Liver and pituitary abnormalities in Hallervorden-Spatz disease

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SUMMARY A 21 year old male with Hallervorden-Spatz disease was diagnosed at necropsy. Previously undescribed abnormalities of the liver and pituitary gland were noted.

Hallervorden-Spatz disease was first described in a sibship of twelve by Hallervorden and Spatz in 1922.¹ The original paper describes patients who demonstrated a range of progressive neurological defects, particularly rigidity, choreoathetosis, tremor, spasticity and dysarthria. The neuropathological features were characteristic, mainly affecting the globus pallidus and substantia nigra and consisting of abnormal accumulations of an iron-containing pigment, decreased myelin in the globus pallidus and widely distributed focal axonal swellings in pallidonigral system and brainstem. The cause of this disease is unknown but the frequent familial occurrence does suggest an inborn error of metabolism.² Patients with Hallervorden-Spatz disease may have systemic abnormalities.³ Sea-blue histiocytes, indicative of ceroid lipofuscin storage, have been reported in bone marrow and abnormal circulating lymphocytes have been described.⁴

This case report describes two previously unrecognised systemic abnormalities in Hallervorden-Spatz disease.

Case report

Clinical features

A 21 year old male presented to hospital with a deep laceration of the head after falling. He was believed to have Friedreich's ataxia and had multiple flexion deformities of his limbs. He demonstrated choreiform movements, agitation, double incontinence and was incapable of speech. He died four days after admission to an observation ward.

Previous medical history included the effects of falls and infections. He had never been seen by a neurologist and no biochemical investigations had been performed. Neurological problems had been manifest from an early age,

the diagnosis of Friedreich's ataxia being considered at the age of 3 years. Review of the case notes also showed that diagnoses of mild cerebral palsy and dystonia musculorum deformans had previously been considered. The drug history included a variety of antibiotics, various mild tranquillisers and he had also received 400 mg of chlorpromazine daily in divided doses. A female cousin had suffered similar neurological problems and had died at the age of 10 years. No further information is available on this patient. There was no apparent history of jaundice in the family.

Necropsy findings

The body was that of a young edentulous Caucasian male of weight 48 kg. The face showed evidence of both recent and previous trauma. Flexion deformities were seen at right wrist, left elbow and both ankles. There was bilateral pes cavus and the spine showed mild dorsal kyphosis with moderate scoliosis. The estimated body length was 163 cm. The skull showed a 6 cm linear fracture at the frontal crest deep to a 5 cm laceration of the forehead. Fractures were also seen at the right side of the jugum of the sphenoid bone and across the petrous part of the temporal bone on the right side. An acute bilateral subdural haemorrhage of 200 ml volume was present. The brain and spinal cord were retained intact. The liver weighed 900 g and had a dark brown colour. The heart (100 g); spleen (80 g); kidneys (each 75 g) and lungs (right 300 g, left 200 g) appeared morphologically normal, although all were of abnormally low weights. Lymphadenopathy was absent and there were no abnormalities of the gastrointestinal tract. Development of the male genital tract appeared normal for that of a 21 year old male. The pituitary was hypoplastic, measuring 5 mm transversely, 4 mm sagittally and 4 mm vertically but other endocrine organs appeared to be of normal size and shape.

Materials and methods

Blocks of tissue from the liver and other organs were fixed for 24 hours in 10% neutral buffered formalin. These were then processed routinely into paraffin wax and 5 µm sections cut and stained as follows: Haematoxylin and Eosin, Reticulin (Gordon and Sweet), van Gieson, Periodic acid-Schiff before and after diastase digestion, Perl's technique, Sudan Black, von Kossa, Congo Red, Masson-Fontana, Singh, Shikata

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and a long Ziehl-Neelsen. The pituitary gland was fixed intact for 48 hs in neutral buffered formalin and then bisected in the horizontal plane. The tissue was then processed routinely in paraffin wax and sectioned at 5 μ m. Sections were stained as follows: Haematoxylin and Eosin, Orange G-Acid Fuchsin-Green. Immunocytochemistry for anterior pituitary hormones (growth hormone, prolactin, thyroid stimulating hormone, follicle stimulating hormone, luteinising hormone and adrenocorticotrophic hormone) was performed using polyclonal antisera (Ortho Diagnostic Systems Ltd) in a peroxidase-antiperoxidase technique following trypsinisation of sections for 15 minutes. Morphometric assessment of the relative density of each hormone-secreting cell type was performed. The largest cross section of the pituitary gland in each immunostained preparation was examined on a light microscope with an eye-piece grid (total magnification $\times$ 400). The entire section was examined using the mechanical stage. The number of positive-staining cells for each hormone (indicated by dark brown cytoplasmic staining) was counted and the total number of parenchymal cells (comprising both negatively and positively staining cells) in the grid areas were counted using standard criteria.⁵⁶ The total number of parenchymal cells and the total number of immunoreactive cells per mm² for each of the antibodies employed were calculated.

