

Cerebral Histiocytosis-X with Endocrine Symptoms

PER OLOV LUNDBERG, YNGVE OLSSON and CHRISTER SUNDSTRÖM

From the Department of Neurology and Neuropathological Laboratory, Department of Pathology, University Hospital, Uppsala, Sweden

ABSTRACT

A neuropathologically verified case of histiocytosis-X in a 21-year-old man with endocrine symptoms is presented. The granulomas were confined to the central nervous system and occupied mainly the pituitary stalk and hypothalamus, thus giving us the opportunity to observe the endocrine symptoms caused by such localized lesions.

1. Diabetes insipidus was one cardinal endocrine symptom and is considered to be caused by a hypothalamic lesion in the supraoptic nuclei or the pathways to the posterior pituitary. In this case the anterior pituitary was not involved by granulomas, but the posterior lobe was atrophic.

2. Severe hypogonadism and probably also a growth hormone defect were present, probably resulting from pituitary insufficiency secondary to the hypothalamic lesions.

3. Hypothyroidism was another symptom but in this case was probably due to thyroiditis. Such a finding has previously been observed by two other authors and may therefore be pathologically connected to histiocytosis-X even though no granulomas were present in the thyroid gland.

4. Repeated X-ray investigations from 9 years of age showed that the development of the sella turcica ceased about the same time as the patient got signs of diabetes insipidus. Increase in sellar volume normally reflects pituitary growth. The lesions in the pituitary stalk or the hypothalamus must therefore have been present from the time when diabetes insipidus started.

INTRODUCTION

Histiocytosis-X with involvement of the central nervous system and endocrine symptoms is a very rare though well known disease. The clinical picture, with a variety of symptoms often appearing one by one, is in most cases very distinct as also is the histopathological localization of the symptom-producing lesions. Therefore, a combined analysis both from the clinical and from the morphological point of view sometimes offers unique opportunities to study the origin and the interpretation of a certain clinical symptom. At times this has also given im-

portant information about human physiology. We report the present case as constituting such an example.

CASE REPORT

Male, 21 years of age at the time of death. Heredity, mother's gestation, birth and postnatal development were normal. Karyotype 46 XY.

At 9 years of age he suffered from an acute gastrointestinal upset with fever. Subsequently he never regained normal fitness. During the following months he suffered from frequent matutinal vomiting and drowsiness. Medical examination revealed a boy normally developed for his age but with anemia (Hb 9.5%) and an elevated erythrocyte sedimentation rate (ESR).

Six months later he complained of increased thirst and voided up to 7 litres of urine per 24 hours. Hypothyroidism (protein-bound iodine (PBI) 1.6 $\mu\text{g}\%$, serum cholesterol 330 mg%) was also diagnosed and he was subsequently treated with thyroxine (Levaxin, 0.1 g a day). Neurological examination showed positional nystagmus. Skull X-ray was normal with a sella turcica of a size compatible with his age. (Fig. 1A). Pneumoencephalography (PEG) did not reveal anything abnormal.

During the following 6 years the boy still suffered from almost regular vomitings after the morning meal and increased urinary volume. However, he was able to attend his regular school classes but did not take part in sports.

At 15 years of age he developed increased drowsiness and his gait became swaying. At neurological examination, positional nystagmus, severe ataxia of both arms and legs and exaggerated tendon reflexes in the right arm and leg were found. Treatment with vasopressin spray three times a day was started to correct his diabetes insipidus.

At 18 years of age he suddenly became ill with fever, signs of dehydration, mental confusion and muscular hypotonia. A hyperosmolar coma with metabolic acidosis was diagnosed and properly corrected within a few days. It was noted at this time that he was short for his age, somewhat obese and still completely lacking in pubertal development. Skeletal age was estimated as 14 years. An insulin tolerance test, repeated on three occasions, displayed a normal increase in plasma cortisol but no in-

