Domino Liver Transplantation for the Pre-emptive Therapy of Compound Heterozygous Familial Hypercholesterolemia : A Case of 3-Year-old Girl

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There is no conflict of interest

Background

Homozygous (compound heterozygous) familial hypercholesterolemia (FH) is a rare and life-threatening disease characterized by markedly elevated plasma low-density lipoprotein cholesterol (LDL-C) from birth, extensive xanthomas, and marked premature and progressive atherosclerotic cardiovascular disease (ACVD)[1)2)]. If untreated, patients develop cardiovascular atherosclerosis resulting in death before the second decade of life[3)]. Medication and apheresis are only partially effective in reducing LDL-C levels, and do not significantly improve the prognosis[4)].

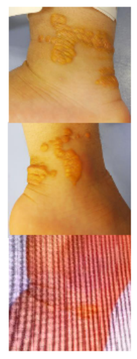
Liver transplantation (LT) can correct the lipid metabolism in the organ most active in the clearance of LDL, resulting in marked improvement of LDL-C levels[1)]. Although a possibly successful therapeutic strategy, there are obvious disadvantages, including the high risk of surgical complication and mortality, the paucity of donors, and the need for life-long treatment with immunosuppressive therapy[5)].

We report a first case received living donor LT (LDLT) from the donor with maple syrup urine disease (MSUD) in early infancy as a preemptive, rather than preventive therapy for compound heterozygous FH.

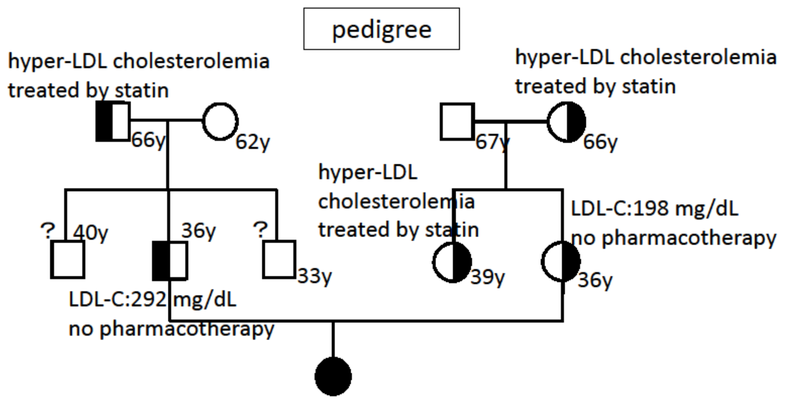
Case

A 1-year-old girl with no past medical history was referred to our institution with xanthoma and hypercholesterolemia. Her both parents and both family have history of FH, there is no early death from coronary disease in the family. Her serum cholesterol levels were extremely elevated; total cholesterol 1007 mg/dl and LDL-C 867 mg/dl. She was diagnosed as FH, presumably Homozygous/compound heterozygous, with apparent family history and the laboratory findings.

Xanthomas



pedigree



Laboratory tests

【Blood test】

[CBC・biochemistry]

W.N.L

no elevation of CK/trop T/BNP

[lipid metabolism]

T-Cho	1092 mg/dL	(125-240)
HDL-C	49 mg/dL	(>40)
LDL-C	975 mg/dL	(70-139)
TG	129 mg/dL	(32-237)
FFA	881 μEq/L	(140-850)
apoA1	114 mg/dL	(126-165)
apoA2	27.1 mg/dL	(24.6-33.3)
apoB	553 mg/dL	(66-101)
apoC2	5.7 mg/dL	(1.5-3.8)
apoC3	13.7 mg/dL	(5.4-9.0)
apoE	12.1 mg/dL	(2.8-4.6)
sitosterol	9.5 μg/mL	(8-60)

【 Lymphocytic LDLR activity】

0%(adult RV:≧80%)

father:51% mother:43%

【Imaging test】

[CXR/ECG/UCG]

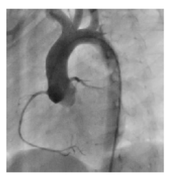
W.N.L

[Carotid US]

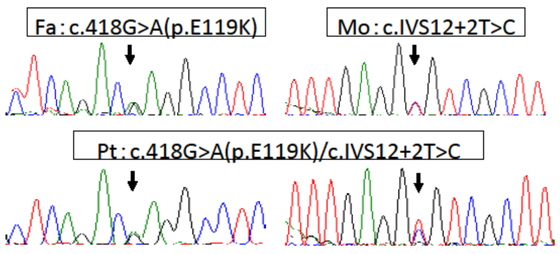
no progression of carotid IMT

[Cardiac angiography]

