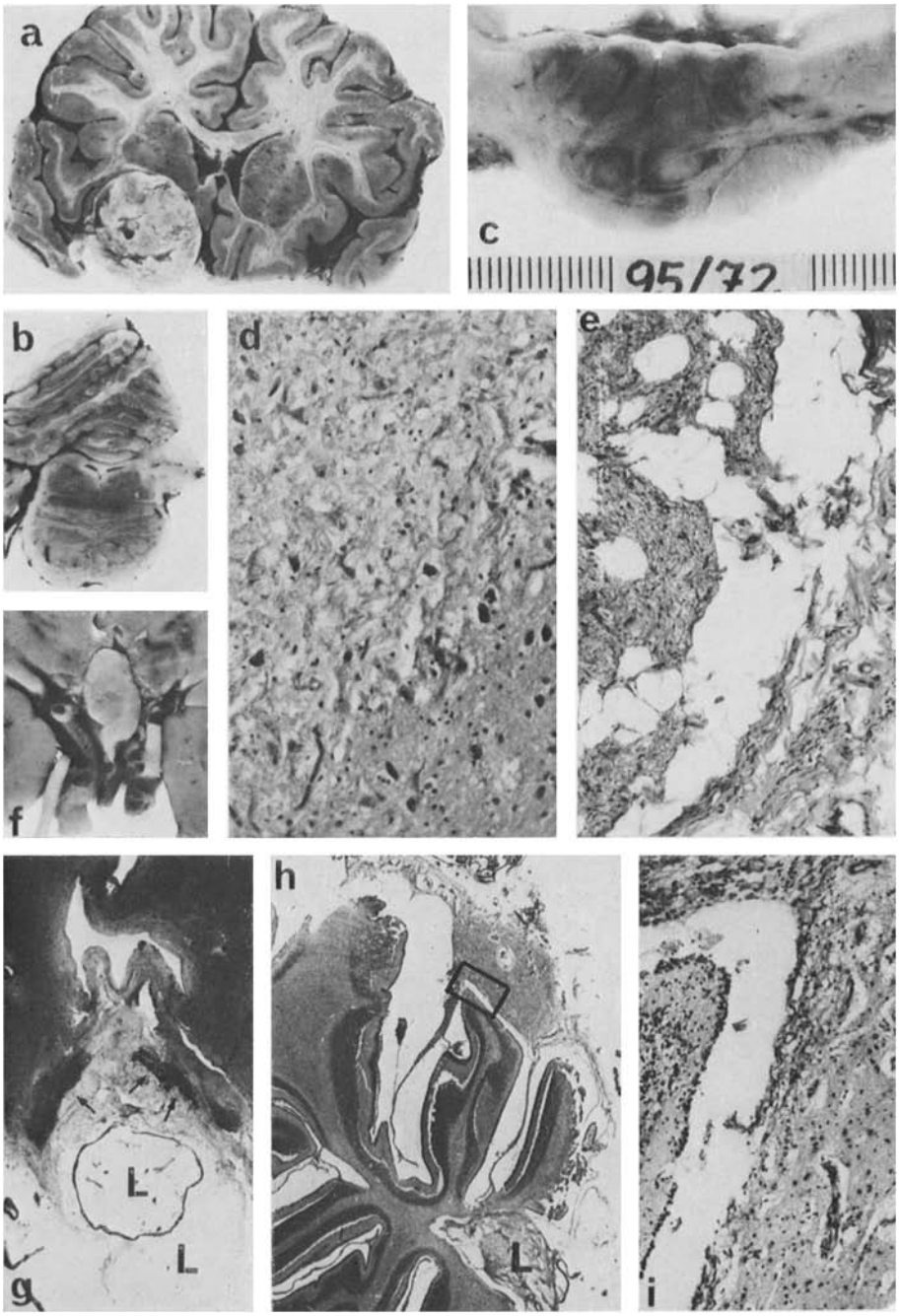

Fig. 2a and b. Case 4. a Large epidermoidal cyst frontobasally. b Fatty nodule above lateral pontine tegmentum

Fig. 2c and d. Case 7. c Adipose tissue in cerebellopontine angle. d Irregular "mixed" tissue with neurons adjacent to normal ventral pontine gray matter (lower right). H.-E. ×100

hypothalamus (Fig. 2f), and once the dorsal and ventral surface of the corpus callosum (Fig. 3g); 2 observations (cases 12, 13) had multiple lesions.

The hamartoma *size* varied from that of a millet to plum-size; in case 11, the fatty tissue extended alongside the whole corpus callosum in sausage-shape; case 13 showed extensive plate-shaped fatty thickening of the cerebellar meninges (Fig. 4a). In every case, the adipose tissue was in direct connection with the leptomeninges; in case 12, the fatty tissue adjacent to a tentorial osteoma adhered to the superficial leptomeninges.

Microscopically, normal-looking large adipose cells with peripheral, sometimes indented ("Lochkern") nuclei composed the lesions; polymorphia, mitoses, and multivacuolated cells were not found. Very rarely, a discrete lympho-plasmocytic infiltration was encountered (Fig. 3h). Some features were often present inside or around the lesions: A fibrous capsule of varying thickness, surrounding the fatty tissue as a whole, best developed in the region bordering the brain parenchyma; there, the fibrous tissue intermingled with adjacent glial tissue into such a close relationship that a tightly-knit, irregularly structured "mixed" glio-mesenchymal tissue resulted. This "mixed" tissue also closely surrounded lipomatous extensions into brain substance (Fig. 1b). Sometimes, "mixed" tissue areas could be seen in brain parenchyma without any apparent connection with the meningeal fatty tissue; an irregular glio-mesenchymal network then replaced the normal neuropil (Fig. 2d). Calcifications in the adjacent brain tissue (Fig. 2g) were found in 3 cases. Both hypothalamic nodules showed ring-shaped ossifications amidst fatty tissue (Fig. 2g). The adipose tissue was not highly vascularized; normal meningeal vessels crossed the hamartoma without any deviation. The cranial nerves were also undisturbed in most cases; only lipomatous distension (case 4) or fibrous endo- and perineural thickening (cases 1—3) of trochlear nerves occurred without impairment. An exception was case 8, where fat cells were detected between damaged, partly demyelinated nerve fibers of the right acoustic nerve (Fig. 2e); a moderate increase of endoneural connective tissue was also present. Apparent atrophy of brain parenchyma adjacent to the hamartoma was seen only once (Fig. 1d). Small clusters of fat cells in cerebellar meninges, distant from the hamartoma, were observed in 2 cases. Glial dystopias in the surroundings of the lesions presented either as dystopic glial bridge (Fig. 1d) or as small to large ectopias in the meninges (Fig. 2h, i).

