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Anatomo-pathological findings in a case of combined deficiency of sulphite oxidase and xanthine oxidase with a defect of molybdenum cofactor

A. Roth [1], C. Nogues [2], J.P. Monnet [1], H. Ogier [3], J.M. Saudubray [3]

[1] Groupe de Pathologie Pédiatrique (PRC. Nezelof), Hôpital Necker-Enfants-Malades, 149, rue de Sèvres F-75743 Paris Cedex 15
[2] C.E.R.M.A., 26, boulevard Victor F-75015 Paris
[3] Département de Pédiatrie, Hôpital Necker-Enfants-Malades, 149, rué de Sèvres, F-75743 Paris Cedex 15, France

Summary. A case of combined deficiency of sulphite-oxidase and xanthine-oxidase with a defect of the molybdenum cofactor, which is vital to the activity of sulphite-, xanthine- and aldehyde-oxidase, is reported here. Seven cases of combined deficiencies have been described with regard to both clinical and laboratory findings. The clinical, laboratory and anatomo-pathological features and, in particular, the central nervous system lesions of the present case correspond exactly to those in the case described Rosenblum in which an isolated deficiency in sulphite-oxidase was present.

As the cerebral alterations in the present case are comparable to those described in Rosenblum's case, they probably result from the defect in sulphite-oxidase acitivity.

Key words: Cerebral lesions – Sulphite oxidase deficiency – Xanthine oxidase deficiency – Molybdenum cofactor

Introduction

Since first observed in 1978 [2], seven cases of combined sulphite- and xanthine-oxidase deficiency have been reported. This disease is the result of a defect in hepatic molybdenum cofactor activity, necessary to the functioning of sulphite-, xanthine- and aldehyde-oxidase [5].

Essentially, its clinical expression involves an encephalopathy of early onset, with microcephaly, dysmorphia, and the appearance of a pyramidal syndrome, epilepsy and ocular lens dislocation [3].

Offprint requests to: A. Roth at the above address

The diagnosis is based on laboratory findings [4, 7] of hypouricaemia combined with hypouricaciduria in contrast to an increased excretion of the oxypurines, resulting from the defect in xanthineoxidase activity. Likewise, mild sulphituria and sulphocysteinuria + taurinuria result from the defect in sulphite-oxidase activity.

At the present time, no effective treatment exists. Genetic counselling is necessary, as the inheritance pattern is autosomal recessive and antenatal diagnosis of the defect in sulphite-oxidase activity can be carried out on fetal fibroblasts [5]. However, in cases of unexplained encephalopathy, the simplest approach is to determine the urinary uric acid (uricaciduria) and the blood uric acid (uricaemia) and to check for sulphituria using a "Sulphitest" [3].

Post mortem examination of Z.K. (5833) made possible the identification of lesions analogous to those observed by W.I. Rosenblum in 1968 [6] and these lesions would appear to result more from the sulphite-oxidase deficiency than from the xanthine-oxidase, or molybdenum cofactor deficiencies.

Clinical summary

Z.K. is the first daughter of young Tunisian parents who are also first cousins. She was born following a normal pregnancy with delivery at term. Neonatal measurements and initial examination were normal. However, feeding problems and failure to gain weight rapidly developed and led to her hospitalization at the age of 2 months. At that time, facial dysmorphia, severe encephalopathy with microcephaly, a pyramidal syndrome, hypertonia with hypertonic seizures, accompanied by myoclonus as well as bilateral radial paralysis, were noted.

CAT scan revealed a ventricular enlargement with cortical and subcortical atrophy and demyelinization. Successive ophthalmological examinations showed the appearance of a bilateral ocular lens dislocation at around 10 months of age.

The child died at 35 months.

Laboratory examinations revealed severe hypo-Wriceaemia (0,01–0,02 mmol/l) (Normal = 0,12–0,35 mmol/l)-, with hypouricaciduria (0,15 mmol/l) (Normal 2–4 mmol/l), contrasting with a xanthinuria (1,07–5,6 mmol/g creatinin) and hypoxanthinuria (0,08–0,70 mmol/g creatinin) (Normal 1,2–9,1 mmol/g creatinin).