No coronary stenosis and valvular disorder

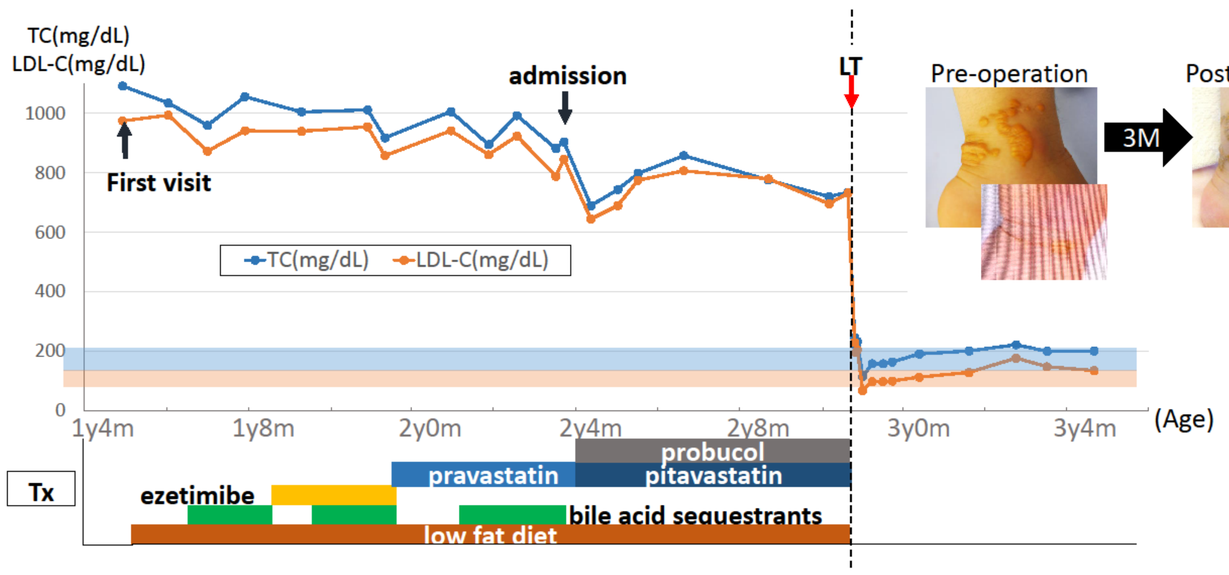


【Genetic test (LDLR)】



Clinical course

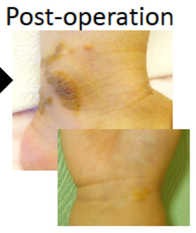
- Medication was only partially effective.
- Apheresis was not available because of her young age.
- LDLT from the donor with MSUD is perfectly effective without major complication.



Pre-operation

3M

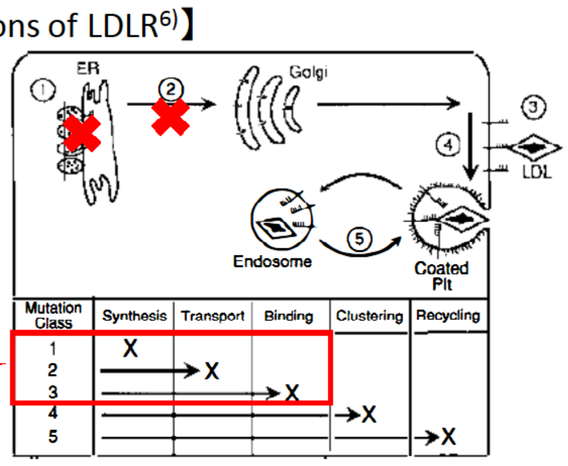
Post-operation



Discussion

【classification of mutations of LDLR[6)]】

Class	Phenotypic effects on the protein
1	No detectable LDLR synthesis
2	Defective LDLR transport
3	Impaired LDL to LDLR binding
4	No LDLR/LDL internalization due to defective clustering
5	No LDLR recycling



known for few expression of LDLR[7)]

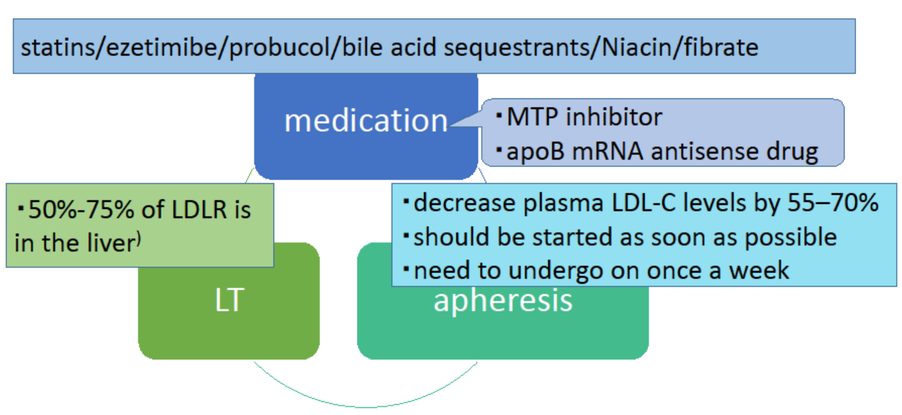
In this case.....

c.IVS12+2T>C → class1

c.418G>A(p.E119K) → class2 [8)]

Causes a severe clinical presentation and resistance to medication.

【Current treatment for severe FH[2)]】



	merit	demerit
Medication	Not invasive	Partially effective
Apheresis	Rather effective	Invasive, Limitation of BW, Low QOL
LT	Mostly effective	Invasive, Immunosuppression, Few donor resources

●LT using the liver from a patient with MSUD

MSUD is an autosomal recessive metabolic disorder that is characterized by impaired activity of the branched-chain a-keto acid dehydrogenase complex (BCKDH) [10)]. LT has been performed for some patients with MSUD who are difficult in medication management [11)]. The liver from a patient with MSUD is used for domino LT. The recipient maintained normal amino acid metabolism, because of normal extrahepatic BCKDH enzyme activity in the recipient without MSUD [12)].

Conclusion

Liver transplantation for severe FH performed in early infancy before onset/progression of atherosclerosis is an effective pre-emptive treatment.

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Fat Metabolism, Obesity

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