A frequently encountered feature, in or around the hamartomas, was central nervous fibres split off from brain parenchyma by adipose tissue; thus a variable number of nerve fibres may irregularly cross extended fatty masses (Fig. 4e). Sometimes, remarkable changes were seen in both these aberrant nerve fibres and

Fig. 2e. Case 8. Fat cells infiltrate acoustic nerve. H.-E. ×55

Fig. 2f and g. Case 10. f Nodule ventrally of posterior hypothalamus. g Ring-shaped ossification in adipose tissue areas (*L*). Broad connective tissue zone dorsally and extensive calcifications (small arrows) in bordering brain substance. Cresylviolet. ×4

Fig. 2h and i. Case 12. h Small lipomatous hamartoma (*L*) above inferior vermis and extensive nervous tissue dystopias (upper right) in cerebellar meninges. H.-E. ×8. i Inset from Fig. 2h. Cresylviolet. ×50

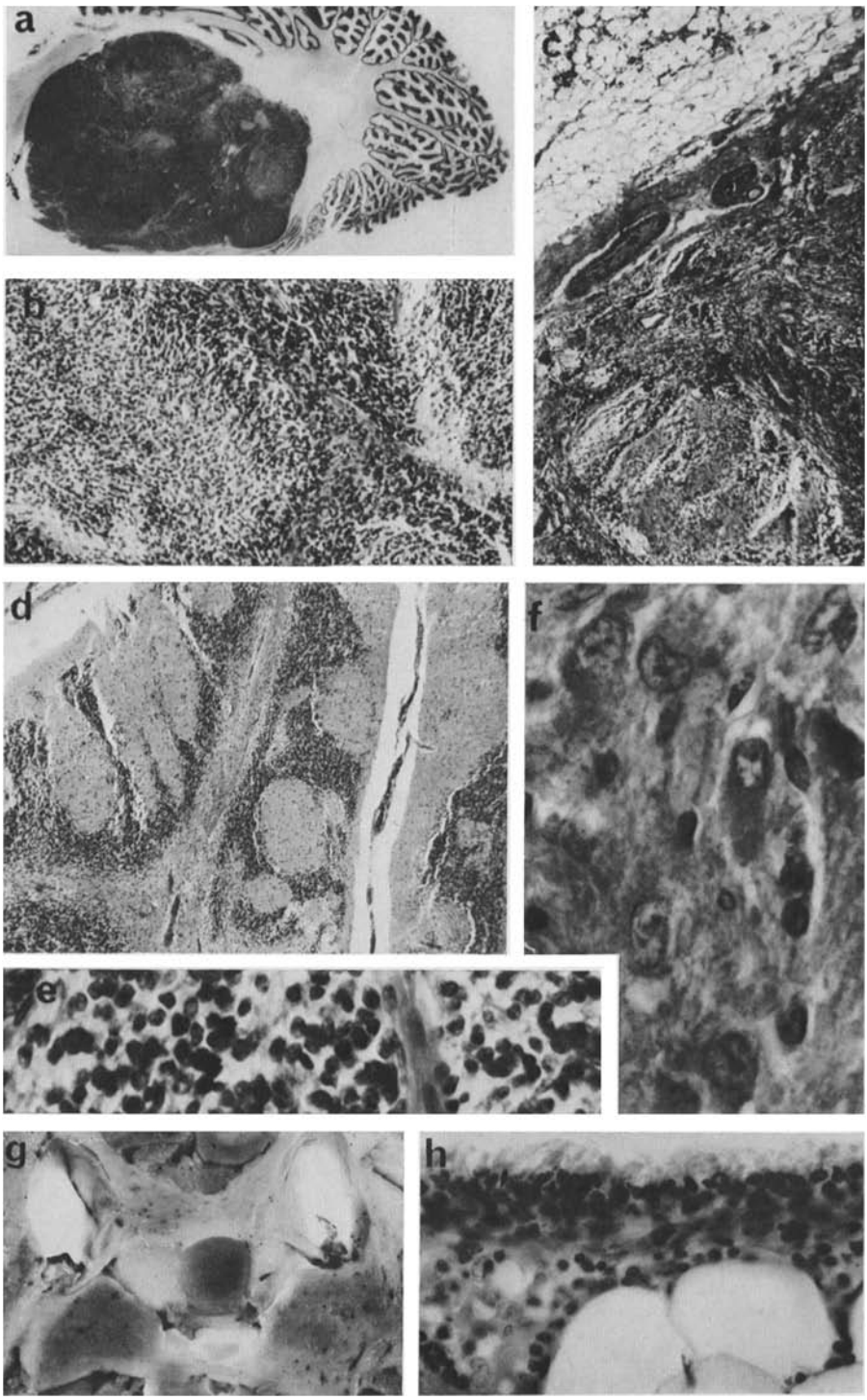

Fig. 3a–h

nerve bundles in "mixed" tissue areas: in a dense collagenous matrix, thick coatings sheathed myelinated or unmyelinated axons or mimicked nerve fibres (Fig. 1e); furthermore, there were numerous Schwann-like cells, sometimes in an arrangement similar to small onion-bulbs, semicircling these "hypertrophic" nerve bundles; several mast cells could also be seen in the same area (Fig. 1f). Similar features were seen around adipose tissue extensions into the cerebellar white matter; a two-layered transitional zone was present there between normal white matter and fatty tissue: first, the axons became distended by a moderate amount of collagen fibres, and then merged into "hypertrophic" nerve bundles in a densely collagenous matrix immediately adjacent to fat cells (Fig. 1g). In areas of "hypertrophic" nerve changes with numerous Schwann-like cells, as well as in some aberrant nerve fibres crossing the adipose tissue (Fig. 4e), myelin sheaths sometimes stained dark blue with the combined PAS-luxol fast blue method [8], indicating a peripheral type of myelin.