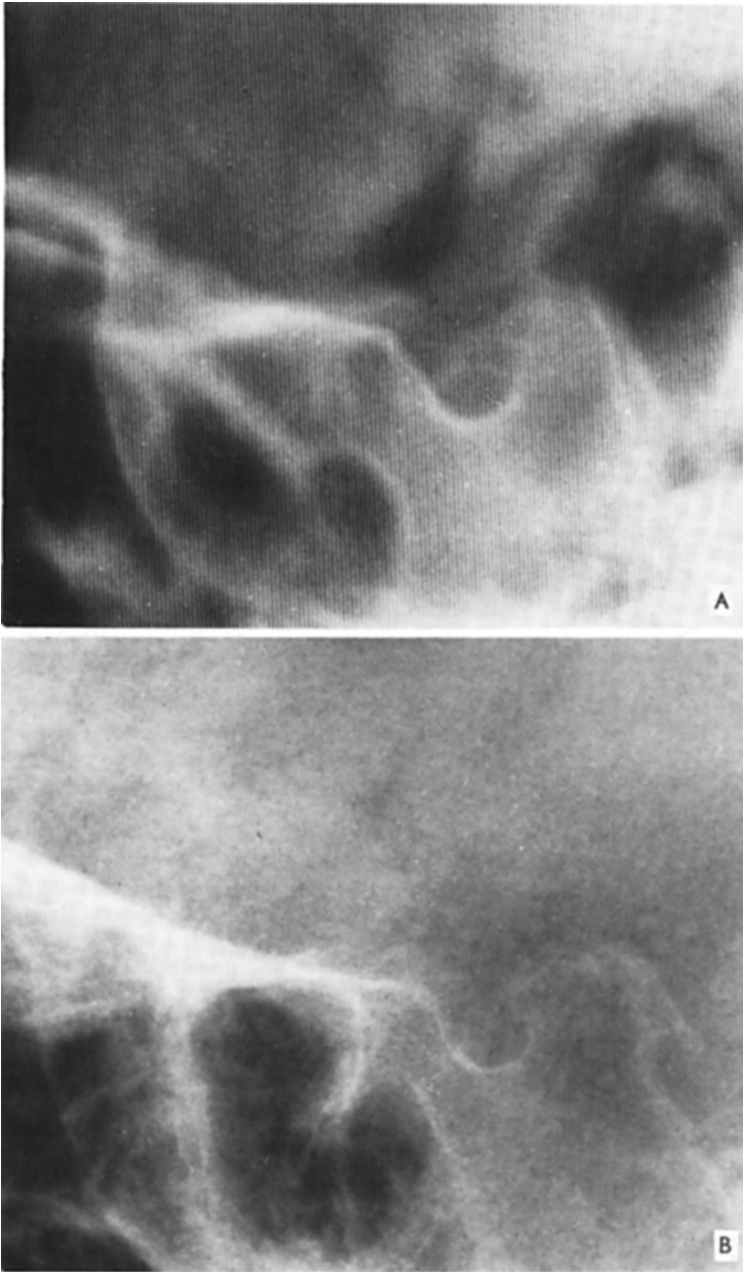


Fig. 1. (A) Lateral pneumoencephalogram of the sellar region at 9 years of age. (B) Plane lateral roentgenogram of the sellar region at 21 years of age. Sella volume at both occasions 190 mm³, indicating absence of normal sellar development. Note normal development of sinuses and clivus.

crease in growth hormone (GH). A metyrapone test resulted in a normal increase of urinary 17-ketogenic steroids. Determination of urinary gonadotropins revealed low, prepubertal values.

After that he was treated with increased doses of thyroxine (0.3 g a day) and injection of testosterone esters. This resulted in growth of sparse pubic hairs and a change in the voice. However, erections or nocturnal emissions were never reported.

At the neurological examination at the Department of

Neurology, Uppsala, it was found that the patient (then 20 years old) could not stand without support, nor could he walk. He had a spastic quadriplegia, more pronounced on the right side and in the legs and an ataxia in the arms. His behaviour was infantile and he was slightly mentally retarded.

He was short in stature, 158 cm, and his body weight was 50 kg. His body proportions were infantile, somewhat eunucoid with slight gynecomastia. The skin texture was soft, he had abundant "pituitary" freckles on his



Fig. 2. (A) Basal view of the brain. Note the ovoid enlargement of the pituitary stalk (*arrow*). (B) Coronal sec-

tion of the brain. Note the numerous small nodules occupying ventricular walls.

face and arms but otherwise only sparse skin pigmentations. He had no facial or axillary hairs and only scanty pubic hairs. The testicles measured 3 ml in volume each.

