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Case reports

Hereditary diabetes insipidus: an immunohistochemical study of the hypothalamus and pituitary gland

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Summary. We report the histological findings in a case of hereditary diabetes insipidus (HDI) using vasopressin (VP) immunohistochemistry. The hypothalamus displayed a marked loss of magnocellular VP neurons, with preservation of the smaller cells. The neurohypophysis was severely atrophic with scanty immunoreactivity. Our results support the hypothesis that HDI results from a selective degeneration of VP neurons affecting chiefly the magnocellular elements projecting to the neurohypophysis. The sparing of the parvocellular component may reflect the projection of these neurons to non-pituitary targets.

Key words: Hereditary diabetes insipidus – Vasopressin – Neurohypophysis – Hypothalamus

Hereditary diabetes insipidus (HDI) is an uncommon disorder which has rarely been studied pathologically [1, 2, 4], and never using vasopressin (VP) immunohistochemistry. We studied the hypothalamus and the pituitary gland of one additional case using an antiserum to VP to determine the pattern of involvement of the vasopressinergic system in this disorder.

Case history

This 72-year-old man had excessive thirst and urination for as long as he can remember. Three sons and a grandson are affected by a similar disorder which has been treated successfully with antidiuretic hormone (ADH). The patient had severe cardiopulmonary disease in recent years and, because of this, has not received any antidiuretic hormone. His HDI was partially controlled with thiazide diuretics. During an 8-h fluid deprivation test, his serum osmolality rose from 282 to 295 mOs/kg and the urine osmolality rose from 148 to 182 mOs/kg. At the beginning of the test, the serum ADH level was 1.5 pg/ml, at 3 h 1.1, 5 h 1.2 and 8 h 1.4 pg/ml. Normal persons who are moderately dehydrated (serum osmolality greater than 285 mOs/kg) usually have ADH levels in the range of 4–15 pg/ml. The patient died of heart failure 5 months after the ADH studies were performed.

Material and methods

Only the hypothalamus and pituitary gland were available for examination. The hypothalamus was fixed in formalin, cut coronally, and embedded in paraffin. It was sectioned step-serially at 0.5-mm intervals over a distance of 5.5 mm, spanning the entire length of the supraoptic (SON) and paraventricular (PVN) nuclei. The hypothalamus of an age-matched male control was similarly processed and sectioned at 0.2-mm intervals. Ten matched levels were stained with cresyl violet at 0.5-mm intervals and seven matched levels were immunostained for VP using the immunoperoxidase method (overnight incubation at 4° C, 1:1000 dilution). The primary antiserum, a gift of Prof. F. A. Laszlo, University of Szeged, Hungary, was raised in rabbits against the vasopressin nonapeptide. Pre-incubation of the antiserum with VP abolished all immunoreactivity. Further characterization of the antiserum was performed by immunoblotting. Two micrograms each of VP (Peninsula) and oxytocin (Peninsula) was diluted in 10 mM HCl and applied to a polyvinylidene difluoride membrane (Millipore IPVH 151 50) in a dot-blot apparatus (BRL). The membrane was blocked using 3% bovine serum albumin (RIA grade, Sigma) in PBS, washed, and incubated overnight with the VP antiserum (1:1000) in PBS. A peroxidase-conjugated goat anti-rabbit antiserum (Cappel, no. 3612-3151) was applied for 2 h and the blot developed with 4-chloro-1-naphthol. The antiserum exhibited specific staining for VP with no cross-reactivity for oxytocin (Fig. 1). The pituitary gland in both cases was similarly processed and immunostained with VP (1:1000), neurofilament (Sanbio, 1:10), adrenocorticotropic hormone (ACTH; NIH, 1:1000), follicle-stimulating hormone (FSH;

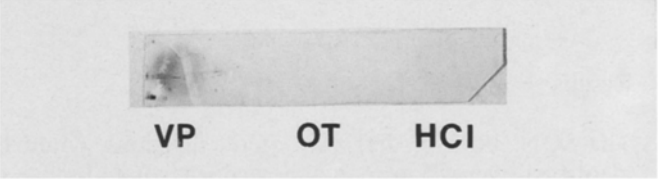

Fig. 1. On dot-blots, the vasopressin (*VP*) antiserum recognizes VP with no cross-reactivity to oxytocin (*OT*) HCl