In 5 cases, the lipomatous hamartoma was associated with other intracranial malformations or tumours; these combinations merit a more detailed description:

Case 4 combined body malformations with suprapontine hamartoma, epidermoid cyst, tentorial osteoma and cerebellar microdysgenesias:

The mentally retarded 8 year-old girl showed multiple body deformities (microcephaly, hypertelorism, microphthalmus on the right side, depression of sternum, vertebral scoliosis) and was operated at age 2 for Fallot's tetralogy. Since age 6, epileptic seizures occurred. Increasing cardiac decompensation caused death at age 8. At autopsy, the small brain showed an egg-sized epidermoid cyst of the left frontobasal region (Fig. 2a) and a cherry-sized lipomatous hamartoma in the right cisterna ambiens (Fig. 2b); a walnut-sized osteoma adhered to the right tentorium. Microscopically, cerebellar microdysgenesias (cortical heterotopias in white matter, Purkinje cell dystopias) were found. Additional signs of perinatal brain damage were ulegyria of the right parietal cortex and scarring of cerebellar folia.

Case 5 represented a unique combination of cerebellar medulloblastoma with fibro-lipomatous hamartoma and cerebellar microdysgenesias:

The girl died at the age of $3^1/_2$ years; clinical diagnosis was cerebral tumour. We could study only histological slides from various cerebellar regions. These showed a rather sharply demarcated tumour of small apple-size in the superior vermis (Fig. 3a). The cell-rich tumour was composed of closely packed, mostly irregularly arranged cells, but sometimes an alveolar ("desmoplastic") pattern could be seen (Fig. 3b). The tumour cells showed darkly stained oval or round nuclei with an inconspucious nucleolus and a rather ill-defined sparse cytoplasm (Fig. 3e); no distinct cytoplasmatic processes, no rosettes and only few mitoses were seen. This tumour infiltrated a superficial lipomatous hamartoma of cherry-size (Fig. 3c) which was located in the angle between tumour and cerebellar folia; some of the latter showed micropolygyria (Fig. 3d). The meningeal hamartoma exhibited, besides fat cells, dense collagenous areas; similar plaques with irregularly structured hamartomatous tissue were seen amidst

Fig. 3a—f. Case 5. a Large solid tumor of superior vermis. Cresylviolet. ×1,2. b Desmoplastic pattern of cell-rich tumor. H.-E. ×100. c Fatty tissue infiltrated by tumor cells (above). Adjacent tumor tissue with several hamartomatous plaques (below). H.-E. ×36. d Cerebellar micropolygyria. H.-E. ×26. e Undifferentiated darkly staining small tumour cells. H.-E. ×450. f Nerve cells in hamartomatous plaque as seen in Fig. 1c below. H.-E. ×600

Fig. 3g and h. Case 11. g Fatty masses dorsally and ventrally of callosal splenium with central colloid cyst. Moderate internal hydrocephalus. h Colloid cyst epithelium with cilia. Underlying connective and fatty tissue with slight inflammatory infiltration. H.-E. ×230