A skull X-ray revealed a sella turcica of the same size as at the first X-ray when he was 9 years of age. The sella volume was only 190 mm³, thus very small (Fig. 1 B).

Ophthalmoneurological examinations showed a defective colour sense, normal visual acuity but a suspect

upper nasal quadrant defect in the right visual field. Electroencephalography (EEG) was normal.

Serum electrophoresis showed a pronounced increase in α_2 globulins and a slight decrease in γ -globulins. In liquor he had an increase of α_2 -globulins, a reduction of τ , but normal γ -globulins.

For results of endocrine tests, see below.

At 21 years of age his illness progressed rapidly. He

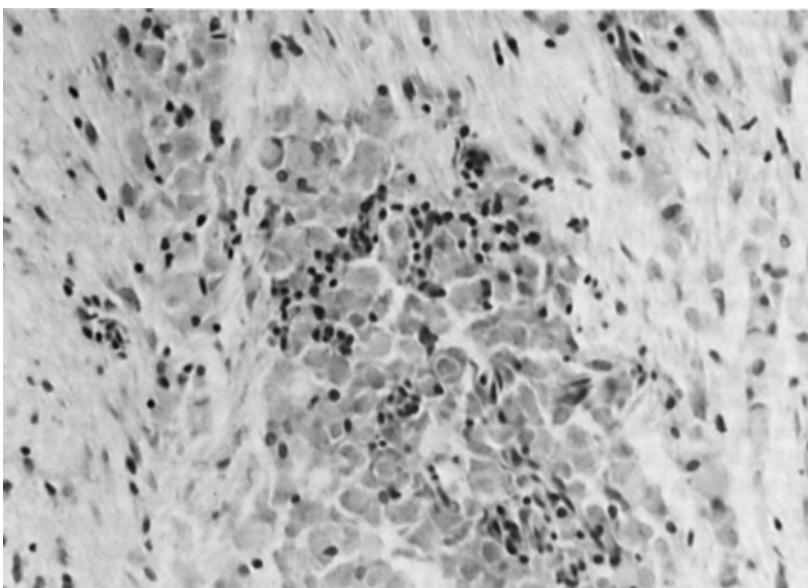


Fig. 3. Histological section from the hypothalamic granulomas. In the centre there is a collection of phagocytes and mononuclear inflammatory cells.