The brain and spinal cord were fixed by immersion for 3 weeks in 10% neutral buffered formalin. After conventional dissection, representative blocks of tissue were processed

routinely into paraffin wax. Sections were cut at 7 μ m and stained as follows: Haematoxylin and Eosin, Cresyl Violet-Luxol Fast Blue, Luxol Fast Blue/Haematoxylin and Eosin, Periodic acid-Schiff before and after diastase digestion, Perl's technique, von Kossa, Sudan Black, and a modified Palmgren technique. Sections for immunocytochemistry were cut at 7 μ m and stained using antisera for the following: glial fibrillary acidic protein (polyclonal, Dako), neurofilament protein (200kD monoclonal, Labsystems), PGP9.5 (polyclonal, Ultraclone), gamma enolase (polyclonal, Incstar) and ubiquitin. The polyclonal antibodies were employed in a peroxidase-antiperoxidase technique while the monoclonal antibody was used in an indirect immunoperoxidase method.

Results

Microscopy of the liver showed a normal architecture with no evidence of inflammation or cholestasis. The hepatocytes demonstrated fine dust-like pigmentation (fig 1a), considerable amounts of pigment being seen in the liver cells of the perivenular zones. The pigment appeared brown on routine Haematoxylin and Eosin sections and showed the histochemical staining reactions of melanin and lipofuscin. The Perl's stain for iron was negative. Electron microscopy of the pigment

Fig 1 (a) Many hepatocytes contain a finely granular pigment in the cytoplasm. Haematoxylin and eosin $\times$ 400. (b) Ultrastructural examination of the pigment shows irregular granular material and lipid within lysosomes. $\times$ 13,500.

Fig 2 (a) Macroscopic examination of the basal ganglia reveals an area of brown discoloration in the medial segment of the globus pallidus. (b) Histology of the globus pallidus shows neuronal loss and reactive gliosis with irregular accumulations of granular pigment and large axonal spheroids (arrows). Haematoxylin and eosin $\times 280$.

showed enlarged lysosomes of irregular shape containing granular material and lipid (fig 1b). Pigment was absent from heart, smooth muscle, kidney, spleen, pancreas and lymph nodes. Histological examination of the pituitary showed no evidence of pigment deposition and no sign of infarction, haemorrhage or the effects of trauma. A normal pattern of immunostaining for anterior pituitary hormones was noted. Morphometric examination found an average of 65.34 parenchymal cells per mm^2 , of which the largest population comprised cells staining for growth hormone (34.7 cells/ mm^2). These values appear to be within the limits of normality.⁵

The fixed brain weighed 1380 g. Blood was present in the subdural space over both cerebral hemispheres and in the subarachnoid space over the occipital poles. A small recent contusion was present over the right frontal pole. There was no evidence of cerebral cortical atrophy but the cerebellar hemispheres were slightly reduced in size. Coronal slices of the cerebral hemispheres showed extensive contusions in the occipital lobes, the largest measuring $4 \times 3 \times 2$ cm. The lateral ventricles were moderately dilated. The globus pallidus appeared shrunken and exhibited a brown-

yellow discolouration, particularly in the medial segment (fig 2a). The remainder of the basal ganglia appeared normal macroscopically as did the thalamus, hypothalamus, mid-brain, pons and medulla. The substantia nigra showed no evidence of either depigmentation or discoloration and appeared normal. Slices of cerebellum showed a moderate degree of cortical atrophy but no other features of note.

Histological examination of the occipital lobes confirmed recent extensive contusions with surrounding oedema. In the globus pallidus, extensive neuronal loss was noted, accompanied by astrocytic gliosis. A brown granular pigment was present in the neuropil, particularly around blood vessels. This gave a strong staining reaction with Perl's technique and also stained positively with Periodic acid-Schiff, Sudan Black and von Kossa techniques. Swollen axonal spheroids were present in the globus pallidus (fig 2b), internal capsule and dorsal thalamus. The pars reticulata of the substantia nigra also contained axonal spheroids and exhibited a patchy loss of neurons. No Lewy bodies or any other inclusions were present and the many surviving neurons were not depigmented. A few small blood vessels in this region

Fig 3 Immunostaining for neurofilament protein shows strong labelling of axonal spheroids in the internal capsule. Indirect immunoperoxidase/haematoxylin $\times 220$.

