

Nephrogenic diabetes insipidus and Werdnig-Hoffmann disease in a child: an unusual association

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SUMMARY The unusual association of Werdnig-Hoffmann disease and nephrogenic diabetes insipidus in a 5-month-old child is described for the first time. The association is casual, considering the different pathways of genetical transmission in these two diseases. The possibility of identifying the heterozygote is discussed and it appears to be limited to nephrogenic diabetes insipidus.

Werdnig—Hoffmann disease is inherited as autosomal recessive; the inheritance of nephrogenic diabetes insipidus is still under discussion, though most authors consider it to be X-linked recessive (McKusick, 1975).

We have not been able to find any other reported case in which both diseases present in the same subject.

Case report

The present case, a boy, was born in July 1975. The family was known to us, because previously we had examined and followed up a relative affected by nephrogenic diabetes insipidus (IV. 5 Fig. 1).

The birth was by caesarian section because of uterine inertia; birthweight was 3700 g. He remained in hospital for about 2 months in the newborn unit from which he was discharged with the diagnosis of meconium pneumonia, fever of unknown origin, and suspected diabetes insipidus. At the age of 5 months he was admitted to our department for persistent fever and generalised hypotonia.

On examination the child appeared to be in poor

general condition, dehydrated, and pale. A persistently high temperature was noted. We started rapid hydration which, in the following few days, produced an improvement in the child's general condition, and a gradual return of temperature to normal values.

The child was discharged in an improved general condition but was readmitted at the age of 10 months when a massive pulmonary atelectasia led to his death from respiratory failure.

NEUROLOGICAL EXAMINATION

On first admission the most outstanding feature was the severe reduction of spontaneous motility in striking contrast to the alert, bright, wide-eyed expression of the child who reacted normally to the various environmental stimulations.

A striking symmetrically diffused hypotonia was more evident in the lower limbs than in the upper. There were slow, rare movements of the hand, severe muscular atrophy of the limbs and chest, and limited movement of the abductors of the hip and the extensor of the knee. The feet were in the equinus position, with limited movement. Paralysis of the intercostal muscles, in the presence of a normal functioning diaphragm,

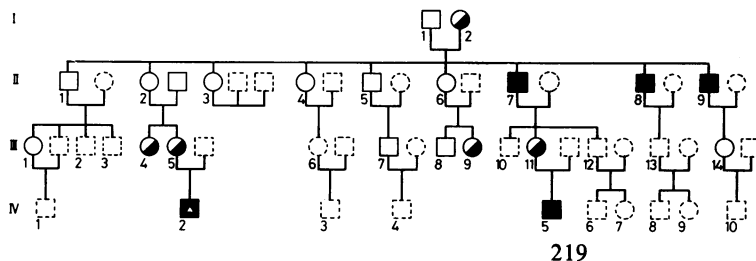


Fig. 1 Pedigree of our patient. I. 2; III. 4, 5, 9, 11: females mildly affected by nephrogenic diabetes insipidus. II. 7, 8, 9; IV. 5: males affected by nephrogenic diabetes insipidus. IV. 2: male affected by nephrogenic diabetes insipidus and Werdnig—Hoffmann disease. ○□ investigated patients; ◐◑ data obtained from history.

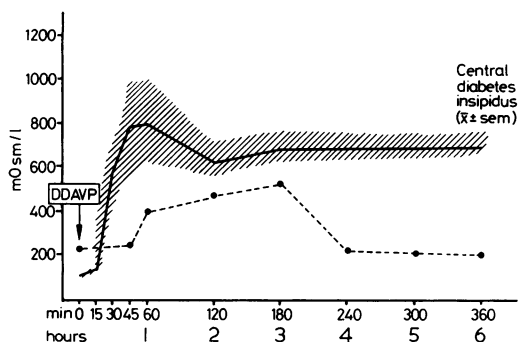


Fig. 2 Variation in urinary osmolarity after DDAVP intravenously in 10 patients with central diabetes insipidus (—) and in our patient with nephrogenic diabetes insipidus (-----).

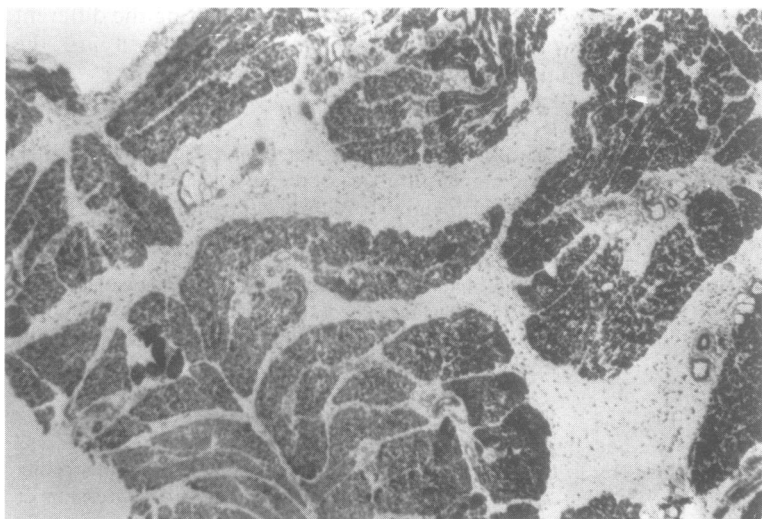
gave rise to the bell-shaped deformity of the chest; the latter showed paradoxical movement. In this condition, coughing to eliminate an accumulation of secretion was rare and weak.

