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Research Article

Childhood Onset Hypoceruloplasminemia Presenting as Early-Onset Cerebellar Ataxia

Adel F Hashish[1], Ayman Kilany[1], Shora Y Darwish[2], Hanaa M Rashad[3], Ehab R Abdelraouf[1], Suzette helal[1]

[1]National Research Centre, Research on Children with Special Needs Department, Giza, Cairo, Egypt.
[2]Al-Azhar University, Departement of Neurology, Cairo.
[3]Neurophysiology Department, Cairo university.

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ABSTRACT

The syndrome of hypoceruloplasminemia is a rare autosomal recessive disorder presenting mainly with neurogegeneration, retinal degeneration, and diabetes mellitus. The syndrome, to the best of our knowledge, is not yet recognized in pediatric age group. We screened cases presenting with unexplained cerebellar ataxia and anemia using serum ceruloplasmin, transferrin saturation, and ferritin as biomarkers for hypoceruloplasminemia. An age and sex matched control group was included. Thirty cases (age range 4–17 years) (18 male and 12 female) have been included. The results showed a statistically significant low serum ceruloplasmin and transferrin saturation (18.9±12.1mg/dl and 10.1±5.1%, respectively), and high serum ferritin (124.7±65.7 ng/ml) compared to control group. Four cases have retinal degeneration. The detection of low serum ceruloplasmin concentration and transferrin saturation with high serum ferritin in patients with unexplained cerebellar ataxia is highly suspicious of hypocerluplasminemia which should be subjected for further molecular study.

Keywords: ceruloplasmin - transferrin saturation – ferritin - cerebellar ataxia.

INTRODUCTION

Hypoceruloplasminemia or aceruloplasminemia (aCP) is a rare autosomal recessive disease in which a mutation in ceruloplasmin (CP) gene results in a defect or dysfunction of CP. The disease has been described in adults since 1987 with the triad of early onset diabetes mellitus (DM), retinal degeneration (RD), and neurodegeneration. The pathological hall mark of the disease is iron accumulation in the brain, retina, liver, and spleen[1]. CP is a copper oxidase which contains almost 95% of the serum copper in human. There are two forms of this protein, the serum and the glycosylphosphatidylinositol (GPI) linked form, the latter being the form expressed in the brain. In the normal brain the serum form does not cross the blood-brain barrier while the GPI-linked form binds to astrocytes. Its main function is to transport iron out, from the astrocytes to capillaries, where it binds to ferritin and joins the blood stream[2,3]. The onset of aCP in the adult form of the disease ranges from 30 to 55 years with anemia (80%), RD (76%), and DM in (70%) of cases. Neurological symptoms present in 68% of cases in the form of ataxia (71%), abnormal movement (64%), parkinsonism (20%), and cognitive dysfunction in 60% of cases, rendering it the only iron-overload syndrome that involves both the systemic and brain iron metabolism. The neurological manifestations appear to be corresponding to the specific regions of brain iron accumulation, generally appearing after the fourth decade of life[3]. The prevalence of aCP is about one per 2000,000, however heterozygote for CP gene was estimated to affect 0.1% of patients with DM in Japan[4]. To the best of our knowledge, the syndrome of hypoceruloplasminemia has not described in children. Here we report the possibility of using 1) a high serum ferrtin concentration accompanied by 2) low ceruloplasmin and transferrin saturation[5], to describe a new syndrome of hypoceruloplasminemia in cases presenting with ataxia in pediatric age group.

SUBJECTS AND METHODS

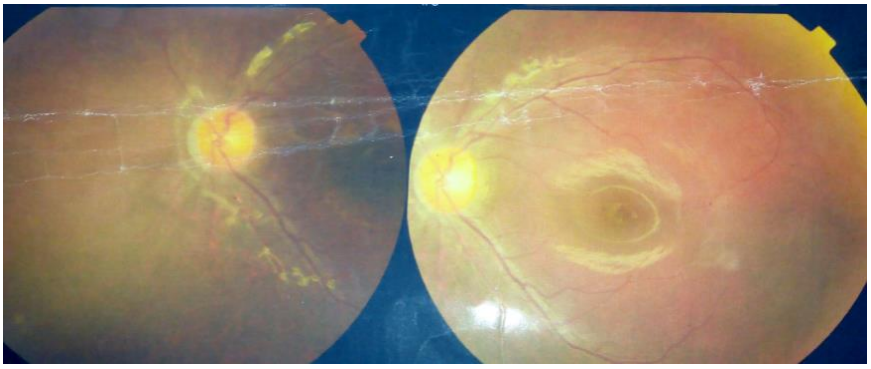
Subjects

The local ethical committee of National Research Center approved the study and a legal written consent was obtained from the parents of all cases and controls. This study included 30 children and adolescents presenting mainly with cerebellar ataxia (age range 4–17 years) in whom the diagnosis was based on clinical assessment by three expert pediatric neurologists. The patients (18 male and 12 female) were recruited randomly from those attending the outpatient clinic, Department of Research on Children with Special Needs, of National Research Center. Thirty clinically healthy children with no history suggesting any medical, neurological, or psychiatric disorders were included as the control group. They were selected from the same population and age group to which the patients belonged.