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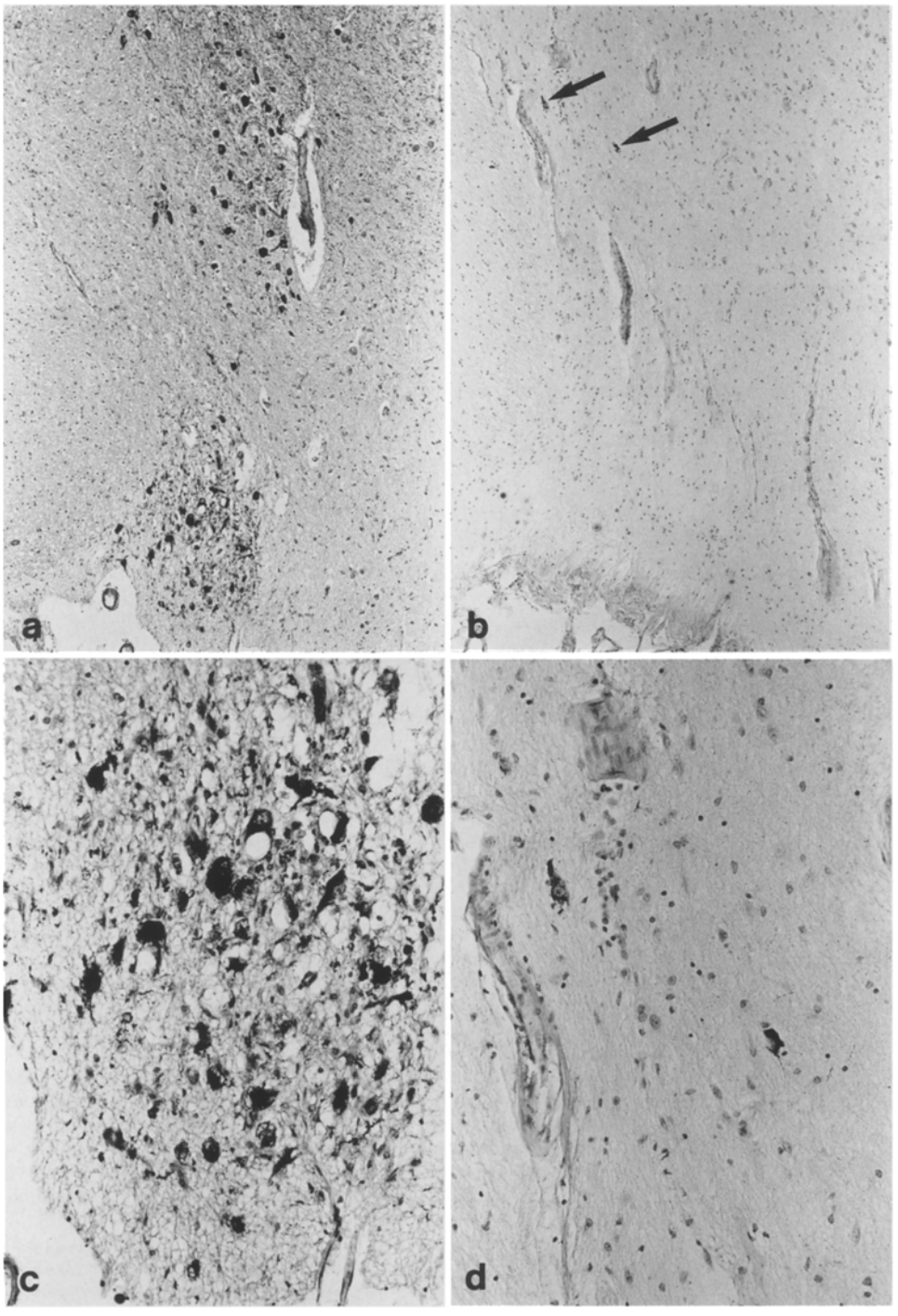