The residual activity of xanthine oxidase on erythrocytes is from 15 to 20%. In addition, a low urinary excretion of sulphate is in contrast with an increased sulphinuria. An excretion of S-sulphocysteine and thiosulphate in the serum and a peak value of S-sulphocysteine is found, corresponding to a deficiency of sulphite-oxidase. In the liver, xanthine- and sulphite-oxidase are absent, as is molybdenum cofactor activity (0,0008, ten times less than normal).

Pathological findings (5833)

1. *Macroscopic examination.* The external appearance is characterized by marked microcephaly with a narrow and very sloping forehead, retrognathia and low set ears, which are not malformed. The nose and mouth show no abnormality. There also exists a pronounced protrusion of the xiphoid process with a bilateral incurving of the rib cage, symmetrical on both sides of the sternum, giving the impression of a double «curve bracket» ({).

There is also marked scoliosis.

No other abnormalities are seen. In particular the fingers and palmar creases are normal. The child measures 75 cm, the normal height for this age being 88 cm.

Macroscopic findings concerning the visceral organs are as follows:

1) The kidneys (55 g each) are in the normal position, showing no abnormalities of the parenchyma, urinary passages or vessels. No haemorrhage, necrosis or lithiasis is seen.

2) The heart is characterized by a thickening of its wall in relation to the volume of the left ventricle. Its weight is normal for the age of the subject.

3) The liver weighs 310 g, the normal weight for this age being 400 g. No inflammatory, necrotic, cirrhotic or malformation abnormality is present.

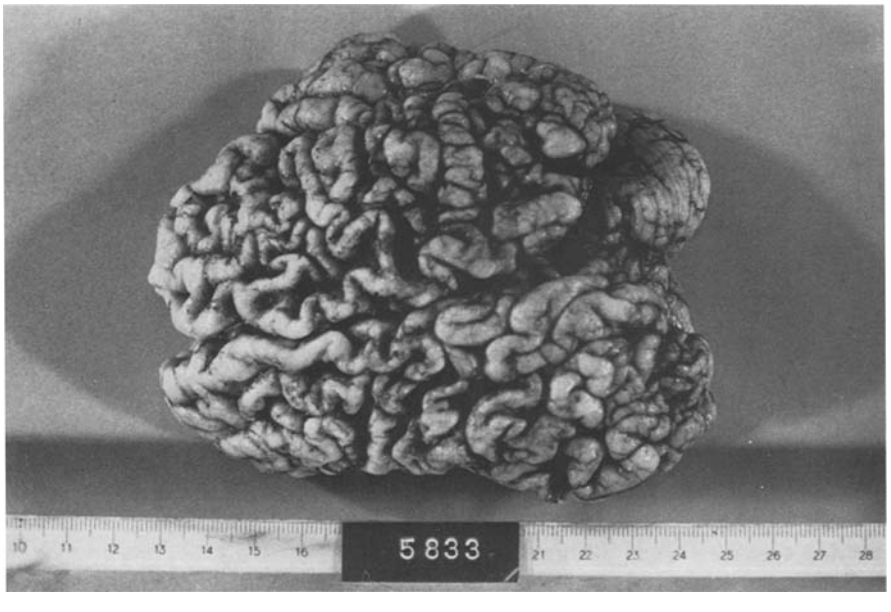

Fig. 1. Cerebral specimen showing, at the level of the convexity in particular, the narrowness of the convolutions in relation to the depth and enlargement of the sulci

