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ORIGINAL ARTICLE

Low High-Density Cholesterol in Patients with Progressive Encephalopathy with Edema, Hypsarrhythmia, and Optic Atrophy (PEHO) Syndrome and PEHO-like Patients

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ABSTRACT

Background: No metabolic cause for Progressive Encephalopathy with Edema, Hypsarrhythmia, and Optic Atrophy (PEHO) syndrome or PEHO-like patients has been found. The goal of this study was to assess the serum-lipid pattern of the patients.

Methods: This study included 8 patients with (PEHO) syndrome (aged 6.3 + 3.28 years) and 10 patients with PEHO-like syndrome (aged 5, 8+ 4.15 years). Serum cholesterol, high-density cholesterol, and triglycerides were measured by enzymatic colorimetric tests. Statistical analysis for comparison of serum cholesterol, HDL cholesterol, and triglycerides in PEHO and PEHO-like groups was done using a nonparametric Mann-Whitney two-tailed test.

Results: Two PEHO and six PEHO-like patients had subnormal values (reference value > 0.93 mmol/L, Helsinki University Laboratory). The other patients showed serum high-density cholesterol within the lower normal limits. The mean serum high-density cholesterol of all PEHO patients was 0, 97 (SD+ 0,14) mmol/L and for PEHO-like patients 0, 85 (SD + 0.19) mmol/L. Total cholesterol and triglycerides were normal or increased in both groups. None of the patients had metabolic syndrome. All patients were extremely hypotonic, showing no spontaneous movements.

Conclusions: The high prevalence of low high-density cholesterol is a novel finding in these patients with many dysmorphic features. However, it is not known whether it is primary or secondary to the neurodegenerative disease.

Keywords: lipid metabolism; progressive encephalopathy with edema; hypsarrhythmia; optic atrophy

BACKGROUND

PEHO syndrome is characterized by profound psychomotor retardation, hypotonia presenting at birth, early onset epilepsy with infantile spasms, and visual failure. The patients have dysmorphic characteristics and peripheral and facial subcutaneous oedema. Microcephaly develops at 12 months. There is narrow forehead, epicanthal fold, short nose, open mouth, small chin, midfacial hypoplasia, protruding lower parts of auricles, and tapering fingers.

Autosomal recessive inheritance is evident. PEHO syndrome seems to be over-presented in Finland. The minimum prevalence is estimated to be 1:70,000. There are also isolated reports of PEHO syndrome occurring in other countries, such as Japan, the Netherlands, Australia, and Canada.

Riikonen published a paper on nine Finnish families with infantile spasms in siblings in 1987 [1]. The medical histories of the patients in five (11 siblings) of these families were compatible with PEHO syndrome. Salonen et al 1991 [2] described 14 patients from 11 families who had a progressive encephalopathy with early onset and called it PEHO syndrome. Dr. Somer [3] presented diagnostic criteria for PEHO syndrome based on 14 PEHO syndrome families (19 patients) in her PhD thesis published in 1993.

Definite hypotonia is noted in all patients before onset of infantile spasms. No motor milestones are reached. The patients cannot roll over or sit unsupported, and they show severe head lag at all ages. The patients have hypomimia and very little voluntary movement in the extremities. They cannot chew their food, but they swallow normally. The patients show increasing spasticity with rigidity of the joints between two and four years of age. Convulsions have their onset at 2-52 weeks of life with myoclonic jerking and infantile spasms and/or hypsarrhythmia on EEG. There is poor or absent visual fixation from the first months of life with atrophy of the optic disks by two years of age. There is progressive brain atrophy as shown by computed tomography or magnetic resonance imaging, particularly of the cerebellum and brain stem with milder supratentorial atrophy.

In patients with PEHO syndrome compared to controls, the levels of CSF insulin growth factor (IGF-1) were reduced [4, 5], and the levels of nitrite/nitrate were markedly elevated. [6] Defective production of IGF-1 probably reflects the

underlying neurodegeneration, and the increase in nitrite/nitrate production reflects the seizure activity or neurodegeneration [6].