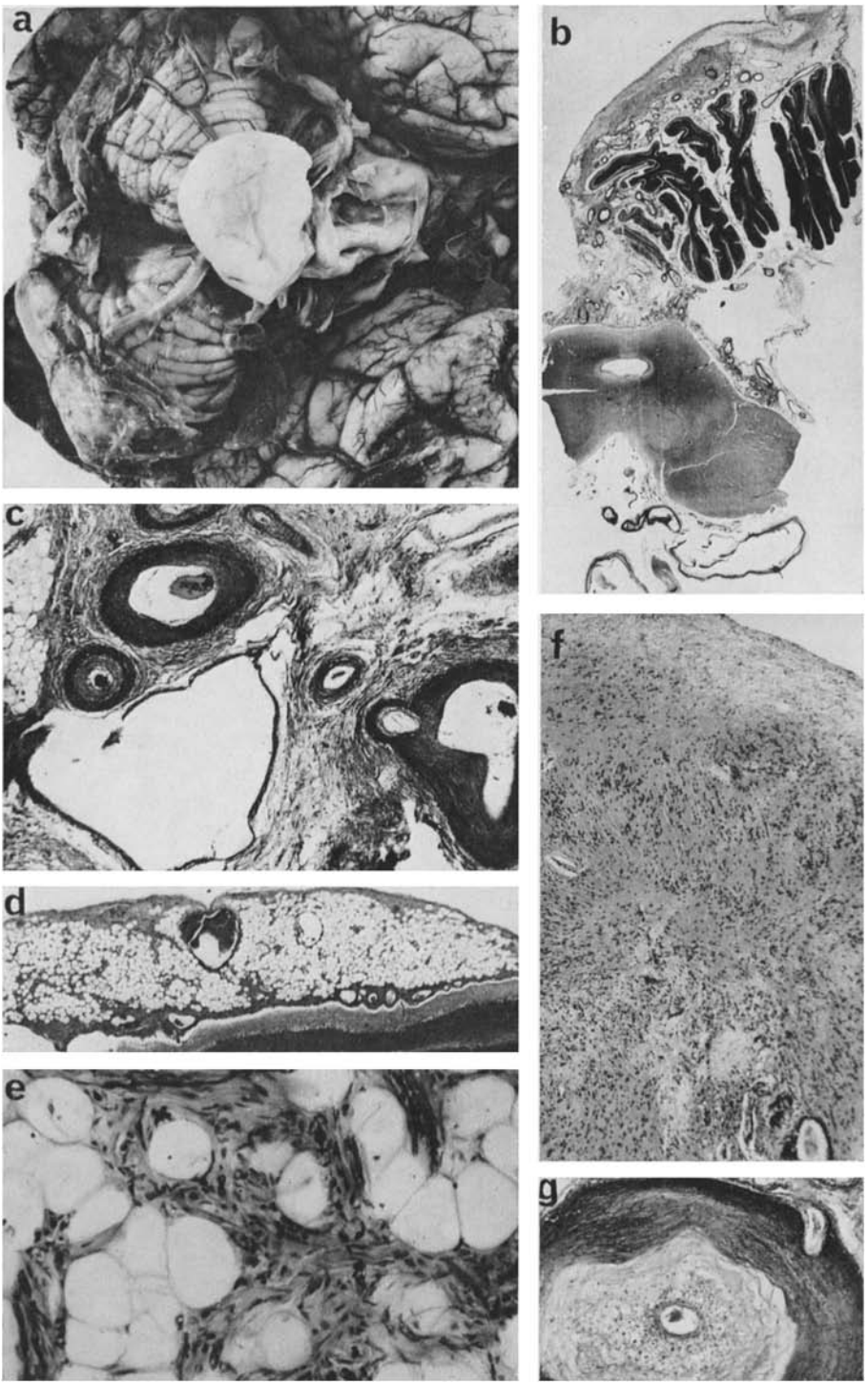

Fig. 4a–g

tumour areas bordering the hamartoma (Fig. 3c below). These plaques were also partly infiltrated by tumour cells and contained a small number of nerve cells with poorly developed Nissl substance (Fig. 3f). These nerve cells showed no similarity to Purkinje cells; their appearance suggested a more immature character. Furthermore, the structure and localisation of the plaques did not suggest cerebellar cortical tissue incorporated into the tumour. The cerebellar nuclei were maldeveloped; additional Purkinje cell heterotopias were found in the cerebellar white matter.

Case 11 displayed an extensive lipomatous hamartoma around the corpus callosum combined with a colloid cyst:

The 73 year-old female had an uneventful clinical history and died after a stroke. The brain showed multiple infarctions and moderate internal hydrocephalus; extensive sausage-shaped fatty masses covered the dorsal and ventral surface of the corpus callosum from genu to splenium, where the adipose tissue encircled a cherry-sized colloid cyst (Fig. 3g) which was lined by a to-one multilayered, mostly cuboidal ciliated epithelium (Fig. 3h) with strongly PAS-positive substances in the apical cell parts. No mucoid goblet cells were seen in the rather uniform epithelium. The cyst contents stained strongly PAS-positive. In the adjacent fatty tissue, several pineal cell nests were scattered, while no other parts of the corpus pineale were discernible.

Case 12 combined facial malformations and multiple cerebellar macro- and microdysgenesias with tentorial osteoma and multiple meningeal fatty nodules:

This female infant showed cheilo-gnatho-palatoschisis and died from recurrent respiratory tract infections on her 21st day. At autopsy, cardiac dextroversion was found; the brain demonstrated severe hydrocephalus internus and marked cerebellar hypoplasia with a large arachnoidal cyst of the cisterna cerebello-medullaris. An olive-sized osteoma attached to the right tentorium with fatty tissue in the adjacent leptomeninges. Another small lipomatous hamartoma was found in the meninges of the inferior vermis (Fig. 2h); multiple nervous tissue dystopias covered the severely hypoplastic cerebellar folia (Fig. 2h, i).

Case 13 represented a unique intracranial hamartomatosis (lipo-fibro-angiomatosis of meninges, megadolichobasilaris, multiple "subependymomas"):

The 40 year-old male had a history of severe mental retardation, club-foot and occasional epileptic seizures. He died after head injury with epidural hematoma. The brain showed left parietal infarctions and severe internal hydrocephalus with multiple ventricle wall nodules of cherry-size. The basilar artery had serpentine configuration and was severely dilated ("megadolichobasilaris"; Fig. 4a, b); however, the cerebral vessels showed no arteriosclerotic changes. A large fatty nodule lay around the caudal oblongata; fatty meningeal thickening was seen above the cerebellum (Fig. 4a, d). A highly vascularized plate of connective and fatty tissues replaced the meninges of midbrain and superior vermis dorsally (Fig. 4b). This region contained an extensive arterio-venous malformation embedded in fibrous and adipose tissue (Fig. 4c); the angiomatous vessels frequently showed severe endangiopathy (Fig. 4g). Multiple well-myelinated aberrant nerve fibres in a "mixed" tissue matrix crossed the large oblongata lipomatous hamartoma (Fig. 4e). The ventricle wall nodules were composed of fibrillary, partly microcystic glial tissue incorporating some ependymal nests and tubuli (Fig. 4f).

Fig. 4a—g. Case 13. a Fatty nodule around medulla oblongata. Dilated serpentine basilar artery. Fatty thickening of posterior cerebellar meninges. b Highly vascularized plate of connective and fatty tissue in meninges dorsally of midbrain and superior vermis. H.-E. ×1,3. c Arterio-venous meningeal angiomatosis adjacent to fatty tissue. van Gieson-Elastica. ×20. d Adipose tissue plate in cerebellar meninges. H.-E. ×9. e Well-myelinated nerve fibers with "mixed" tissue matrix in oblongata lipomatous hamartoma. Klüver-Barrera. ×150. f Ventricle wall nodule composed of fibrillary glial tissue and some ependymal nests and tubuli (lower right). H.-E. ×40. g Endangiopathy of meningeal angiomatosis vessel. H.-E. ×30

Discussion

This series of 13 cases of intracranial lipomatous hamartoma is the largest one reported to date. 9 instances were found among 1956 neuropathological autopsies (selected material); 4 cases belonged to a series of 1560 routine autopsies of one neuropsychiatric hospital. This represents a rather high incidence of intracranial lipomatous hamartoma, when compared with 4 cases in 5000 routine autopsies reported by Vonderahe and Niemer [54]. The fact that all of our 12 autopsy cases were only incidental findings suggests that more instances of intracranial lipomatous hamartoma will be found at thorough investigation of the brain, particularly in the presence of other malformations.

