HEPATOLENTICULAR DEGENERATION: IRON AND COPPER CONTENTS OF TISSUES OF AUTOPSY MATERIAL

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The natural history of hepatolenticular degeneration has been summarized by Canelas et al.[6]. The exuberant symptomatology is justified by the accumulation of copper in several tissues and organs disordering their functions, leading to this quite simple definition[2]: "Wilson's disease: an inborn error of metabolism with multiple manifestations". Diagnosis is made by absence of ceruloplasmin in the blood serum and by the presence of the Kayser-Fleischer ring in the Descemet membrane. Treatment at the present time consists in the administration of penicillamine, adjusting the doses such as to elimination of about 1 mg copper in the urine of 24 hours.

In the present paper the contents of copper and iron of several tissues of one patient with hepatolenticular degeneration were determined.

MATERIAL AND METHODS

In the case under consideration the patient (F.N.P., male, 26 years old, Brazilian, white, from the rural zone of the Paraná State, file card N.º 721.168) presented involuntary movements of the upper and lower limbs, increasing during emotional excitation, alterations of the swallowing process and also of audition, as well as difficulties in answering questions and alterations of writing. Physical examination indicated an height of 1.80 m, weight of 78 kg, arterial pressure 12 × 8.5, pulse 82, temperature 36ºC — in short, fairly good general conditions. The liver and spleen could not be palpable, and the lungs were apparently normal. A discrete systolic murmur was heard at the pulmonary area. Laboratory examination presented blood values in the range of normality for sodium, potassium, chloride, calcium, phosphorus, alkaline reserve, urea, glucose, mucoproteins, albumine, anti-streptolysin 0 and blood count; however *cholesterol* (160 mg/100 ml), *alkaline phosphatase* (1.4 Bodansky unit/100 ml) and *uric acid* (2.3 mg/100 ml) presented levels below normal, while *glutamic-oxalacetic* and *pyruvic transaminases* (125 and 50 Reitel-Frankel unit/ml) levels were increased. *Sedimentation rate* was 35 mm in the first hour. *Hanger test* with 4 crosses, *Kunkel test* with 15 units, *thymol test* with 5 units, *Weltman test* flo-

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culating in the 5th tube, while te *creatinine* concentration was 1.7 mg/100 ml. *Albuminuria* was of 1.12 g/liter. These results indicated alteration in hepatic function, albuminuria, hypouricemia, and disturbances in sedimentation rate. The cerebrospinal fluid did not present any abnormalities. Ophtalmological examination with slit-lamp revealed the presence of bilateral Kayser-Fleisher ring and laboratory tests showed *absence of ceruloplasmin* in the blood serum as well as *hypocupremia* (28 μg/100 ml). The resulting diagnosis was hepatolenticular degeneration. In the infirmary the patient presented aggressive behavior, being treated with Gardenal and Amplictil. The specific treatment for Wilson disease was started with 1 g D-penicillamine per day and a diet poor in copper. In the 3rd day he had high temperature (39ºC), arthralgies, dyspnea, and was apathetic, the above treatment being then interrupted. He died two days later due to bronchopneumonia, which seems to be a common cause of death in patients with Wilson's disease.

During autopsy samples of tissues were collected for copper determination by diethyldithiocarbamate method (De Jorge et al.[9]), and for iron determination by tiocyanate method (Wong[27]). The autopsy was made at the Faculty of Medicine of the Santa Casa de Misericórdia, São Paulo, and the samples were collected by Prof. O. J. Aidar.

RESULTS

The results are summarized in tables 1 and 2.

DISCUSSION

The neurological symptoms corresponded to a case in the 2nd grade of Goldstein (Goldstein et al.[12]). Hypocupremia, absence of ceruloplasmin, hypouricocemia, Kayser-Fleisher ring, disturbances of hepatic function and albuminuria found in this patient are symptoms usually described in Wilson disease. He also had psychiatric symptoms, fairly common in such patients (Galvão-Bueno et al.[11]). Urinary copper excretion of 865 μg/day increased after the administration of penicillamine to 3.389 μg in the 2nd day.

Copper concentrations were increased in all tissues, the highest levels being found in globus pallidus, liver, putamen, amygdaloid nucleus, thalamus, adrenal gland, nucleus caudatus and lungs. Iron contents were very high in almost all of the studied tissues, especially in spleen, liver, lungs, globus pallidus, abdominal ganglia and putamen.

The accumulation of copper and iron in several tissues may justify some of the clinical and laboratorial findings at the time when the patient was examined, as for instance hepatic disturbances (André[1], Bearn et al.[3], Bickel et al.[4], Bush et al.[5], Scheinberg and Sternlieb[21], Taylor et al.[23]). Albuminuria has already been referred by several investigators (Bearn et al.[3], Bickel et al.[4], Cartwright et al.[7]).

The aggravation of the illness with fulminating course after administration of medicines for copper chelation has been described by Hollister et al.[17], and it is likely that this may have happened in our patient.