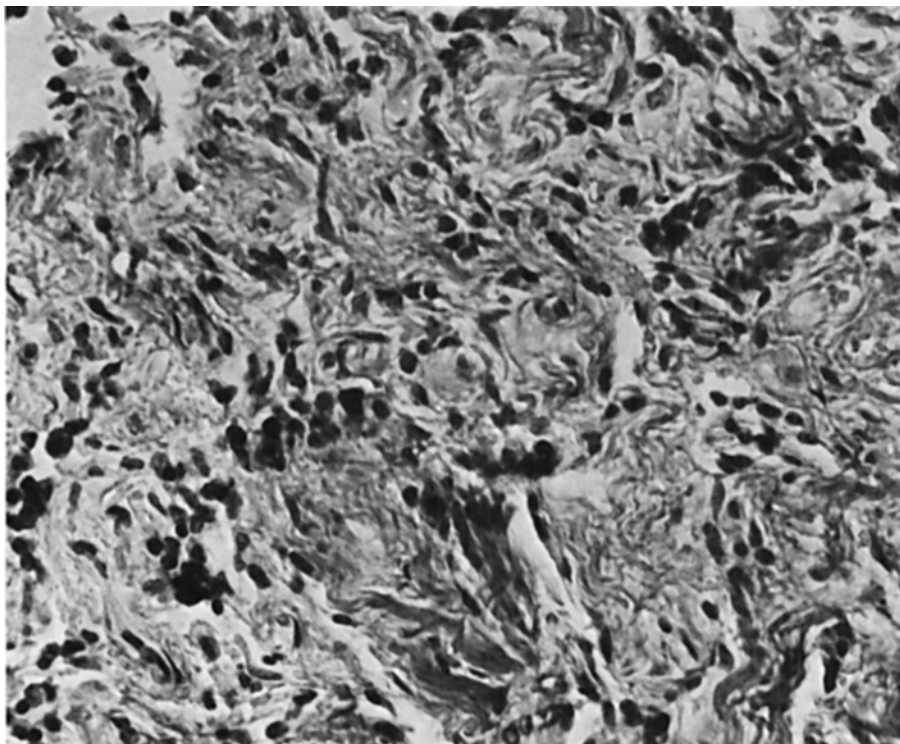


Fig. 4. The posterior lobe of the pituitary was highly atrophic with extensive fibrosis. The fibrotic tissue was

relatively rich in fibroblasts, lymphocytes and macrophages. van Gieson. $\times 400$.

developed venous thrombosis in his left leg, spontaneous pneumothorax and melaena. A defect of the skull bone was seen at X-ray. Then he suddenly lost consciousness and died from an extensive bleeding in the oesophagus.

Results of endocrine tests (20 years of age): For methods and normal values in this hospital, see refs. 8, 10 and 11.

Thyroid function: (10 years of age, subsequently treated with thyroxine). PBI 1.6 mg%, Basal metabolic rate -15% . I^{131} uptake in thyroid after 24 hours, 26%. No increase in thyroid uptake was noted after thyrotropin (TSH) administration. (20 years of age): TSH 2.0 μ U/ml (normal), no increase in blood TSH after thyrotropin-releasing hormone (TRH). This indicates a thyroid insufficiency, probably of a thyroid origin.

Adrenal gland function: Diurnal cortisol curve normal. Dexamethasone suppression of plasma cortisol normal. Basal excretion of urinary 17-hydroxycorticoids normal. Normal increase in urinary 17-OH after corticotropin (ACTH) and metyrapone administration. Thus, no indication of adrenocortical insufficiency was found.

Gonadal function: Basal follicle-stimulating hormone (FSH) in blood decreased (0.37, 0.33 ng/ml), after administration of luteinizing hormone-releasing hormone (LH-RH) increase to a maximum of 0.49 ng/ml (pathological). Basal luteinizing hormone in blood very low (<0.2 , 0.2 ng/ml), after LH-RH increase to a maximum of 0.6 ng/ml (significant but low). Basal plasma testosterone

0.6 mg/ml (very low). Urinary excretion of 17-ketosteroids 3.9 mg/24 h (low). This indicates a severe gonadal insufficiency, probably of pituitary origin.

AUTOPSY FINDINGS

At autopsy, specimens from brain and other organs were fixed in 10% formalin, embedded in paraffin and stained by routine histological methods. Frozen sections from hypothalamus and cerebellum were also made for demonstration of cholesterol and cholesterol esters according to Schnabel. Pearse trichrome staining was done on sections from the pituitary gland.

Central nervous system

The cranial dura and the leptomeninges appeared entirely normal. The brain showed a moderate generalized supratentorial swelling (1400 g) and the examination revealed several important changes:

Infundibulum was markedly enlarged and had a yellow tint. It reached 0.5 cm in diameter but the distal part of the pituitary stalk was abnormally thin (Fig. 2A). Histologic examination showed a