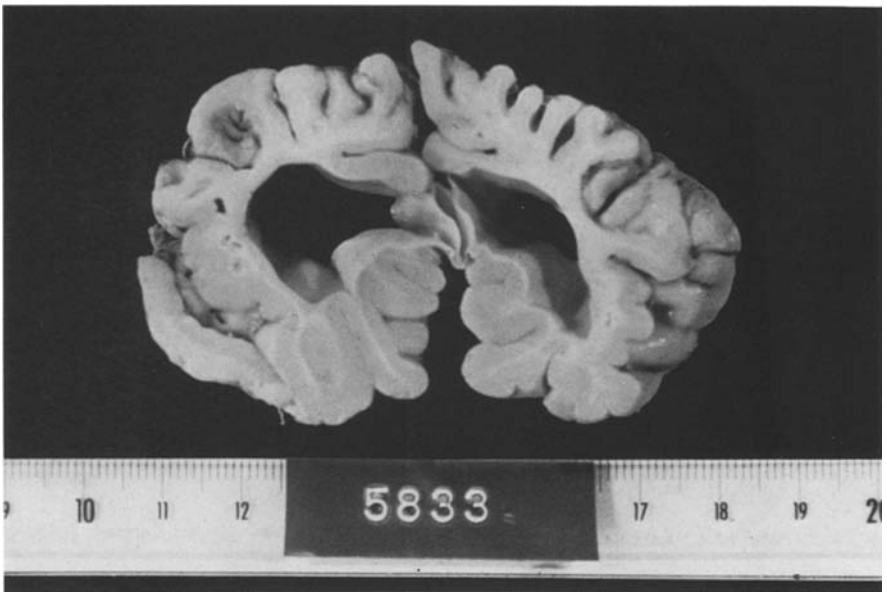

Fig. 2. Vertico-frontal section showing firstly the narrowness of the convolutions, the depth and enlargement of the sulci and, secondly, the marked bilateral ventricular enlargement

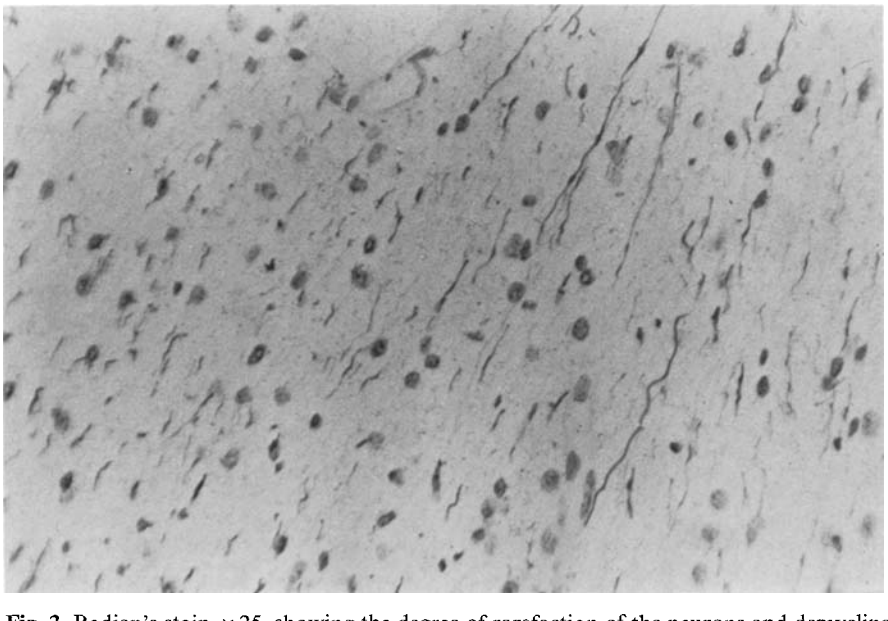

Fig. 3. Bodian's stain × 25, showing the degree of rarefaction of the neurons and demyelinated axonal fibers