In accordance with previous surveys [20], no preponderance for distinct age groups or one sex was found; this contrasts with spinal "lipomas" which are more common in children or juvenile persons [10]. In a total of 188 connatal intracranial tumours, 2 "lipomas" were found [25].

In none of our 12 autopsy cases were *clinical symptoms* directly related to the intracranial lipomatous hamartoma. Mental retardation and epileptic seizures, commonly associated with this type of lesion [5, 29, 47], and frequent mental troubles [4] should be ascribed to co-existing CNS dysgenesias (cases 4, 13) [20]. Symptoms of a space-occupying lesion are very rare [63]; the slowly progressing local symptoms in our case 8 are comparable to the typical protracted clinical course of spinal "lipomas" [52]. Thus, a clear clinical distinction exists between the usually asymptomatic intracranial lipomatous hamartomas [60, 42] and their symptom-prone spinal counterparts [10]. The extreme rarity of focal symptoms is stressed by the fact that among 4290 neurosurgical biopsies, intracranial lipomatous hamartoma was found only once. Only "lipomas" of the corpus callosum may be easily detected during life because of their characteristic sickle-shaped paramedian calcifications on plain X-ray films [39, 42], by angiography [47], ventriculography [35] or scanning methods [59]. Sexual disturbances, frequently related to hypothalamic hamartomas [40], were not present in our cases 9 and 10. Neurosurgical treatment of callosal "lipomas" gave bad results [4, 23, 33, 39].

The *site* of intracranial lipomatous hamartoma in more than 50% is the callosal region [4], while McLean [37] found only 28% in the callosal region, 20% in the tuber cinereum region, and 8% in the quadrigeminal plate. In our series, the cisterna ambiens region was the most frequent site (5 cases); only one callosal hamartoma was found. Generally, midline structures and basal cisterns are preferred sites [30], but fatty masses above the cerebral convexity also have been described [4, 5, 48, 60]. Multiple lesions (cases 12, 13) are not uncommon; a callosal "lipoma" may combine with one in the choroid plexus [3, 30, 34].

The *size* of intracranial lipomatous hamartomas varies from that of a millet (case 12) to such extended fatty masses (case 13) [16, 48] that the term "hamartomatosis" seems appropriate. Internal *hydrocephalus* may be unrelated to the hamartoma (probably cases 10, 11) or be caused by the specific site of the lesion "compressing" the aqueduct [46, 61] or may be an integrated part of a complex malformation (cases 12, 13) [16].

Combination with *extracranial malformations* was present in 4 instances (cases 4, 8, 12, 13); associated congenital cardiac defects (case 4) have been described

only once [62], whereas spina bifida (case 8) has been observed in some callosal "lipomas" [4, 47]. This and other dysraphic disorders are very often found in spinal "lipomas" [11, 41]. A facial cleft syndrome (case 12), present in one case of spinal "lipomatosis" [58], has never been reported in intracranial lipomatous hamartoma.

The *microscopic* features of intracranial lipomatous hamartoma and its surroundings stress the malformative character of this lesion. The tightly-knit, irregularly structured glio-mesenchymal "mixed" tissue at the hamartoma—brain junction (Fig. 1 b and 2 d) may be found also in other developmental disorders of the CNS in the transitional zone between nervous parenchyma and leptomeninges [4]. The intimate relationship of neuroglial to mesenchymal elements in intracranial lipomatous hamartoma is further stressed by the possible occurrence of muscle fibres, nerve cells and neurites, calcifications and bone formation [42]. The nerve cells seen in Fig. 2 d should be interpreted as normal, mature neurons of the pontine nuclei lying in a hamartomatous matrix replacing the neuropil; on the other hand, the immature-looking nerve cells in case 5 seem to be an integral part of the hamartomatous plaque. At least in the hypothalamus, lipomatous hamartomas (cases 9, 10) may pass through intermediate types to mere nerve cell-hamartomas [40].

Aberrant nerve fibres crossing a lipomatous hamartoma have been observed previously [1, 30, 44, 62]. "Hypertrophic" nerve changes with Schwann-like cells and massive collagenous ensheathing of nerve fibres were noted "beneath pial lipomas where pathological incorporation of connective tissue in the white matter of the CNS occurs" [46]. The transition of normal white matter to "hypertrophic" nerves is reminiscent of the Redlich-Obersteiner-zones where spinal roots penetrate the pia. The presence of peripheral type myelin in some of these aberrant fibres, suggested by histochemical methods, may strengthen the Schwannian nature of the ensheathing cells. Schwann cells and peripheral myelin within the CNS have been observed in a variety of experimental conditions [21] and human diseases, chiefly in multiple sclerosis [9, 24]; they have been interpreted as regenerative proliferations of Schwann cells originating from pial or vascular nerves. Though the histological appearance of the "hypertrophic" nerve changes is rather similar to hypertrophic neuropathy and amputation neuroma, their microdysgenetic nature is suggested by the incorporation into a malformative lesion, associated with other microdysgenesias, e.g. glial dystopias (cases 3, 9, 12) or cerebellar microdysgenesias (cases 4, 5, 12) [55].

Micropolygyria adjacent to intracranial lipomatous hamartoma (case 5) has been observed in the cerebral [4, 5, 16, 48] or cerebellar cortex [49]. Cortical atrophy may be distinguished from malformative changes only with difficulty, if ever; true atrophic nervous tissue changes around intracranial hamartoma have therefore been denied to exist [47].

Calcifications and bone formation, to a less extent cartilagineous areas, are frequently found in lipomatous hamartoma and/or in the surrounding brain tissue [3, 5, 28, 34, 40, 42, 48, 49, 54, 55] and interpreted in most cases as metaplasia [62]. However, the possibility that these components may result from a complex malformation has also to be considered.

In contrast to spinal "lipomas" which sometimes infiltrate spinal roots [10], cranial nerves are unaffected by intracranial lipomatous hamartomas [30]. An exception is case 8, where fat cells could be demonstrated inside the acoustic nerve. This histological finding and the progressive symptoms are evidence of extremely

rare, secondary growth in the primary malformative lesion. Nevertheless, rapid growth and malignant change with metastasis have never been reported [28, 63].