There was normal function of the intrinsic and extrinsic muscles of the eye; fasciculation of the tongue; normal fundus oculi; and absence of the osteotendinous reflexes in both upper and lower limbs.

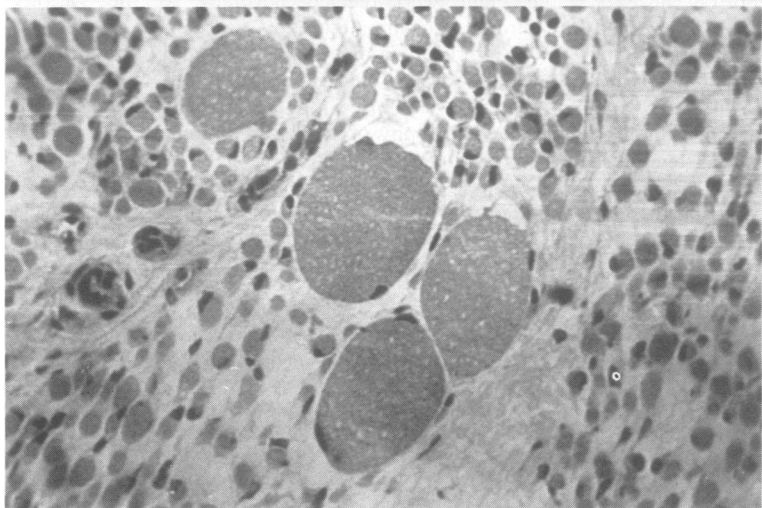
Distinct head lag occurred during the traction test, with the characteristic posture in ventral suspension. There was normal functioning of the sphincters.

LABORATORY EXAMINATION

Haemograms, erythrocyte sedimentation rate, glycaemia, BUN, plasma proteins, sodium, potassium, calcium, phosphorus, transaminases, alkaline



(a)



(b)

Fig. 3 Biopsy of muscle from left quadriceps showing infantile spinal muscular atrophy: (a) NADH-TR $\times 60$; (b) HPE $\times 200$.

phosphatases, creatine kinase, electrocardiogram, and chest and head x-ray films were all within normal limits.

The electroencephalogram showed no relevant anomaly and registered only the presence of rapid activity anteriorly.

Nephrogenic diabetes insipidus was ascertained from the clinical history of the family, by fever after dehydration, by excessive diuresis (800 to 1000 ml/24 hr) with a specific gravity of 1004, and by the DDAVP test (1-deamino 8D-arginin-vasopressin) (Fig. 2).

Werdnig-Hoffmann disease was ascertained by clinical means and by muscular biopsy, obtained from the left quadriceps muscle; the sections were stained by histological and histochemical methods (Fig. 3a, b).

Light microscopical studies showed proliferation of perimysial connective tissue and replacement of fibres by adipose tissue. The bundles showed many uniformly atrophic fibres and groups of isolated, single, rounded fibres of type I. Fibre type differentiation was impaired and atrophic fibres reacted strongly to NADH-TR and ATPase.

In conclusion the histological and histochemical pattern of denervation (large-group atrophy and scattered hypertrophic rounded fibres) substantiates the clinical diagnosis of Werdnig-Hoffmann disease.

Discussion

The finding of two genetically determined diseases is unusual in the same child: one characterised by an autosomal recessive trait, the other being X-linked recessive.

Several associations of Werdnig-Hoffmann disease with other diseases have been reported (Radu *et al.*, 1974; Meier *et al.*, 1975) but none with nephrogenic diabetes insipidus, that is with a sex-linked disease. This is clearly a casual happening, considering the different pattern of inheritance of these diseases.

Regarding nephrogenic diabetes insipidus, we agree with many authors (for example, Forsmann, 1956) on the hypothesis of an X-linked recessive inheritance, with different expression in heterozygotes, as shown in this family by the presence of mildly affected females (Fig. 1, I. 2; III. 4, 5, 9, 11).

As for Werdnig-Hoffmann disease, the proband is the only case of type I spinal muscular atrophy in the family and we cannot discriminate definitely on its hereditary nature, because such has not been proved in other members of the family. The published reports show that this disease can be transmitted with a recessive autosomal trait (Zellweger, 1971) or, more rarely (5% of the cases), with an irregular dominant autosomal trait (Zellweger *et al.*, 1972). In our case we must, however, also consider the possibility that a recent mutation occurred in the patient.

Regarding the identification of heterozygotes in nephrogenic diabetes insipidus this seems possible with the tests (Bernasconi *et al.*, 1976) carried out by us on the family, but it is not the case in Werdnig-Hoffmann disease.

In fact the attempt to show the heterozygote state by measuring the amplitude of potential of the quadriceps muscle of the mother has not been sufficiently discriminating (Emery *et al.*, 1973).

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