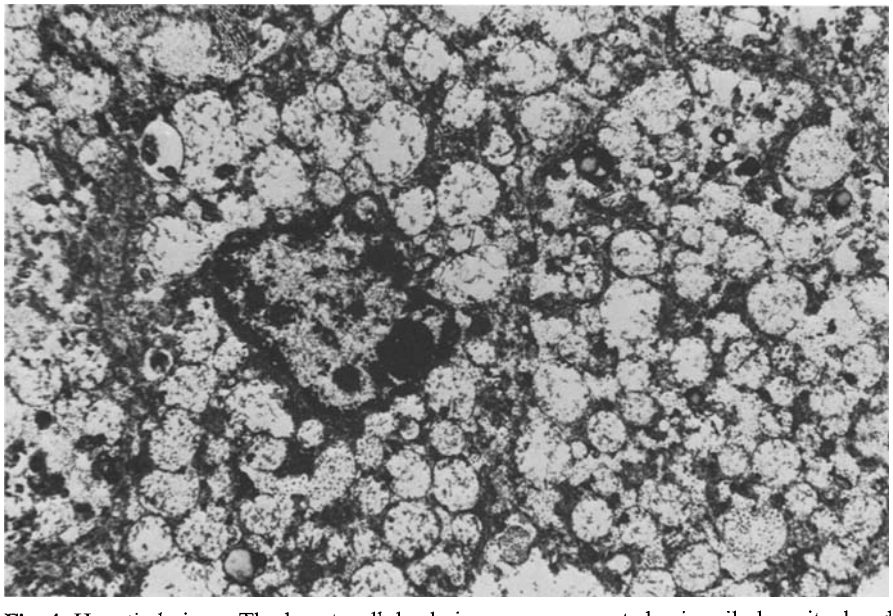

Fig. 4. Hepatic lesions: The hepatocellular lesions are represented primarily by mitochondrial changes. The mitochondria are hypertrophied with a very clear matrix and with either fragmented or, at times absent, crests. (M × 7,400)

4) The walls of the stomach and intestines are thick and whitish, with no observable lesions.

5) The *cerebrum* weighs 225 g, the cerebellum 55 g (1140 g is the normal weight for this age).

There are extensive cerebral lesions. The meninges are edematous and shiny. The cerebrum is characterized by a median biparietal depression, which gives it a scaphoid, or saddle-like, appearance. There is also an extreme microgyria with very fine, vermiform, tortuous convolutions, separated by wide and deep sulci, a change less marked in the gyri hippocampi.

The blood vessels of the base are normal.

Sections of the cerebrum, fixed in neutral formaldehyde at 10%, shows a very large, bilateral, symmetrical ventricular enlargement. No necrosis, softening, haemorrhage or tumours are seen.

In addition, zones of small cavities can be seen in the white matter, especially in the insular region, but also in the sub- and juxta-cortical regions, the gray matter and along the edges of the lateral ventricle.

The cerebellum is normal; the fourth ventricle is enlarged.

In sum there is extreme microgyria, bilateral ventricular enlargement and enlargement of the fourth ventricle, multicystic subcortical and juxta-cortical focal lesions in the white matter.

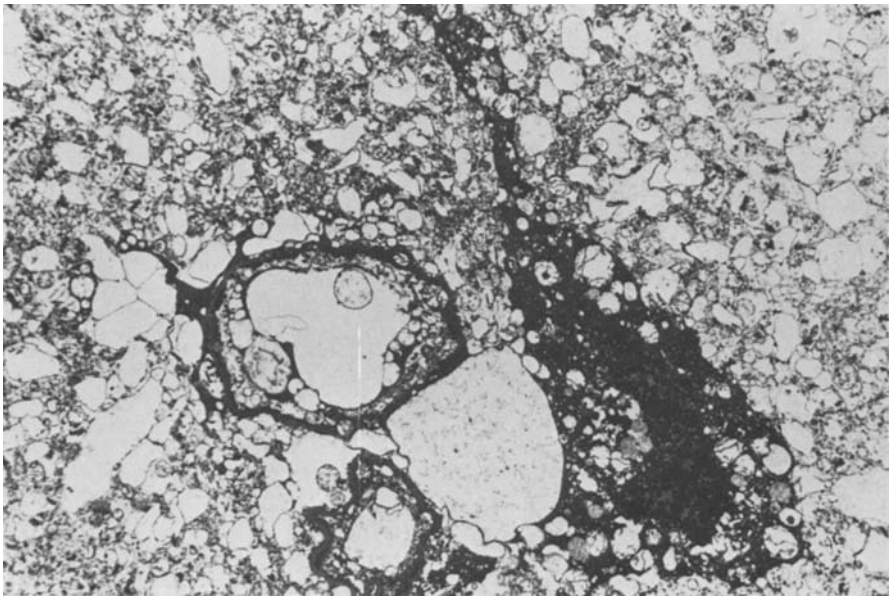

Fig. 5. Cerebral lesions: Vacuolization and edema of the processes of the astrocytic cells, localized around the capillaries and in the neuropile. The neuron is dark-colored, with a densification of the hyaloplasm and mitochondrial edema. (M × 7,400).