The *origin* of intracranial fatty tissue is still a matter of speculation; besides theories of only historical interest, two mechanisms are generally discussed: 1. Displacement of tissues or of their "anlage" during development; and 2. Dysgenesia of indigenous tissue without displacement. The displacement theory, holding that mesenchyma [40]—possibly accompanied by fragments of the neuraxis [46]—or parts of the dermal anlage (as in dermoid and epidermoid cysts—2) become dislocated during CNS development, is based on dysraphic disturbances frequently associated with spinal and, to a lesser degree, intracranial "lipomas" and the preferred midline location. Agenesis of the corpus callosum, occurring in 48% of all lipomatous hamartomas of this region [62] and interpreted as a dysraphic disorder [40], also argues in favour of the dislocation hypothesis. However, a co-existing epidermoid cyst (case 4) is the only feature in our series which might support this theory. On the other hand, it was argued convincingly that even callosal "lipomas" cannot be due to dysraphism alone [62]; the various hamartoma sites, sometimes distant from the midline and from areas prone to dysraphic disorders, evidently rules out a direct pathogenetic connection of intracranial lipomatous hamartomas to dysraphism [30]. Therefore, only the theory stressing dysgenesia of indigenous tissue, without displacement, may explain the wide spectrum of maldevelopmental features found in intracranial lipomatous hamartomas. Krainer [30] suggested abnormal differentiation of the meninx primitiva which may persist in the cisternal spaces. Demus [4] adopted that scheme, modifying it according to Wassermann's [56] theory of adipose tissue development from capillary mesenchyma; he interpreted CNS "lipoma" to originate from persisting mesenchyma of the embryonic capillary net, stressing the high vascularisation found in some CNS "lipomas" [48, 51, 54]. In our series, however, vascularisation of the adipose tissue was not considerable. A high content of blood vessels in some CNS lipomatous hamartomas is better explained as dysgenetic "angiomatous" feature; associated vascular malformations support that suggestion (case 13) [5, 16, 51]. In our opinion, it is not very relevant whether intracranial fatty tissue develops from the primitive meninges [30] or persisting pericapillary mesenchyma [4]. More interesting are the frequent dysgenesias of the surrounding brain tissue and meninges, found in 8 of 13 cases, which suggest a more complex malformation. Therefore, a intracranial lipomatous hamartoma has to be understood as a true dysgenetic lesion, affecting both mesenchymal and neuroectodermal tissue components. Since at least part of the leptomeninges is likely to develop from the neural crest [18, 19], as well as a great part of the cranial mesenchyma ([22]; "ectomesenchyma"), a complex malformation, affecting both the cerebral ectomesenchyma and the neuroglial tissue [55], may produce the features of intracranial lipomatous hamartoma.

Interesting pathogenetic aspects arise in combination with colloid cyst (case 11), cerebellar medulloblastoma (case 5) and "subependymomas" (case 13):

Case 11, featuring a colloid cyst amidst callosal lipomatous hamartoma, is comparable to a "lipoma" of the corpus callosum in direct communication with a subcutaneous scalp "lipoma"; in the centre of the callosal "lipoma", a cherry-sized colloid cyst with ependymal lining was observed [39]. Since intracranial lipoma-

tous hamartoma is frequently associated with dysgenesia of the surrounding tissue, a malformative origin of these cysts from the neighbouring third ventricle roof may be suggested. The cyst epithelium resembled ependyma, a finding recently confirmed by ultrastructural investigation of a colloid cyst of the third ventricle [32].

Combination of intracranial lipomatous hamartomas with intracranial tumours (case 5) is very rare. Nippe [38] described a parietal "gliosarcoma" completely encircling a fatty tissue mass. Henschen [20] observed a "lipoma" above the quadrigeminal region associated with a walnut-sized "spongioblastoma" of the cerebellum. Treip [53] reported a medulloepithelioma of midbrain and cerebellum with adjacent large meningeal lipomatous hamartoma. In our case, the tumor is classified as partly "desmoplastic" medulloblastoma [45]. The fibro-lipomatous hamartoma, the nerve cell-containing plaques, the cerebellar micropolygyria—all this is in such an intimate relation to the medulloblastoma that we cannot avoid suggesting a developmental connection. We do not interpret the nerve cells in tumour border areas as gangliomatous maturation in medulloblastoma [7,27,46] nor as Purkinje cell remnants of infiltrated cerebellar cortex, but as part of a large meningeal, mostly lipomatous hamartoma, infiltrated secondarily by tumour cells. On morphological grounds, the histogenesis of medulloblastoma is still under discussion [26,43 vs. 13,15,36], whereas recent neurochemical studies give some evidence for a neuroectodermal histogenesis [17]. Our case of medulloblastoma associated with meningeal hamartoma and cerebellar micropolygyria emphasizes the maldevelopmental nature of medulloblastoma; hence, the term "hamartoblastoma" might characterise the dysgenetic origin of some medulloblastomas. This is in accordance with medulloblastomas associated with congenital malformations [6] and teratoid formations observed in homologous twins [12].

Case 13 represents a unique intracranial hamartomatosis, comprising "lipofibro-angiomatosis" of meninges of the posterior fossa, megadolichobasilaris, internal hydrocephalus and multiple ventricle wall nodules. The histology of the latter fits exactly into the description of "subependymomas" [42], which are considered to be built up by subependymal astroglia. Combined with the extensive intracranial hamartomatosis, these ventricle wall nodules demand to be regarded also as hamartomas [46]. Since such fibrillary subependymal glial nodules and angiomatous malformations are sometimes encountered in central neurofibromatosis and other phakomatoses [31,42], this observation may emphasize the links between intracranial lipomatous hamartoma(tosis) and the phakomatoses, a connection already suggested by the description of "encephalocraniocutaneous lipomatosis" [16].