Fig. 2. Supraoptic nucleus (SON), medial portion. Severe loss of VP neurons in hereditary diabetes insipidus (HDI) (**b, d**) as compared to age-matched control (**a, c**), with only rare immunoreactive cells (*arrows*). Slight gliosis and attenuation of the capillary network is also evident (**d**). VP immunostain, **a, b** ×80, **c, d** ×250

NIH, 1:1000), thyroid-stimulating hormone (TSH; NIH, 1:4000), prolactin (gift of Dr. Friesen, University of Manitoba, 1:2000) and growth hormone (GH; Dako, 1:1500). All primary antisera were incubated 18 h at 4° C.

Results

The SON, both medial and lateral divisions, could be identified over 4.5 mm and showed a virtual absence of magnocellular neurons, slight gliosis with numerous corpora amylacea, and severe attenuation of the capillary network. Only rare immunoreactive VP magnocellular neurons were seen in either division (Fig. 2). A small cluster of parvocellular VP neurons, 12–16 μm in diameter, was observed at the medial margin of the lateral division (Fig. 3b), at the posterior limit of the optic chiasm, over approximately 0.5 mm. Examination of the control revealed similar parvocellular neurons in the same location, intermingling in part with the magnocellular VP neurons of SON and other unreactive parvocellular elements (Fig. 3a). The location of this nucleus is in keeping with that of the suprachiasmatic nucleus [3, 8]. The PVN exhibited a marked loss of VP neurons at all levels,

