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Abstract

The distribution of copper among the organs of an aborted, male foetus, expected to develop Menkes' syndrome, was entirely different from the distribution in three normal foetuses. Copper concentrations determined by neutron activation analysis showed a considerably reduced content in the liver, but increased concentrations in the other organs analysed; total foetal copper was probably norm

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INTRODUCTION

The kinky hair syndrome described by Menkes et al. (1) is an X-linked neurodegenerative disorder, leading to death in early childhood.
The genetic defect was shown by Danks et al. (2) to be associated with abnormal metabolism of copper, and very low levels of serum copper, ceruloplasmin, and liver copper were reported for 7 males with ages ranging from 4 to 28 months.

Oral administration of copper failed to correct the serum copper levels, but high concentrations were found in biopsies of duodenal mucosa more than four weeks later (3). Intramuscular injection of copper-EDTA, as well as intravenous administration of copper-albumen complex, were in some cases (4) effective in raising serum copper and ceruloplasmin levels to normal, but failed to stop the progression of the disease.

The characteristic symptoms are in agreement with those of animals suffering from copper deficiency, but with few exceptions these symptoms are not observed until the second or third month after birth.

These findings indicate a postnatal disturbance in the transport mechanisms of copper ions (5), with intestinal malabsorption and consequent deprivation of copper as the basic defect leading to Menkes' syndrome (3).

Recently the adequacy of this mechanism was questioned by Møllekær (6), reporting typical signs of Menkes' syndrome in a neonate.

Until now no investigations of the copper status of children with Menkes' disease have been made in the period preceding the onset of characteristic symptoms. During gestation intestinal absorption is not active, and there are no reports on abnormal foetal development. Prenatal myelination is also normal (5), and the supply of copper-albumin complex from maternal blood across the placental barrier should thus be adequate.

FOETAL COPPER DISTRIBUTION

We now report the abnormal distribution of copper in a foetus, expected to develop Menkes' syndrome, demonstrating a prenatal defect in the transport of copper.

The case concerns a pregnant woman, 25 years of age, who had previously given birth to two sons with Menkes' syndrome, and is therefore a carrier of this X-linked genetic defect. Amniocentesis was performed, and chromosomal analysis of cultured cells proved the foetus to be male. The defect proper cannot be diagnosed by chromosomal analysis, but with only an even chance of a normal infant it was decided to terminate her pregnancy in the 18th week of gestation.

The weight of the foetus was 200 gram, and the autopsy revealed no macroscopical or microscopical abnormalities. Copper was determined along with other trace elements by neutron activation analysis (7) on samples of 0.5 to 1 gram wet weight.

Results are presented in Table 1 for the foetus in question as well as for three controls with foetal ages of from 15-21 weeks.

DISCUSSION

Our control values for copper in liver are in acceptable agreement with other recent determinations (8); for the remaining organs our values can only be compared with those of Fazekas et al. (9). In a very comprehensive study of the copper distribution in 109 foetuses, they found that the liver invariably showed the highest values, and the brain lower than the other organs chosen in the present study. No distinction between the other organs was possible, and a large fraction of their results was at or below the detection limit of a few parts per million. This distribution is in qualitative agreement with our controls, but with the exception of the liver our actual results for the organs are significantly lower than previously reported.

The results for the foetus suspected of Menkes' disease, however, are significantly higher than previously reported (9) for the organs: kidney, spleen, pancreas, and placenta. The distribution of copper in the foetus is therefore significantly different from the distribution in the controls.

Table 1

Concentrations of copper in foetal organs in µg/g wet tissue

Organ	Menkes foetus	Controls		
	M	M	M	F
Placenta	14.5	2.24	0.76	0.84
Brain	1.04	0.52	0.39	0.35
Lung	1.84	0.57	0.52	0.51
Muscle and Skin	2.57	1.02	-	0.45
Spleen	15.4	1.15	0.62	0.74
Kidney	17.3	1.14	0.74	0.80
Pancreas	15.3	1.60	1.33	1.74
Extra-hepatic *	2.48	0.68	(0.53)	0.44
Liver	11.8	34.1	29.5	37.9

* Weighted average of the above 6 results, assuming identical body composition in all cases

With an assumed, average body composition of the controls, as well as of the subject foetus, the organs analyzed represent about 60% of the total weight of the foetus, and their total content of copper is just as high in the subject foetus as in the controls. Thus no indication of copper deficiency is found, and in addition, serum copper of the carrier mother was 2.6 µg/ml, which is just as high as values reported for late, normal pregnancy (10). This supports the assumption that the supply of copper to the foetus by placental transport is normal in all cases.

The abnormal distribution in the foetus suspected of Menkes' disease is characterised by a much lower fraction of total copper found in the liver: 25% compared with 80 ± 5% in the controls. It is conceivable that this extra-hepatic store can be used to maintain normal development of the infant for a limited period after birth.

With a normal supply of copper from the mother, the high concentration in the placenta and, in particular, the predominantly extra-hepatic storage of copper in the foetus indicate that the assumed defective, intestinal transport is only a secondary effect in Menkes' syndrome. A more fundamental metabolic defect must be found that also affects the transport of copper in utero.

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