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References

1. Bailey, P., Bucy, P. C.: The origin and nature of meningeal tumors. Amer. J. Cancer **15**, 15—54 (1931)

2. Boström, E.: Über die pialen Epidermoide, Dermoide und Lipome und duralen Dermoide. Zbl. Path. **8**, 1—98 (1897)
3. Capon, A., Flament-Durand, J., Potvliege, R.: Deux cas de lipome du corps calleux. Acta neurol. psychiat. belg. **66**, 9—28 (1966)
4. Demus, H.: Neue Gesichtspunkte zur Entstehung der pialen Lipome. Ein Beitrag zur Klinik, Pathologie, Entstehungsweise und Herkunft der Fettgeschwülste des Zentralnervensystems. Arch. Psychiat. Nervenkr. **209**, 426—442 (1967)
5. Dragojević, S., Mehraein, P., Bock, H.-J.: Beobachtung eines Lipoms der Temporalregion mit Rindenmißbildung und Epilepsie. Klinisch-pathologische Studie. Arch. Psychiat. Nervenkr. **217**, 335—342 (1973)
6. Duckett, S., Claireaux, A. E., Pearse, A. G. E.: Histoenzymatic study of fetal medulloblastoma with associated congenital malformations. Neurology (Minneap.) **16**, 283—287 (1966)
7. Durity, F. A., Dolman, C. L., Moyes, P. D.: Ganglioneuroblastoma of the cerebellum. Case report. J. Neurosurg. **28**, 270—273 (1968)
8. Feigin, I., Cravioto, H.: A histochemical study of myelin. A difference in the solubility of the glycolipid components in the central and peripheral nervous system. J. Neuropath. exp. Neurol. **20**, 245—254 (1961)
9. Ghatak, N. R., Hirano, A., Doron, Y., Zimmerman, H. M.: Remyelination in multiple sclerosis with peripheral type myelin. Arch. Neurol. (Chic.) **29**, 262 (1973)
10. Giuffrè, R., Gambacorta, D.: Lipoma of the spinal cord. Case report. J. Neurosurg. **35**, 335—337 (1971)
11. Gold, L. H. A., Kieffer, S. A., Peterson, H. O.: Lipomatous invasion of the spinal cord associated with spinal dysraphism. Myelographic evaluation. Amer. J. Roentgenol. **107**, 479—485 (1969)
12. Griepentrog, F., Pauly, H.: Intra- und extrakranielle, frühmanifeste Medulloblastome bei erbgleichen Zwillingen. Zbl. Neurochir. **17**, 129—140 (1957)
13. Gullotta, F.: Vergleichende Untersuchungen zur Morphologie und Genese der sogenannten Medulloblastome. Acta neuropath. (Berl.) **8**, 76—83 (1967)
14. Gullotta, F.: The specific localisation of mesenchymal tumours of CNS. Proc. VIth Internat. Congr. Neuropath. (Paris), pp. 974—975. Paris: Masson 1970
15. Gullotta, F., Kersting, G.: The ultrastructure of medulloblastoma in tissue culture. Virchows Arch., Abt. A, Path. Anat. **356**, 111—118 (1972)
16. Haberland, C., Perou, M.: Encephalocraniocutaneous lipomatosis. A new example of ectomesodermal dysgenesis. Arch. Neurol. (Chic.) **22**, 144—155 (1970)
17. Haglid, K. G., Stavrou, D., Rönnbäck, L., Carlsson, C.-A., Weidenbach, W.: The S-100 protein in water-soluble and pentanol-extractable form in normal human brain and tumors of the human nervous system. A quantitative study. J. neurol. Sci. **20**, 103—111 (1973)
18. Harvey, S. C., Burr, H. S.: The development of the meninges. Arch. Neurol. Psychiat. (Chic.) **15**, 545—567 (1926)
19. Harvey, S. C., Burr, H. S., VanCampenhout, E.: Development of the meninges. Further experiments. Arch. Neurol. Psychiat. (Chic.) **29**, 683—690 (1933)
20. Henschen, F.: Tumoren des Zentralnervensystems und seiner Hüllen. In: Handb. spez. path. Anat. Histol., Bd. 13/3, S. 413—1040. Berlin-Göttingen-Heidelberg: Springer 1955
21. Hirano, A., Zimmerman, H. M., Levine, S.: Electron microscopic observations of peripheral myelin in a central nervous system lesion. Acta neuropath. (Berl.) **12**, 348—365 (1969)
22. Hörstadius, S.: The neural crest. Its properties and derivatives in the light of experimental research. London: Oxford University Press 1950
23. Huber, K., Hammer, B., Seitelberger, F.: Ein operiertes intrakranielles Lipom im Dach des 3. Ventrikels. Wien. Z. Nervenheilk. **7**, 104—114 (1953)
24. Jellinger, K.: Einige morphologische Aspekte der Multiplen Sklerose. Wien. Z. Nervenheilk., Suppl. II, 12—37 (1969)
25. Jellinger, K., Sunder-Plassmann, M.: Connatal intracranial tumours. Neuropädiatrie (Stuttg.) **4**, 46—63 (1973)

