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Familial benign copper deficiency: an old case re-examined

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Seven years follow-up and re-examinations of a boy and his mother with "familial benign copper deficiency" revealed repeatedly subnormal serum copper and normal caeruloplasmin levels with relatively good psychosomatic development in the 9-year-old index patient. ^{64}Cu-uptake was elevated in the mother's and normal in the proband's fibroblasts. The pathomechanism of the condition remained unknown, but the biochemical findings and the clinical course did not correspond to any of the previously described forms of congenital defects of copper metabolism.

In 1982 we reported on a 21-month-old boy admitted to hospital because of recurrent seizures and failure to thrive, in whom hypocupraemia with normal caeruloplasmin levels was found [4]. His serum copper level became normal and there was a significant improvement in his condition with supplemets of oral copper but as soon as these were stopped hypocupraemia and seizures resumed. Family investigations revealed decreased serum copper level with seborrhoeic skin and loss of hair in the mother and her only brother.

This report on familial benign copper deficiency has been included under the No. 12127 in McKusick's catalogue [3], and it has been commented in several personal communications and also in publications [1, 6]. The main point of criticism was the disparity between the low serum copper and normal caeruloplasmin levels. Considering the comments, it seems worthwhile to report on observations made after the original publication.

Caeruloplasmin determinations

To exclude possible analytical errors, parallel examinations were carried out with our immuno-diffusion method and with an enzymatic method [5]. Slightly higher values were obtained by the latter but consequently normal levels were measured in both the proband and his mother.

^{64}Cu-uptake of fibroblasts

In 1983 and in 1985 skin biopsies of the index patient and of his mother were tested at the John F Kennedy Institute, Glostrup/Denmark. Abnor-

mal uptake values (29.7—37.0 ng ^{64}Cu per mg protein per 20 h) were observed in four out of five cultures from both biopsies of the mother. (Controls, 95% limits: 11.1—26.7 ng ^{64}Cu per mg protein per 20 h). For the proband one skin biopsy gave uptake values of 12.2—37.9 and the second biopsy resulted in values of 20.1—24.5 ng ^{64}Cu per mg protein per 20 h. (Matched controls, 95% limits: 9.0—33.3 ng ^{64}Cu per mg protein per 20 h). The marginal increase observed in the first biopsy was thus not seen in the second one.

Clinical course

Until September 1982 supplement of 7.5 mg elementary copper per 24 h kept the serum copper level of the child normal, and he had no neurological or dermatological symptoms. Then the mother stopped supplementation and the proband's blood copper level decreased to 4.4 μmol/l within 12 days, and he became hypotonic and seborrhoeic. After restoring the supplementation his copper level increased to the normal range and his complaints disappeared.

Between 1983 and 1985 the cooperation of the family diminished. However, they permitted skin biopsies for isotope-investigations. During these years both the child and his mother received copper supplementation at irregular intervals and dosage. The child was symptomless, thrived well, the mother's hair loss was moderate.

For the next two years we lost sight of them, and the proband was seen again in June 1987, when he visited his brother hospitalized for an accident. At this occasion only his serum copper level was determined, which proved to be extremely low, 2.6 μmol/l. Therefore the child was recalled and he and his mother were re-examined on 24th August 1987.

The *9-year-old child* had received no copper supplements for the last two years, and had no seizures or other neurological symptoms. His weight was 23.0 kg, his height was 126 cm, both between the 10th and 25th centiles of the local growth chart. His intelligence could not be tested but according to the mother's oral information he had had slight learning and behavioural difficulties. At physical examination seborrhoeic face and blond curly hair was noticed but no other pathological signs were seen. Lacking permission for a more detailed examination, only the following biochemical tests could be performed:

Hb 11.2 g/dl, haematocrit 38%, WBC 7.9×10^9/l, serum bilirubin 10 μmol/l, GOT 11 U/l, GPT 4 U/l, serum iron 9.0 μmol/l, TIBC 69.5 μmol/l. The serum copper concentration was low, 10.0 μmol/l, the caeruloplasmin level was in the lower normal range, 0.31 g/l. Normal levels in our laboratory: serum copper 12.5—20.0 μmol/l (atomic absorption spectrophotometry), caeruloplasmin 0.30—0.56 g/l (radial immunodiffusion).

At the same time, the *mother* was symptomless except for seborrhoea and very thin hair. She had normal haematological and liver function val-

ues, her serum copper levels were 12.2 and 8.9 μmol/l, caeruloplasmin 0.36 and 0.32 g/l at repeated examinations.

Conclusions

Because of laboratory limitations and poor cooperation of the family, the investigation could not be completed. In spite of the difficulties some conclusions may be drawn:

1. Analytical errors in caeruloplasmin measurement can be ruled out. We have not been able to characterize the caeruloplasmin or determine its copper content. Therefore we still do not know an explanation for the discrepancy between low copper and normal caeruloplasmin levels; we can only speculate on the existence of a mutant caeruloplasmin, an excess of an apocaeruloplasmin with an unusual structure.

2. The normal ^{64}Cu-uptake in the proband and the elevated one in his mother are certainly puzzling. However, they refer to a somehow altered copper metabolism in the family examined. This also suggests that the copper deficiency cannot be merely due to a mutant caeruloplasmin.

3. The natural course of the disease obviously differs from that of Menkes's or "pseudo-Menkes's" syndrome. Instead of deterioration, in our patient improvement of the general condition with age was observed, and his copper deficiency responded well to supplementation. This confirms the assumption that a familial benign copper deficiency exists. The mechanism of this condition is not understood, but it differs from the hitherto described forms of congenital disorders of copper metabolism. How far it is related to the sporadic cases in which copper therapy proved to be beneficial [2], and personal communications by A. M. Gerdes and WG Sherwood to T Tønnesen) can not be judged from the data available for us.

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