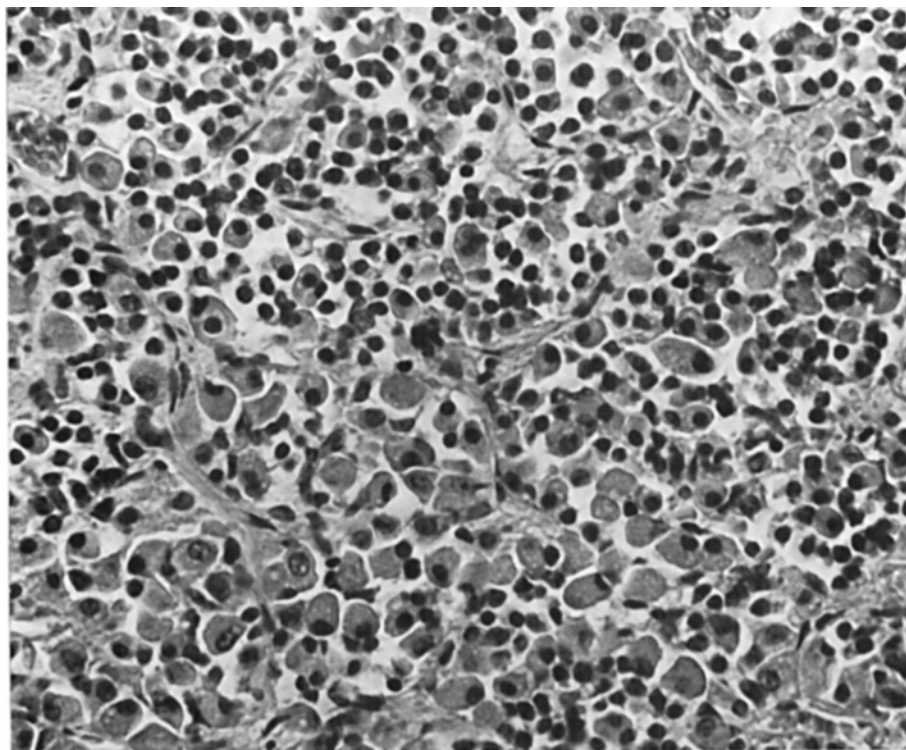


Fig. 5. The anterior lobe of the pituitary was of normal microscopic appearance with ordinary proportions between the different cell types. Pearse, $\times 400$.

pronounced destruction of the infundibulum and the pituitary stalk. In these areas there was a marked granulomatous reaction, with collections of phagocytes, mononuclear inflammatory cells and glial elements, particularly around vessels (Fig. 3). The blood vessels themselves had thick walls and in luxol-stained preparations no myelinated fibres could be detected.

Similar granulomas were present particularly in the most ventral areas of the *hypothalamus*. In a few areas deposits of cholesterol-positive material were present. Scattered lesions also existed close to the walls of the third ventricle where multiple foci of proliferated astrocytes were found. They corresponded to multiple small nodules on gross inspection of ventricular surfaces (Fig. 2B).

The *cerebellum*, particularly the vermis, was markedly atrophic. This part was very hard on palpation and the grey cut surface contained several yellow areas in the dentate nuclei. Microscopically there were multiple foci of granulomas of the same

kind as in the infundibulum. In addition, small areas of calcification and demyelination were present.

Pons was moderately atrophic, corresponding to the loss of fibre connections to the cerebellum. In addition, there were several subependymal foci of astrocytic gliosis.

In lateral parts of both *occipital lobes* we found small cortical infarcts, pallor of myelin, and astrocytosis in the adjacent parts of the white matter. Otherwise, no essential changes could be detected in the cerebral parenchyma. The choroid plexus and basal arteries had a normal appearance.

Endocrine organs

The *pituitary* was markedly atrophic (weight 0.27 g) corresponding to a loss of parenchyma in the posterior lobe which was wholly replaced by a cellular fibrous tissue containing fibroblasts, lymphocytes and macrophages (Fig. 4). However, no obvious changes were seen in the anterior lobe (Fig. 5).