26. Kadin, M. E., Rubinstein, L. J., Nelson, J. S.: Neonatal cerebellar medulloblastoma originating from the fetal external granular layer. J. Neuropath. exp. Neurol. **29**, 583—600 (1970)
27. Kane, W., Aronson, S. M.: Gangliogliomatous maturation in cerebellar medulloblastoma. Acta neuropath. (Berl.) **9**, 273—279 (1967)
28. Kernohan, J. W.: Tumors of congenital origin. In: Pathology of the nervous system, J. Minckler, Ed., Vol. 2, 1927—1937. New York: McGraw-Hill 1971
29. Koehl, R. H., Solitare, G. B., Heffner, R. R., Jr.: Lipomatous hamartoma involving the midbrain and cerebellum of a mentally retarded man. J. ment. Defic. Res. **14**, 227—234 (1970)
30. Krainer, L.: Die Hirn- und Rückenmarkslipome. Virchows Arch. path. Anat. **295**, 107 bis 142 (1935)
31. Kramer, W.: Lesions of the central nervous system in multiple neurofibromatosis. Psychiat. Neurol. Neurosurg. **74**, 349—368 (1971)
32. Landolt-Weber, U. M.: Ultrastruktur einer Kolloidcyste des dritten Ventrikels. Acta neuropath. (Berl.) **26**, 59—70 (1973)
33. List, C. F., Holt, J. F., Everett, M.: Lipoma of the corpus callosum: A clinico-pathologic study. Amer. J. Roentgenol. **55**, 125—134 (1946)
34. Machacek, F.: Lipom des Balkens und symmetrische Plexuslipome. Wien. klin. Wschr. **78**, 390—392 (1966)
35. Manganiello, L. O. J., Daniel, E. F., Hair, L. Q.: Lipoma of the corpus callosum. Case report. J. Neurosurg. **24**, 892—894 (1966)
36. Matakas, F., Cervós-Navarro, J., Gullotta, F.: The ultrastructure of medulloblastomas. Acta neuropath. (Berl.) **16**, 271—284 (1970)
37. McLean, A. J.: Intracranial tumors. In: Handb. Neurol., Bd. 14, S. 131—241. Berlin: Springer 1936
38. Nippe, M.: Traumatisch entstandenes Gliosarkom mit Lipom des Gehirns. Frankfurt. Z. Path. **11**, 466—471 (1912)
39. Nordin, W. A., Tesluk, H., Jones, R. K.: Lipoma of the corpus callosum. Arch. Neurol. Psychiat. (Chic.) **44**, 300—307 (1955)
40. Ostertag, B.: Die hyperplastischen Hamartome des Hypothalamus und ihre allgemeinpathologische Bedeutung. Acta neuropath. (Berl.) **4**, 107—125 (1964)
41. Rogers, H. M., Long, D. M., Chou, S. N., French, L. A.: Lipomas of the spinal cord and cauda equina. J. Neurosurg. **34**, 349—354 (1971)
42. Rubinstein, L. J.: Tumors of the central nervous system. In: Atlas of tumor pathology, ser. 2, fasc. 6. Washington, D.C.: AFIP 1972
43. Rubinstein, L. J.: Cytogenesis and differentiation of primitive central neuroepithelial tumors. J. Neuropath. exp. Neurol. **31**, 7—26 (1972)
44. Rubinstein, L. J.: Personal communication (1972)
45. Rubinstein, L. J., Northfield, D. W. C.: The medulloblastoma and the so-called "arachnoidal cerebellar sarcoma". A critical re-examination of a nosological problem. Brain **87**, 379—412 (1964)
46. Russel, D. S., Rubinstein, L. J.: Pathology of tumours of the nervous system, 3rd ed. London: Edward Arnold Ltd. 1971
47. Sabouraud, O., Pecker, J., Simon, P., Chatel, M.: Lipomes du corps calleux. Données angiographiques et discussion pathogénique de leur séméiologie clinique. Rev. neurol. **117**, 557—570 (1967)
48. Scherer, E.: Über die pialen Lipome des Gehirns. Beitrag eines Falles von ausgedehnter meningealer Lipomatose einer Großhirnhemisphäre bei Mikrogyrie. Z. ges. Neurol. **154**, 45—61 (1936)
49. Schmid, A. H.: A lipoma of the cerebellum. Acta neuropath. (Berl.) **26**, 75—80 (1973)
50. Stefan, H.: Lipom lokalisiert im Kleinhirnbrückenwinkel als Nebenbefund einer tuberkulösen Meningitis mit histologischem Befund. Z. ges. Neurol. **145**, 445—453 (1933)
51. Tanaka, K.: Rare intracranial tumors. Folia psychiat. neurol. jap. **5**, 167—175 (1952)
52. Thomas, J. E., Miller, R. H.: Lipomatous tumors of the spinal cord. A study of their clinical range. Proc. Mayo Clin. **48**, 393—400 (1973)

53. Treip, C. S.: A congenital medulloepithelioma of the midbrain. J. Path. Bact. **74**, 357—363 (1957)
54. Vonderahe, A. R., Niemer, W. T.: Intracranial lipoma. A report of four cases. J. Neuropath. exp. Neurol. **3**, 344—354 (1944)
55. Vuia, O.: Multiple lipomata. Krabbe disease. In: Handbook of clinical neurology, P. J. Vinken and G. W. Bruyn, Eds., Vol. 14, pp. 405—413. Amsterdam: North-Holland 1972
56. Wassermann, F.: Die Fettorgane des Menschen. Entwicklung, Bau und systematische Stellung des sogenannten Fettgewebes. Z. Zellforsch. **3**, 235—328 (1926)
57. Willis, R. A.: The pathology of the tumours of children. Edinburgh-London: Oliver & Boyd 1962
58. Wolbach, S. B., Millet, J. A. P.: Diffuse subdural lipomatosis of the spinal cord in an infant. Boston med. Sci. J. **168**, 681—686 (1913)
59. Wolpert, S. M., Carter, B. L., Ferris, E. J.: Lipomas of the corpus callosum. An angiographic analysis. Amer. J. Roentgenol. **115**, 92—99 (1972)
60. Yalcin, S., Fragoyannis, S.: Intracranial lipoma. Case report. J. Neurosurg. **24**, 895—897 (1966)
61. Zelengurov, V. M., Galaiko, R. A.: Lipoma of the brain. Arch. Pat. (Moscow) **12**, 62—64 (1969) (in Russian)
62. Zettner, A., Netsky, M. G.: Lipoma of the corpus callosum. J. Neuropath. exp. Neurol. **19**, 305—319 (1960)
63. Zülch, K. J.: Biologie and Pathologie der Hirngeschwülste. In: Handb. Neurochir., Bd. 3, S. 1—702. Berlin-Heidelberg-New York: Springer 1956

Addendum

Since the submittance of this paper, one additional case was observed (case 14): A 64 year-old female with a clinical diagnosis of dementia presented at autopsy a pea-sized lipomatous hamartoma in the right paramedian fossa interpeduncularis; the right oculomotor nerve was split into several bundles with severe proliferation of endoneural tissue. Unique in our series, numerous striated muscle fibres crossed the hamartoma, thus stressing once more the primarily malformative character of intracranial lipomatous hamartoma.

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