were surrounded by a brown granular pigment similar to the pigment in the globus pallidus. Reactive gliosis was inconspicuous. The remainder of the substantia nigra was histologically unremarkable. The spheroids gave a strong staining reaction with antibodies to gamma enolase, PGP9.5, ubiquitin and neurofilament protein (fig 3). The accumulation of axonal spheroids in the basal ganglia and thalamus was accompanied by loss of mainly large neurons in these sites. The cerebral cortex was not atrophied and appeared histologically normal, with no neurofibrillary tangles, senile plaques, Lewy bodies or amyloid deposition. The neuronal population in the hippocampus and nucleus basalis of Meynert were also of unremarkable appearance. No abnormalities were identified in the white matter of the centrum semiovale, but the corticospinal pathways in the brainstem and spinal cord exhibited pallor of myelin staining with evidence of axonal loss. The neuronal population of the other main thalamic nuclei appeared normal, as did the hypothalamus. No spheroids were present in the brainstem or cerebellum. The locus coeruleus was histologically normal. The neurons in the cerebellum appeared to be of normal morphology with no evidence of axonal torpedoes. Reactive gliosis was a prominent feature in areas of neuronal loss; this was strikingly demonstrated by immunostaining for glial fibrillary acid protein, which labelled reactive astrocytes but not the axonal spheroids.

Discussion

The neuropathological features in this case indicated a diagnosis of Hallervorden-Spatz disease. The pattern of immunostaining in the spheroids is consistent with a neuronal (axonal) origin and suggests an irregular accumulation of cytoskeletal filaments in these structures.⁷ Abnormalities of the pituitary and liver do not

appear to have been described previously in this disorder.

The normal pituitary measures 13–17 mm transversely, 10–13 mm sagittally and 5–6 mm vertically.⁸ The pituitary in this case was therefore hypoplastic. There was no good clinical evidence of hypopituitarism, although this is well recognised in association with hypoplasia.⁹ Chlorpromazine, at doses similar to but predominantly greater than that received by this patient, is recognised to interfere with secretion of hormones from the anterior pituitary.¹⁰ There is no evidence that pituitary hypoplasia is a complication of chlorpromazine therapy. This patient had a brain of normal weight and an apparently normal adult male genital tract. Many of his organs, however, demonstrated splanchnomicria. While it is tempting to speculate that this splanchnomicria was linked to the pituitary hypoplasia, the true explanation is probably dietary. A similar pattern of splanchnomicria has been described in a child with infantile neuroaxonal dystrophy,¹¹ a disorder related to Hallervorden-Spatz disease.

There are a number of possible explanations for the pigment in the liver. One is that the pigment is lipofuscin, the parenchymal accumulation of which is a normal concomitant of ageing and atrophy.¹² The absence of pigment in other parenchymal organs however, is against this explanation. Chlorpromazine, in the dose taken by this patient, is recognised to be a potential source of a wide range of liver abnormalities, including lipofuscin-like pigmentation.¹³ The liver pigment in this case, however, demonstrated striking melanin-like staining. The histological, histochemical and ultrastructural features of this pigment are morphologically similar to the hepatic pigment which has been described in Dubin-Johnson syndrome.^{14 15} In the absence of overt clinical evidence of conjugated hyperbilirubinaemia and bilirubinuria this diagnosis cannot be proven in our case. The melanin-like hepatic pigment in Dubin-Johnson syndrome is also seen in the liver of mutant Corriedale sheep and is thought to be derived from certain catecholamines.¹⁶ It is interesting to note that speculation as to the aetiology of Hallervorden-Spatz disease has focused on similar catecholamines and also on their metabolite dopa.²

A derangement of dopamine metabolism can perhaps be postulated as an explanation for some of the neurological abnormalities, the pituitary hypoplasia and the hepatic pigmentation. It is recognised that patients with Hallervorden-Spatz disease may show temporary improvement when treated with dopa.^{2 17} The neuropathological features described in this case involved areas of brain recognised to include the nigro-striatal dopamine pathway;¹⁸ neurochemical analysis in a case of familial Hallervorden-Spatz disease revealed marked loss of dopamine in the nigro-

striatal areas.¹⁹ In the hypothalamo-hypophysial axis, dopamine is the primary physiological inhibitor of prolactin secretion²⁰ and is also inhibitory to other anterior pituitary functions in man.²¹ Dopa and dopamine are recognised sources for substances polymerised to form various melanins²² and could therefore be the source of the hepatic pigment.

In conclusion, this case exhibited the typical neuropathology of Hallervorden-Spatz disease. The diagnosis, which is important because of its genetic implications, was not made in life. Hepatic and pituitary abnormalities have not been previously described in this disorder and those described in this case were not accompanied by any overt clinical manifestations. Such abnormalities may be linked to an underlying metabolic defect in this disorder. Further studies are required to elucidate the metabolic and genetic cause of this uncommon inherited disorder and such studies should include investigation of tissues other than central nervous system.

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