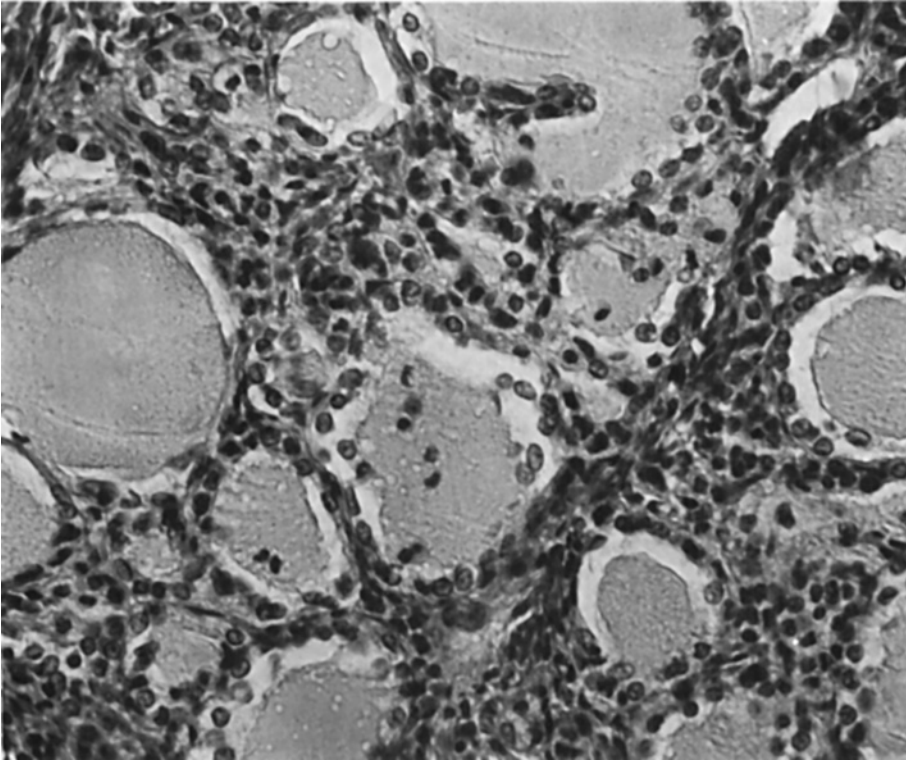


Fig. 6. In the thyroid there was destruction of the acini with extensive fibrosis and infiltrations of lymphocytes. H.-E., $\times 400$.

The *drenals* were also small and weighed only 3.0 and 3.65 g, respectively. Histology showed that the zona glomerulosa was normal. In the zona fasciculata the fat content of the cells appeared reduced and in the reticularis the cells were often degenerated showing signs of karyorrhexis. No changes were noticed in the medulla.

The *thyroid gland* was small and hard (weight 4.5 g). Histological examination revealed that the glandular parenchyma to a great extent was destroyed. Extensive fibrosis with fibroblasts, collagen, and inflammatory cells was present. No lymphoid follicles were noted. In small areas where the glandular epithelium remained, colloid was sometimes present in the lumina (Fig. 6).

Both *testicles* were extremely atrophic (weights 1.6 and 1.75 g) and markedly fibrotic. The tubuli had a prepubertal appearance. Only Sertoli cells were present and no signs of spermiogenesis could be seen. No Leydig cells were detected in the interstitium. Both epididymidi were partly atrophic, with

increased fibrotic tissue. No sperms could be seen in the tubuli.

Other organs

The heart was normal and in both pulmonary arteries multiple small emboli were found. The spleen and pancreas were normal and no important changes were seen in the kidneys. The liver was congested and there was a slight fat vacuolization in parenchymal cells. In the distal part of the oesophagus the mucosa was of the ventricular type, ulcerated with an open vessel. The ventricle also contained coagulated blood to such an extent that this bleeding had probably led to death.

DISCUSSION

Hand-Schüller-Christian's syndrome or histiocytosis-X with cerebral nervous involvement was suspected but never proven during life. From the neuropathological observations it is obvious, however, that the patient had a granulomatous disease

with lipid inclusions typical of histiocytosis-X. The character of the histopathological changes in this rare disease has previously been discussed in great detail by several authors (for ref., see Kepes & Kepes, 1969).

Our main reasons for publishing this case report are that the lesions were strictly localized, destroying primarily hypothalamus and pituitary stalk and that we had made long-term observations on the patient's neuro-endocrinological development. In the following we will therefore restrict the discussion to this aspect of the disease.

Diabetes insipidus is the cardinal endocrine symptom of Hand-Schüller-Christian's syndrome. It is usually the initial endocrine symptom and often the only one. Diabetes insipidus is a hypothalamic (not a pituitary) symptom and results from a destruction of the supraoptic nucleus or the pathways leading from this nucleus to the posterior pituitary. It is interesting to note that the granulomatous lesions in the present case were confined to the hypothalamus and pituitary stalk and that no lesion of the anterior pituitary was seen. From the descriptions in other cases (3, 4, 5, 6, 9, 12) the same observations can be made.