The other half of Dr. Somer`s original patients were called PEHO-like patients [3]. PEHO-like patients have a similar clinical disorder, but they do not have cerebellar atrophy or optic atrophy. Clinical features alone are not sufficient for diagnosing the PEHO syndrome. The true Finnish PEHO patients have now been shown to have mutation in gene 17 but not the PEHO-like patients (Lehesjoki E, personal communication 2012). The group of PEHO-like patients seems to be a heterogenous condition.

METHODS

This study included 18 children with PEHO or PEHO-like syndrome. PEHO patients were 6.3 + 3.28 and PEHO-like patients were 5.81 + 4.15 years old. The diagnosis of PEHO was confirmed by the genetic analysis (mutation in gene 17). All patients, except one, had been included in Dr. Somer's study, but special attention was paid to cholesterol values.

The Apgar scores of the patients ranged from eight to ten. The mean birth weight, length, and head circumference was average. The weights ranged from 2,800 to 3,970 g, heights from 49 to 52 cm, and head circumferences from 35 to 37 cm at term. The heights fell to 2 SD below normal by the second year of life, and thereafter, gradually to 3-5 SD below normal. The patients were usually slim. Growth standards that allow direct reading of relative height (SD score) and relative weight (percentage deviation of weight from median weight for height and sex) were used. The head was small in relation to age but not in relation to body size. They had constipation and decreased frequency of urination.

The following laboratory investigations were performed: complete blood cell count; vacuolization of lymphocytes; glycosylated haemoglobin (HBA1C); blood gas values; blood glucose; serum electrolytes; serum alkaline phosphatase (AFOS); aspartate aminotransferase (AST); creatine kinase (CK); lactate dehydrogenase (LD); gammaglutamyltransferase (GT); serum protein; urea-N; creatine; urate; serum copper; ceruloplasmin; vitamin E; postprandial blood ammonia; lactate and pyruvate in blood, drawn 5 minutes after the puncture; urinanalysis (specific gravity, cells, protein, glucose, bacterial culture); diurnal urate; orotic acid; arylsulfatase; cerebrospinal fluid protein; glucose; cells; lactate; and puruvate. Screening studies for urinary aminoacids and mucopolysaccharides were performed. Other studies performed were plasma and urinary levels of aminoacids, urinary organic acids, serum levels of long chain fatty acids, phytanic acids, serum total and free carnithine, carbohydrate deficient glycoprotein, and serum biotidinase. There was no evidence of any mitochondrial, peroxisomal, or lysosomal disorder in any of the patients.

Thorough laboratory studies were previously conducted in order to find biochemical markers for the PEHO syndrome, but no metabolic defect was found.

The goal of this study was to assess the serum lipid pattern of the patients.

A Hitachi Modular PP-analyzer (Hitachi Ltd., Tokyo) was used for analysis of total cholesterol, HDL cholesterol, and triglycerides. Serum cholesterol was measured by an enzymatic colorimetric test using the Roche Diagnostics Cholesterol CHOD-PAP method (Cat. no. 1491458). The intra-assay variation (CV) of the method is 0.7 % at the level of 4.9 mmol/L. The interassay variation (CV) of the method is 1.5 % at the level of 3.3 mmol/L and 1.2 % at 7.1 mmol/L. The lowest detection limit of the method is 0.1 mmol/L.

Serum HDL cholesterol was measured by a homogeneous enzymatic colorimetric test using the Roche Diagnostics HDL-C plus 3rd generation method (Cat.no. 4713109). The intra-assay variation (CV) of the method is 0.9% at the level of 1.2 mmol/L and 0.8% at 2.0 mmol/L. The interassay variation (CV) of the method is 3.0% at the level of 0.9 mmol/L and 2.5% at 1.9 mmol/L. The lowest detection limit of the method is 0.08 mmol/L.

Serum triglycerides were measured by enzymatic colorimetric tests using the Roche Diagnostics Triglycerides GPO-PAP method (Cat. no. 1730711). The intra-assay variation (CV) of the method is 0.9% at the level of 1.1 mmol/L. The interassay variation (CV) of the method is 3.8% at the level of 0.96 mmol/L and 2.9% at 2.00 mmol/L. The lowest detection limit of the method is 0.05 mmol/L.