Material	Water g/100 g	Iron (mg/100 g) fresh weight		Iron (mg/100 g) dry weight
		Patient	Normal values	Patient
Tongue	76.89	2.61	3.4 — 5.9[22]	11.29
Stomach	80.63	3.38	1.6 — 8.0[22]	17.45
Large intestine	82.24	0.74		4.16
Small intestine	67.02	1.50		4.54
Gall bladder	85.20	1.73		11.68
Submaxillary gl.	80.76	2.65		13.77
Lung	81.67	15.32	2.0 — 2.2[7]	83.57
Diaphragm	80.89	2.29		12.04
Aorta	75.97	0.99		4.11
Heart	78.61	4.35		20.34
Spleen	76.83	30.95	28[7]	133.58
Liver	73.02	32.66	13.4[7]	121.07
Pancreas	76.07	6.90	1.6[22]	30.02
Left kidney	83.31	5.30	4.0[7]	31.75
Right kidney	80.42	6.66		34.01
Suprarenal gl.	74.25	6.77		26.28
Prostat gl.	80.76	1.12		5.82
Abdominal gang.	77.26	10.67		46.91
Thyroid gl.	76.32	3.19		13.47
Urinary bladder	79.19	1.50		7.20
Psoas muscle	76.72	3.48	2.5 — 3.0[7]	16.49
Skin	47.41	2.06		3.91
Thoracic vertebra	60.65	9.48	10.3 — 16.1[7]	24.08
Superior frontal gyr.	83.18	4.24		25.20
Superior temporal gyr.	81.58	2.95		16.01
Semi-oval center	68.79	4.44		14.22
Amygdaloid nucl.	81.43	3.41		18.36
Putamen	80.98	7.92		38.32
Insula	83.17	3.02		17.94
Globus pallidus	78.81	14.71		69.41
Thalamus	79.89	5.14		25.56
Cervical spinal cord	74.45	1.34		5.24
Sciatic nerve	42.95	1.39	5.1[22]	2.75

Table 1 — Iron content in tissues of the patient F.N.P. (Wilson's disease) as compared to normal values.

The findings of Holbrook [16] should also be considered, namely, that tranquilizer drugs may increase cupremia and the amount of copper in tissues of the brain of guinea pigs. In the present case, these drugs were administrated to the patient before the treatment with penicillamine was started.

In conclusion, the illness was aggravated, ending with death of the patient, after treatment with penicillamine was started. Copper and iron contents were increased in all the tissues studied, with greater accumulation in parts of brain, liver, lungs and suprarenal gland.

Material	Copper (μg/100 g) fresh weight		Copper (μg/100 g) dry weight	
	Patient	Normal values	Patient	Normal values
Tongue	478		2068	
Stomach	1808		9332	1200[4], 1980[18]
Large intestine	452		2546	1300[4]
Small intestine	711		2155	1800[4]
Gall bladder	1633		11034	
Submaxillary gl.	813		4225	1430[8]
Lung	6875		37503	1700[4], 1400[7]
Diaphragm	832		4376	
Aorta	582		2421	
Heart	2350	340[7], 320[15]	10988	2200[4], 3100[18]
Spleen	5089	120[7], 116 — 216[24]	21964	1500[4], 900[14]
Liver	28608	1660[6], 510 — 2280[24]	106049	4400[4], 5920[6]
Pancreas	1592	600[6], 220 — 379[24]	6928	850[6], 1220[18]
Left kidney	1376	220[15], 200 — 400[7]	8243	1400[4], 3090[18]
Right kidney	1565		7992	
Suprarenal gl.	11390	150[19]	44227	700[4], 420[21]
Prostat gl.	460		2390	
Abdominal gang.	3405		14971	
Thyroid gl.	701		2961	
Urinary bladder	470		1258	
Psoas muscle	1154	90[15]	4956	640 — 1300[7]
Skin	1145	125[20]	2177	451[20]
Nails	1390		1579	900[6], 531[28]
Hairs	1620		1783	1500[6], 786[29]
Cerumen	17430	2430[10]	20637	
Thoracic vertebra	238		604	650[7], 450[18]
Superior frontal gyr.	5823	430[6]	34617	2620[25]
Superior temporal gyr.	4492	540 — 800[6]	24387	1400 — 2660[6]
Semi-oval center	3144		10073	
Amygdaloid nucl.	10884		58610	
Putamen	17695		93022	3290[25]
Insula	5883		34956	
Globus pallidus	24800	1300[13]	117031	3030[25], 4310[13]
Thalamus	9735	560[13]	48412	1600[25], 2490[13]
Nucleus caudatus	7314	640[13]	42545	3000[4], 3370[13]
Cervical spinal cord	2057	170[16]	8049	850[25], 900[4]
Meninges	1144		4813	
Sciatic nerve	439		869	220[25]

Table 2 — Copper contents in tissues of the patient F.N.P. (Wilson's disease) as compared to normal values.

SUMMARY

Hepatolenticular degeneration: iron and copper contents of tissues of autopsy material.

Iron and copper contents in tissues of one patient with hepatolenticular degeneration, with fulminating course, are reported. It seems that

the disease's course was aggravated by tranquilizer drugs, when treatment with penicillamine was started. This observation may be of clinical interest. Copper and iron contents were increased in the brain tissues, in the liver, lungs, kidneys, spleen, suprarenal gland and in other organs.

RESUMO

Degeneração hepatolenticular: conteúdos de ferro e cobre em tecidos de material de autópsia.

Os autores apresentam os resultados das dosagens de ferro e cobre nos tecidos de um paciente com degeneração hepatolenticular, no qual a moléstia teve curso fulminante. Parece que o curso da moléstia foi agravado pela administração de drogas tranqüilizantes quando foi iniciado o tratamento com penicilamina. Esta observação pode ser de interêsse clínico. Os teores de cobre e ferro estavam muito aumentados nos tecidos cerebrais, no fígado, nos pulmões, nos rins, no baço, na suprarenal e em outros órgãos.

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