In the present case we know that at nine years of age the patient got a basal hypothalamic or pituitary stalk lesion from the fact that at that time he contracted diabetes insipidus. An X-ray of the sella turcica at that age revealed a sella of normal shape with a volume of 190 mm³—normal for age. He was then followed up with repeated skull X-rays. Subsequently his sella failed to display normal size increase. Twelve years later he still had the same sellar volume. The increase in sellar volume normally reflects the increase in pituitary growth. It seems obvious that the large granuloma of the pituitary stalk seen at autopsy and suspected on the PEG had totally disrupted the hypothalamo-pituitary contact necessary for anterior pituitary development during puberty.

A sellar volume of 190 mm³ is too small for an adult male. In another study from this department the sellar volume of 45 healthy males aged 18 to 31 was found to range between 220 and 1070, with a mean of 610 mm³ (1). In an adult a normally shaped but too small sella should be called "infantile sella" in contrast to the concept "dysplasia of the sella" described by Lundberg & Gemzell (1966). The latter is probably the result of a prenatal malformation.

At autopsy the thyroid gland showed changes consistent with Hashimoto's thyroiditis. This fact and the fact that the uptake of radio-iodine in the thyroid did not increase after TSH stimulation speaks in favour of a primary hypothyreosis and against a hypothyreosis secondary to the hypothalamo-pituitary lesion. Thyroiditis has been described in at least two other cases of cerebral histiocytosis-X (2, 5).

The patient displayed essentially normal hypothalamo-pituitary-adrenal function. On the other hand the boy had a severe hypogonadism and probably also a growth hormone insufficiency. Thus, the defect in hypothalamo-pituitary regulation of the endocrines was partial. It is probable that the selectivity was caused by the fact that the lesions of the hypothalamus and pituitary stalk only involved certain anatomical structures.

REFERENCES

1. Bergström, K., Lundberg, P. O. & Sjövall, A.: The volume of the sella turcica in patients with anorexia nervosa. *Europ Neurol* 9: 183-189, 1973.
2. Bernhard, J. D. & Aguilar, M. J.: Localized hypothalamic histiocytosis-X. *Arch Neurol* 20: 368-372, 1969.
3. Chiari, H.: Über Veränderungen im Zentralnervensystem bei generalisierter Xanthomatose vom Typus Schüller-Christian. *Arch Pathol Anat* 288: 527-553, 1933.
4. Cureton, R. J. R.: A case of intracerebral xanthomatosis with pituitary involvement. *J Pathol Bacteriol* 61: 533-540, 1949.
5. Kepes, J. J. & Kepes, M.: Predominantly cerebral forms of histiocytosis-X. *Acta neuropath (Berl.)* 14: 77-98, 1969.
6. Lindeman, R. D., Owen Sear, R. & Lee, T. D.: Hand-Schüller-Christian disease with occult diabetes insipidus. *Arch Intern Med* 116: 131-137, 1965.
7. Lundberg, P. O. & Gemzell, C.: Dysplasia of the sella turcica: clinical and laboratory investigations in three cases. *Acta Endocrinol* 52: 478-488, 1966.
8. Lundberg, P. O. & Wide, L.: The response to TRH, LH-RH, metyrapone and vasopressin in patients with hypothalamo-pituitary disorders. *Europ J. Clin Invest* 3: 49-56, 1973.
9. Müller, D.: Zum Substrat des vorübergehenden Diabetes insipidus beim Hand-Schüller-Christian-Syndrom. *Acta Neuroveget* 30: 303-313, 1967.
10. Osterman, P. O., Lundberg, P. O. & Wide, L.: The level and circadian rhythm of plasma free 11-hydroxycorticoids in patients with localized intracranial processes, especially of the sellar region. *Acta Neurol Scandinav* 49: 115-132, 1973.
11. Osterman, P. O. & Wide, L.: The insulin tolerance after pretreatment with dexamethasone. *Acta Endocrinol* 83: 341-356, 1976.

12. Smolik, E. A., Devecerski, M., Nelson, J. S. and Smith, K. R. jr.: Histiocytosis-X in the optic chiasm of an adult with hypopituitarism. *J Neurosurg* 29: 290-295, 1968.

Received February 3, 1977

Address for reprints:

Per Olov Lundberg, M.D.
Department of Neurology
University Hospital
S-750 14 Uppsala
Sweden