Statistical analysis for comparison of serum cholesterol, HDL cholesterol, and triglycerides in PEHO and PEHO-like groups was done using a nonparametric Mann-Whitney two-tailed test.

Laboratory studies were considered to be part of the routine clinical studies of the patients.

RESULTS

Total cholesterol, HDL cholesterol and triglycerides were measured in 8 children younger than 4 years and in 10 children 4-12 years of age [Table 1].

The total serum cholesterol was 4.95 +1.36 mmol/L in PEHO and 4.03 + 0.94 mmol/L in PEHO-like patients (NS). The HDL cholesterol in PEHO patients was 0.97 (+ 0.14) mmol/L and 0.85 (SD+ 0.19) mmol/L in PEHO-like patients (NS). Eight of 18 patients showed subnormal HDL concentrations (< 0.93): two PEHO and six PEHO-like patients.

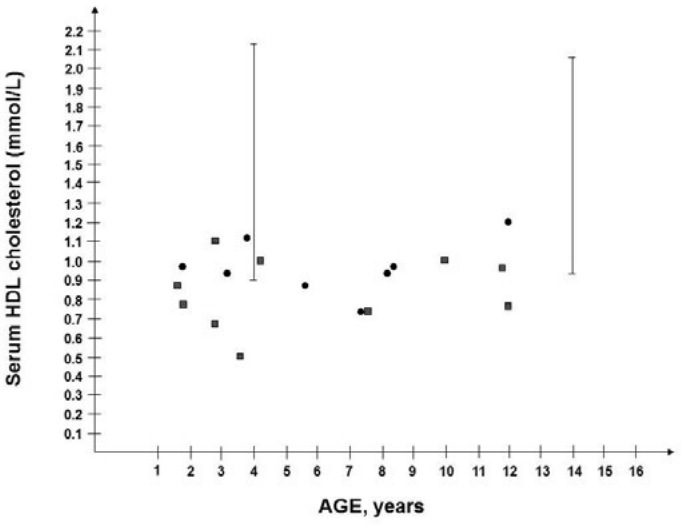

Fig 1. Serum HDL Cholesterol levels among the study subjects against their age in years

TABLE 1. Lipid metabolites of the patients.
Serum cholesterol, serum high-density cholesterol, and serum triglycerides in patients with PEHO (patients 1-8) and PEHO-like syndrome (patients 9-18).

Patient	Sex	Age (years)	S-Chol* (mmol/L)	S-HDL* (mmol/L)	S-Trigly* (mmol/L)	Height (SD)	Weight (Percent)
1.	male	1.9	5.0	0.96	0.9	2.5	15
2.	female	3.3	3.4	0.95	0.7	-3.0	-10
3.	female	3.9	5.9	1.11	N.D.	-0.5	-10
4.	male	5.6	N.D.	0.86	0.9	-5.5	-15
5.	female	7.6	4.8	0.74	0.8	-3.5	-30
6.	female	8.1	3.0	0.94	1.0	-4.0	-15
7.	female	8.2	5.9	0.96	0.9	-5.0	-20
8.	female	12.0	6.7	1.20	0.7	N.D.	N.D.
9.	male	1.6	4.0	0.87	1.1	-2.0	-10
10.	female	1.9	4.6	0.78	0.8	-0.5	-10
11.	female	2.7	3.6	0.68	1.8	0.5	10
12.	male	2.7	6.1	1.10	1.0	-0.5	0
13.	female	3.7	3.0	0.50	2.1	0	0
14.	male	4.1	4.4	1.05	0.7	2.5	15
15.	female	7.5	3.3	0.75	0.8	-5.0	-10
16.	female	10.0	3.7	1.02	0.9	-6.0	5
17.	female	11.9	4.6	0.99	1.4	-2.0	30
18.	male	12.0	3.0	0.77	0.6	N.D.	-10

S-Chol; serum cholesterol, S-HDL; serum high-density cholesterol, S-Trigly; serum triglyseride,
SD; standard deviation, N.D.; no data
* The Finnish reference values for children for S-Chol are 2.85-4.0 mmol/L, for S-HDL 0.91±2.12 mmol/L at 1- 4 years and 0.93±1.94 mmol/L at 5 to 14 years of age, and for S-Trigly 0.27 – 1.86 mmol/L (Helsinki University Laboratory).

