Clinical features and genetic analysis of childhood dyslipidemia

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Introduction

Dyslipidemia is a disease characterized by a genetic or multifactorial disorder of lipid and/or lipoprotein metabolism. Childhood dyslipidemia is a rare genetic metabolic disease that can cause serious cardiovascular disease and seriously endanger children's health. we uses second-generation sequencing to identify the related pathogenic genes in children, and elucidate the pathogenesis of gene mutation, and summarize the diagnosis and treatment of dyslipidemia in children.

Methods

We retrospectively analyzed the clinical data of 10 patients with dyslipidemia who were admitted to the Department of Endocrinology, Children's Hospital of Zhejiang University School of Medicine from June in 2009 to August in 2017. Seven probands and two of their parents underwent next generation sequencing. Based on the detected mutation sites, the relevant pathogenic genes were identified by data analysis and their mechanism was analyzed

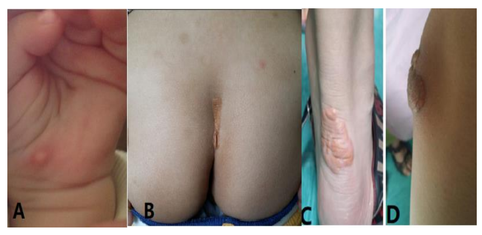

Figure 1. Cutaneous features of children with dyslipidemia. Xanthomas that caused by lipid deposition in the endodermal layer of tend to occur in areas susceptible to friction. A, metacarpal bone;B the hips ;C the heel; D the elbow.

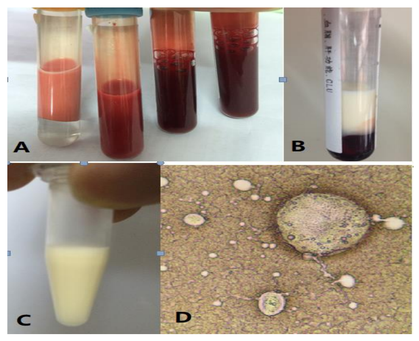

Figure 2 Blood color characteristics of P1with high chylomicronemia : (A) the blood appears pink; (B) the whe "creamy" top layer is visible in the blood; (C) the serum is completely milky white; (D) Chylomicron are visible in the blood smear.

Results

1. Clinical phenotypes: (1) 10 cases of proband were from Zhejiang Province, there was 5 males and 5 females,(2) The median age of diagnosis is 4.7 years old,(3) The symptoms and the clinical manifestations were mostly xanthomas. Three of probands (P1 ,P2 and P10) were found that the creamy plasma appearance,(5) Among the clinical phenotypes, 5 cases were hypercholesterolemia, 4 cases were combined hyperlipidemia, and 1 case was hypertriglyceridemia.Two of them were low high density lipoproteinemia.
2. Molecular genetic results: LPL c.808C>T gene missense mutation was found in P2; the mutation c.2054C>T of LDLR gene were found in P3. There were ABCG5 gene mutations in P4 and P5. There was a complex heterozygous mutation in P4.Another is heterozygous missense mutations of c.5002G>A and c.3121C>G of ABCA1. In P5, there was a homozygous nonsense mutation of c.751C>T in ABCG5. None of the above gene mutations were new mutations, and no pathogenic gene was found in P6 and P7.
3. Treatment and prognosis: They were all given dietary control of cholesterol intake, infants were controlled long-chain fatty acid intake. 2 probands were given drug control .6 cases (P1、P4-P7、P10)can control the blood lipid level at normal or near the upper limit levels; xanthoma of 2 cases, sitosterolemia (P4 and P5) became larger. But after controlling animal cholesterol and phytosterol intake simultaneously, the xanthoma has improved. No early-onset coronary heart disease has been found in these probands.

Table 1 Results of genetic variation in patients with dyslipidemia

Number	Gene	Mutation	Location		Protei
P1	ABCG5	nonsense mutation	Exon3	c.342delT	p.(Tyr114*)
	HFE2	missense mutation	Exon4	c.1034G>T	p.(Arg345Leu)
P2	LPL	missense mutation	Exon6	c. 808C > T	p. (Arg270Cys)
P3	LDLR	missense mutation	Exon14	c.2054C>T	p.(Pro685Leu)
P4	ABCG5	missense mutation	Exon9	c.1166G>A	p (Arg389His)
	ABCA1	missense mutation	Econ37	c.5002G>A	p.(Val1668Ile)
		missense mutation	Exon22	c.3121C>G	p.(Leu1041Val)
P4father	ABCG5	missense mutation	Exon9	c.1166G>A	p (Arg389His)
	ABCA1	missense mutation	Econ37	c.5002G>A	p.(Val1668Ile)
		missense mutation	Exon22	c.3121C>G	p.(Leu1041Val)
P4mother	ABCG5	missense mutation	Exon9	c.1166G>A	p.(Arg389His)
P5	ABCG5	nonsense mutation	Exon6	c.751C>T	p.(Gln 251*)
P5father	ABCG5	nonsense mutation	Exon6	c.751C>T	p.(Gln 251*)
P5mother	ABCG5	nonsense mutation	Exon6	c.751C>T	p.(Gln 251*)

Conclusion

(1) Children with dyslipidemia have diverse clinical phenotype and symptoms are not typical. It is easy to be missed;
(2) Children with dyslipidemia have high genetic heterogeneity.Genetic test can increase the accuracy of clinical diagnosis and contribute to early diagnosis and treatment of diseases.
(3) Sitosterolemia may be an important cause of hypercholesterolemia in China.The restriction of cholesterol and phytosterol intake should be suggested for sitosterolemia.