Exclusion criteria

Patients with evident perinatal insult (e.g. ataxic cerebral palsy), established metabolic disorder, CNS malformation,

**Author for Correspondence: aladelomar@gmail.com*



A B

Figure 1: Fundus photographs of affected cases showing retinal and subretinal lesions in A and B in addition to retinal degeneration in B.

Table 1: Characteristics of patients and control groups.

	case	control	test	p
Age	8.5±6.9	8.2±6.4	Z	0.9 (NS)
Sex	12 male 18 female	10 male 20 female	$\chi 2$	0.46 (NS)
Consanguinity	17 cases	None		
Family history	8 cases			

NS=Non-significant.

major dysmorphism, and those with neurologic association suggestive of specific heredofamilial ataxia (e.g. Freidrich ataxia (FA) or autosomal dominant spinocereblellar ataxia (SCA)) were excluded. Ataxia due to vitamin E deficiency and cases with gross abnormality on brain MRI suggestive of alternative diagnosis was excluded.

Methods

All cases were subjected to full clinical neurological evaluation including: Age at onset and course of ataxia. Associated neurologic symptoms. Family history of same disorder. Thorough general examination including simple anthropometric measures (weight, height, and head circumference). Detailed neurological examination. Ophthalmological assessment was carried by direct ophthalmoscopy examination. Magnetic Resonance Imaging (MRI) study of the brain was done to all cases using routine protocol.

Serum biomarkers analysis

Measurement of serum levels of Ferriten, Transferrin, Iron, total iron binding capacity (TIBC), Transferrin saturation, Ceruloplasmin, and Copper were carried out using commercial Enzyme Linked Immunosorbent Assay technique (ELISA) following the manufacturer's instructions. Blood was drawn from patients at the clinic and from the healthy control group during routine follow up of school children. The samples were left to clot and sera were separated and stored at -70 °C until assay. Serum samples were assayed in duplicate.

Statistical methods

Data were analyzed using SPSS computer package version 20 (SPSS, Chicago, IL, USA). Data are presented as mean± SD for normally distributed data. Student's t-test was used for comparison of normally distributed data between groups. Spearman's correlation coefficient was used to correlate various variables in the studied groups. For all tests $P < 0.05$ was considered to be statistically significant.

RESULTS

Clinical parameters

The study included 30 patients with early onset cerebellar ataxia with a mean age of 8.5±6.9 years and 30 controls matched for age and sex. The mean age of onset of ataxia in the patient group was 2.2 ±0.8 years (Table-1). Fundus examination, using direct ophthalmoscope, revealed 4 cases with retinal degeneration appearing as white rounded and oval lesions which are retinal and subretinal. Those lesions extended to the macula in one case (Figure-1). The mean serum HbA1c and fasting blood glucose was 5.1%±0.6 and 82.4mg/dl±7.2, respectively. The serum level of Hemoglobin of cases and controls was 9.7±1.4mg/dl and 11.2±2.3mg/dl, respectively.

Imaging

The MRI of all cases was reported as normal by two different expert neuroradiologists.

Serum biomarkers

Serum level of copper and ceruloplasmin was measured in both case and control groups and was found to be lower than normal. Also, Ferriten, Transferrin, Iron, TIBC, and Transferrin saturation were measured in both case and control groups. A statistically significant difference was found between groups (Table-2).

DISCUSSION

The known neurological diseases associated with decreased serum ceruloplasmin include Wilson disease, Menkes disease (MD), copper deficiency myelopathy (CDM), and hereditary aceruloplasminemia[1]. The patients with aCP develop retinal pigment degeneration, diabetes mellitus, and extrapyramidal system dysfunction after middle age. The first reported cases, presenting mainly with cerebellar ataxia and low ceruloplasmin, was by Edwards et al. (1979)[6], who studied this syndrome in a kindred in which 14 members had low serum ceruloplasmin and low serum copper without the abnormalities of Wilson disease and was termed hypoceruloplasminemia. Miyajima et al. (1987)[7], described a 52-year-old woman with blepharospasm,

Table 2: Serum level parameters of studied patients.