The serum HDL values were not associated with age [Figure 1].
The total cholesterol was usually normal or increased (reference values for children 2.85-4.0 mmol/L). The cholesterol-HDL cholesterol ratio was abnormal (>3.5) in all except one (Case 6). Triglycerides were normal except for one PEHO-like patient (Patient 5, non-fasting): 0.84+ 0,11) mmol/L in PEHO and 1.12 + 0.50 mmol/L in PEHO-like patients [Table 1].

DISCUSSION

In this study, the main finding was a high prevalence (eight of 18 patients) of low HDL cholesterol < 0.93 mmol/L in PEHO and PEHO-like patients.

Recent Finnish values for HDL are higher. In a large Finnish cohort, HDL cholesterol for children aged more than 3 years has been > 1.4 mmol/L both for females and males [8]. This cohort included 3,596 individuals. Serum cholesterol values in Finnish boys have been high in international comparison, and coronary artery disease incidence in Finnish adults has been very high [9].

Cholesterol is an essential component required to establish proper membrane fluidity. It is not clear if a lower than average cholesterol is directly harmful in children. It is often encountered in various illnesses. Low HDL is connected with the metabolic syndrome, diabetes, obesity, cholestasis, and malnutrition. There are some rare metabolic inherited syndromes with low cholesterol, e.g. the Smith-Lemli-Opitz syndrome (a genetic disorder with a high incidence of autism). In this disorder, there is a deficiency of enzyme in the sterol synthethic pathway that converts 7-dehydrocholesterol to cholesterol [10]. Low serum HDL (0.27 mmol/l) and low LCAT (lecithin-cholesterol acyltransferase) activity was found in a proband of a Finnish family. These patients showed corneal opacities, proteinuria, and anemia with somatocytosis. This disease was described by Miettinen et al. in 1995 [11]. With an association to autism, an early cholesterol supplementation started before the age of five years has been reported to reduce the risk of autism in children with the Smith-Lemli-Opitz syndrome but not if supplementation was given later [12].

The patients in the present study did not have the metabolic syndrome and were not obese. CSF IGF-1 was low, but it was considered to be due to neurodegenerative process [6]. Unfortunately, no plasma values were available. Also, diabetes and choleaststasis were excluded. The children had a short stature, but they were not malnourished. The HDL values were not associated with age.

It is known that exercise in obese children may improve the lipid profile [13]. The effect of physical activity on serum total and low-density lipoprotein cholesterol concentrations varies according to the apolipoprotein E phenotype [14]. It is not known if almost total immobility, as seen in all the

patients with PEHO or PEHO-like patients, could cause low HDL cholesterol.

We do not know if low concentrations of HDL cholesterol are secondary or primary to the disease. Low values were seen both in genetically conformed PEHO patients and PEHO-like patients, a disease that seems to be heterogenous and without any known cause. Unfortunately, the amount of plasma was limited, and we could not perform further analyses. It would be urgent to study the lipid metabolism (synthesis and absorption) in new cases. If the lipid dysfunction is primary, interventions might be possible.

CONCLUSIONS

No metabolic cause of Progressive Encephalopathy with Edema, Hypsarrhythmia, and Optic Atrophy (PEHO) syndrome or PEHO-like patients has been found. The goal of this study was to assess the serum lipid pattern of the patients. In this study, eight children with PEHO syndrome (all genetically confirmed to have the "true" PEHO syndrome) and ten with PEHO-like syndrome were studied.

The high prevalence of low high-density cholesterol is a novel finding in these children with many dysmorphic features. However, it is not known whether it is primary or secondary to the neurodegenerative disease. If the lipid dysfunction is primary, interventions might be possible.

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Competing interests

The author declares that she has no competing interests.

Author contributions

The author has collected, analysed, interpreted the data and written the paper.

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