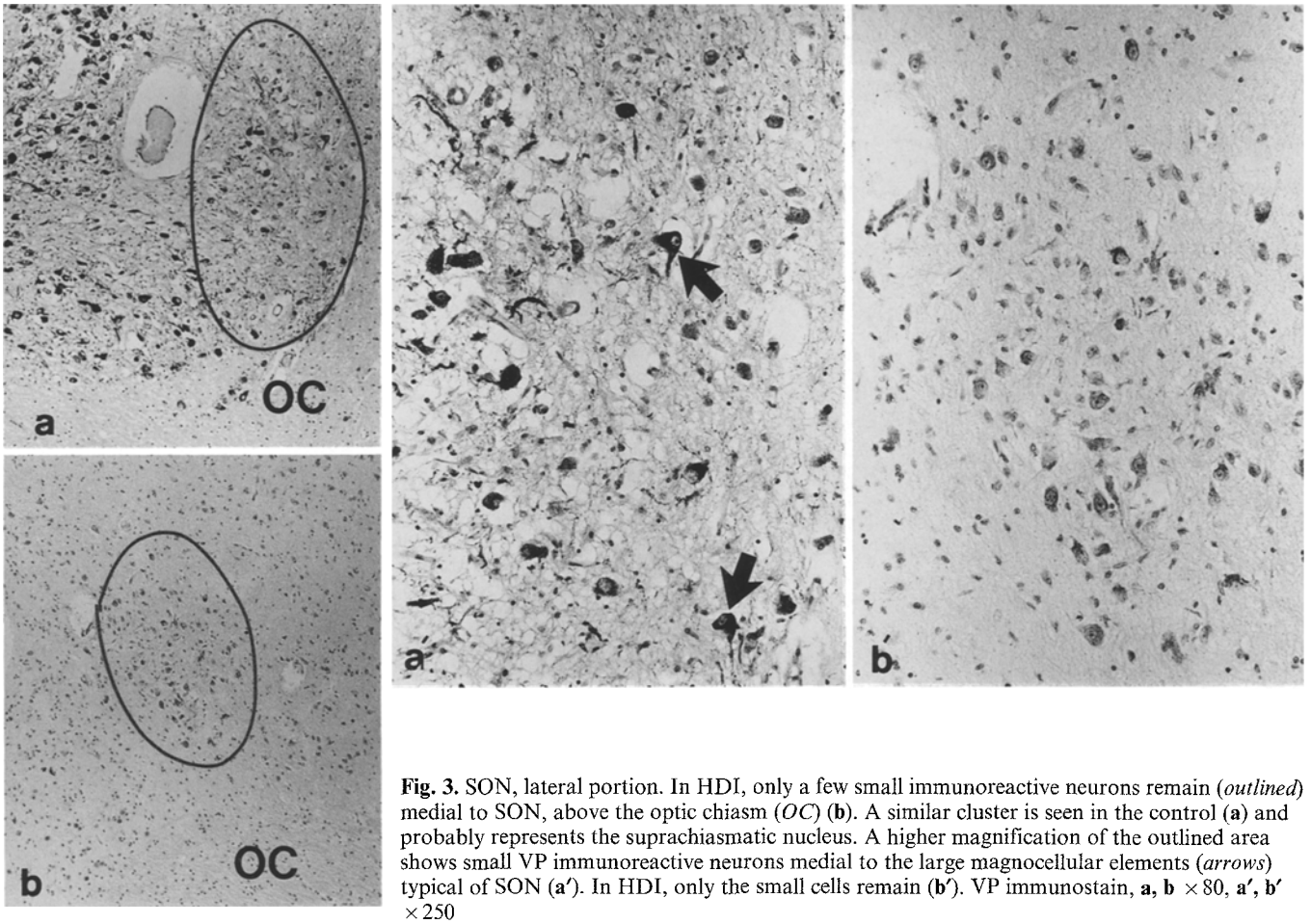

Fig. 3. SON, lateral portion. In HDI, only a few small immunoreactive neurons remain (*outlined*) medial to SON, above the optic chiasm (*OC*) (**b**). A similar cluster is seen in the control (**a**) and probably represents the suprachiasmatic nucleus. A higher magnification of the outlined area shows small VP immunoreactive neurons medial to the large magnocellular elements (*arrows*) typical of SON (**a′**). In HDI, only the small cells remain (**b′**). VP immunostain, **a, b** ×80, **a′, b′** ×250

affecting chiefly the magnocellular VP neurons with relative preservation of the parvocellular elements (Fig. 4). Non-immunoreactive magnocellular and parvocellular neurons were seen in both HDI and control PVN (Fig. 4). Scattered VP immunoreactive cells were observed between the main nuclear masses in both cases. In the control, most of these VP cells were magnocellular, with a small admixture of parvocellular elements. Single cells were seen, but small clusters were more frequent. Numerous VP projection fibers were observed between PVN and SON, as well as in the supraoptico-hypophysiary pathway. In HDI, these accessory VP cells were more often single, generally smaller, and far fewer than in the control. The VP projection fibers between the PVN and SON as well as those of the supraoptico-hypophysiary pathway were also markedly decreased. The pituitary stalk showed a dramatic decrease in the number of immunoreactive fibers in HDI, and the neurohypophysis was extremely atrophic. Neurofilament immunostaining disclosed a paucity of axons scattered among pituicytes, with only a rare immunoreactive VP profile. The anterior lobe was unremarkable, including immunostains for ACTH, GH, prolactin, TSH, luteinizing hormone (LH), and FSH.

Discussion

The histological findings in the present case are similar to those previously described in hereditary and sporadic DI [1, 2, 4], and identical to the changes seen after hypophysectomy or high-stalk section [5, 6]. VP immunostaining shows that the loss of neurons affects chiefly the magnocellular component with relative sparing of the parvocellular VP neurons, including the suprachiasmatic nucleus [4, 5]. Tracing studies in rats [7] indicate that all magnocellular VP neurons in SON, PVN and accessory nuclei project to the neurohypophysis, while the smaller elements project to non-pituitary, neural targets. Our study, therefore, supports the concept that idiopathic and hereditary DI represent a selective degeneration of the VP magnocellular system that projects to the posterior lobe of the pituitary, with sparing of the parvocellular component projecting to non-pituitary, neural targets.