		Number	Mean±SD	*p*
Ferritin (ng/ml)	Case	30	124.7±65.7	0.002**
	Control	30	68.7±26.4	
TF (mg/dL)	Case	30	206.1±55.5	0.001**
	Control	30	266.3±29.0	
Iron (µg/dL)	Case	30	37.4±17.07	0.013*
	Control	30	68.2±31.3	
TIBC(µg/dL)	Case	30	305.2±30.9	0.001**
	Control	30	228.9±23.0	
TS (%)	Case	30	10.1±5.1	0.02*
	Control	30	30.0±15.0	
CP(mg/dL)	Case	30	18.9±12.1	0.001**
	Control	30	37.3±10.5	
Cu(µg/dL)	Case	30	64.27±26.44	0.001**
	Control	30	106.50±25.87	

TF=Transferrin, TIBC= Total iron binding capacity, TS= Transferrin saturation, C= Ceruloplasmin, Cu= Copper

retinal degeneration, and high density areas in the basal ganglia and liver by CT scan. Serum ceruloplasmin was less than 0.6 mg/dl which is extremely low. In the present study, to the best of our knowledge, this is the first case series of hypoceruloplasminemia in the pediatric age group. The clue to the diagnosis of hypoceruloplasminemia was provided by the presence of progressive cerebellar ataxia (which is not fulfilling the criteria for either FA or SCA) with anemia. The low incidence of RD and absence of DM in our series could be attributed to the young age of the case group. RD has been reported to occurs in ninety-three percent of Japanese individuals, has no specific age of onset, and there is no early subjective symptoms[8]. In our series, RD was documented in 4 cases appearing typically as white oval lesions affecting the retinal and subretinal layers extending to affect the macula. The age of onset of DM was found to be above 20 year old and affecting almost 65% by the age of 40 year, thus explaining the absence of DM in our patients. It is well known that low serum CP is not specific to aCP as it is deficient in Wilson's disease also, but serum and urine copper levels are elevated in the latter while serum copper is deficient in the former. In Menke's disease, low CP level is due to deficient intestinal copper absorption, leading to low serum copper and CP. Menke's disease appears in the first year of life and can be easily distinguishable from aCP by the characteristic hair appearance. There is also report of case with hereditary hemochromatosis presenting with ataxia. This differential diagnosis can be ruled out by the age of onset, as cases are adult onset, and by low transferrin saturation which should be elevated. In subjects with hypoceruloplasminemia, Wilson disease should be considered. However, in contradistinction to Wilson disease, individuals with hypoceruloplasminemia do not display increased hepatic and urinary copper levels or corneal copper deposition (Kaiser–Fleischer rings) on slit-lamp examination[9]. Also, cerebellar dysfunction and T2 signal loss (iron deposition) in the dentate nuclei may occur in both FA and hypoceruloplasminemia with a similar mode of inheritance (autosomal recessive) but can be readily distinguished by dorsal column and cardiac involvement in the former, and diminished circulating CP in the latter. Low CP levels also complicate acquired copper deficiency, but the associated myelopathy is not characteristic of heritable hypoceruloplasminemia[10]. In the brain, iron bound to transferrin is endocytosed by endothelial cells, where it is released into the interstitial fluid and oxidized by GPI ceruloplasmin. Then the iron binds to the transferrin synthesized by oligodendrocytes, and is transported into neurons. Thus, the known functions of the iron metabolic molecules suggest the presence of a cycle of iron exchange between the blood, astrocytes, and the neurons. In aCP, the brain ferroportin (the protein responsible for iron efflux from astrocytes) is markedly reduced, probably due to degradation caused by the absence of ceruloplasmin. Animal models of aCP showed that the neuronal loss might result from iron deficiency where astrocytes were unable to mobilize iron to the extracellular space, making it unavailable for neuronal uptake. Later, the iron accumulate in neurons (suggesting other pathways for iron uptake). Neuronal cell injury may therefore result from iron deficiency in the early stage and from iron-mediated oxidation in the late stage affecting neurons and astrocytes. In conclusion, it seems that GPI-linked ceruloplasmin is essential for normal iron homeostasis in the CNS. In conclusion, detecting a high ferritin and low CP concentration in patients with cerebellar ataxia may motivate physicians to further investigate copper metabolism. Further molecular study in cases suspected to have hypocerluplasminemia is highly recommended to reach at definite diagnosis.

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