2. *Microscopic examination.* After fixation in formaldehyde at 10%, embedding was performed in paraffin, sectioning at 3 μ and 5 μ and staining with HES, PAS, Luxol fast blue and Bodians technique. Other cerebral samples were fixed in glutaraldehyde.

In the frontal, temporal and occipital cortex, the lesions are characterized by a marked loss of neurons, replaced by an astrocytic gliosis and accumulations of microgliocytic granular bodies.

In the deeper layers, the cortical lesions are accompanied by microcavitations and spongiosis with an essentially astrocytic granulosis and microgliocytic granular bodies. There are also some very rare foci of microcalcification. In the white matter, demyelinization is noted. Combined with a very marked axonal loss.

In the cerebellum, the scarcity of granular and Purkinje cells is noted, but no other noteworthy lesions are associated.

The other visceral samples show no significant alterations.

No karyotyping was performed.

Discussion

Molybdenum is a metal crucial to the proper functioning of the enzymes sulphite-, xanthine- and aldehyde-oxidases, all of which are present in man, and to nitrite reductase. These enzymes contain a metallic complex of an

organic nature, the molybdenum cofactor [4], a defect in the activity of which has been demonstrated in our patient.

Although an isolated deficiency in xanthine oxidase does not result in encephalopathy, an isolated deficiency in sulphite oxidase, described by Irrevere and Mudd [3], is characterized by a similar clinical picture. No observation of an isolated deficiency in aldehyde-oxidase has been reported to date.

The similarity between the lesions seen in the present case and those seen in Rosenblum's case, suggests that the clinical manifestations of combined deficiencies may be linked to the deficiency in sulphite-oxidase alone. In fact, an isolated deficiency in xanthine-oxidase can only be demonstrated by urinary lithiasis and, even then, in less than 50% of cases [1]. Comparison of the central nervous system lesions, particularly the cerebral lesions, seen in the case reported here, with the lesions described in Rosenblum's patient [6], indicates a high degree of similarity. There was massive loss of neurons and their axons, with intense demyelinization, and glial proliferation consisting of multiple, discrete, cavitary formations, located essentially in the cerebral white matter. These cavities were also observed to a lesser degree in the thalamus and cerebellum.

No architectural malformation, vascular thrombosis, necrosis, inflammation or tumour were observed in either of the two cases.

Rosenblum considere that these lesions cannot be a result of either ischaemia or acute or prolonged anoxia, nor do they correspond to the cystic encephalopathies of early childhood, leucodystrophies or Schilder's diffuse sclerosis. Deficiency in sulphite-oxidase, however, be it isolated or combined with xanthine-oxidase deficiency, produces identical central nervous system lesions-, neuron- and axon-loss, demyelinization, gliosis and cavitation of the white matter.

The lesions seen in our subject, Z.K., which bear such strong resemblance to those seen in the case of isolated sulphite-oxidase deficiency, would seem to suggest that it is this deficiency which is responsible for the cerebral lesions.

As the molybdenum cofactor does not exist in the brain there is all the more reason to incriminate the sulphite-oxidase deficiency as the only factor responsible.

Conculsion

A 35-month old child, presenting a hepatic deficiency in molybdenum cofactor activity, with deficiency in sulphite-oxidase and xanthine-oxidase activity, shows clinical and laboratory findings identical to those in the case already published in the literature.

On post mortem examination, central nervous system (cerebral) lesions were found to be identical to those of the subject who presented an isolated sulphite oxidase deficiency.

Therefore, from the standpoint of clinical, laboratory and anatomopathological findings, there are no specific lesions which make it possible

to distinguish isolated sulphite-oxidase deficiencies from combined sulphite-oxidase and xanthine-oxidase deficiencies.

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