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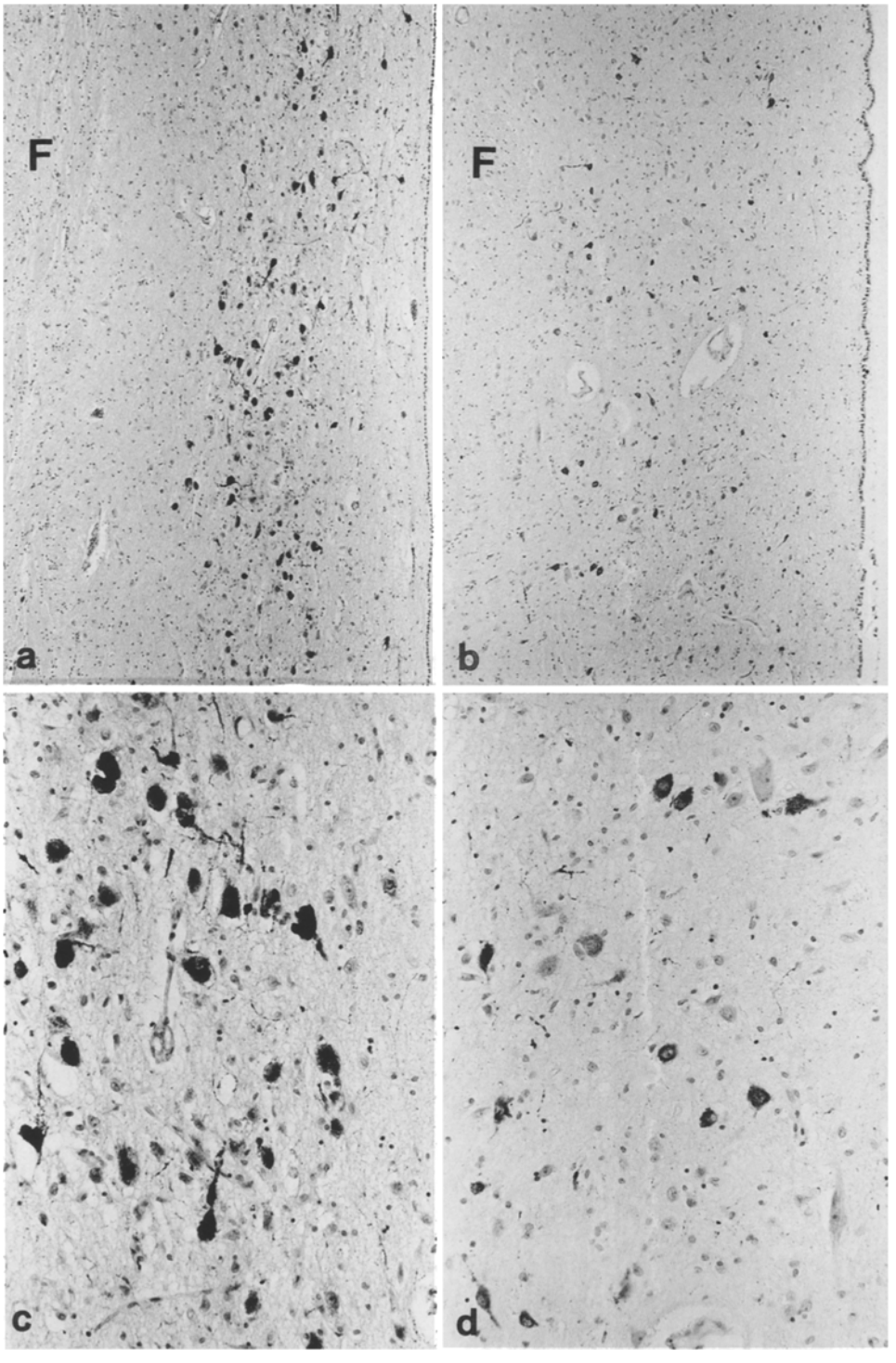

Fig. 4. The paraventricular nucleus (PVN) reveals a marked loss of immunoreactive neurons in HDI. The control (**a, c**) shows a mixture of parvo- and magnocellular VP neurons, many unreactive parvocellular elements, and rare unreactive large neurons. In HDI (**b, d**), the few residual magnocellular neurons are unreactive, and all the VP immunoreactive cells are small. Many unreactive parvocellular neurons are evident. The capillary network ist attenuated in HDI. Midportion of PVN medial to fornix (*F*). VP immunostain, **a, b** ×80, **c, d** ×250

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