CLINICAL QUIZ (p258) ANSWER

What is the diagnosis?

The clinical features of this child with history of Hirschsprung's disease, microcephaly, failure to thrive, developmental delay, postaxial polydactyly and bilateral 2/3 syndactyly of toes were compatible with Smith-Lemli-Opitz syndrome (SLOS). Therefore plasma sterol for investigation of cholesterol biosynthesis defects was performed. It showed normal plasma cholesterol level with markedly elevated 7-dehydrocholesterol and 8-dehydrocholesterol. Diagnosis of SLOS was biochemically confirmed and he was then put on cholesterol supplement and HMG CoA reductase inhibitor. His failure to thrive was gradually improved with latest body weight and height centile at 50th and 25th centile respectively. *DHCR7* genetic analysis was then carried out which showed compound heterozygous pathogenic variants DHCR {NM_001360.2}:c.[1A>G]; [575C>T]. Both parents were asymptomatic heterozygous carriers.

SLOS (OMIM #270400) is an autosomal recessive disease resulted from deficiency of the final enzyme in the cholesterol synthesis pathway. It was first described in 1964 by Department of Pediatrics at the University of Wisconsin, Madison.[1] The birth prevalence of SLOS is estimated to be approximately 1:20,000 to 1:40,000 live births in western population

It is characterised by prenatal/postnatal growth retardation, microcephaly, moderate to severe intellectual disability and/or multiple malformations. The malformations included distinctive facial features, cleft lip/palate, cardiac defects, underdeveloped external genitalia in males, postaxial polydactyly and 2/3 syndactyly of toes (Y-shape). The clinical presentation is highly heterogeneous. Clinical diagnostic criteria have not been established. High index of suspicion is required. And this case is the first molecularly confirmed case in Chinese population.

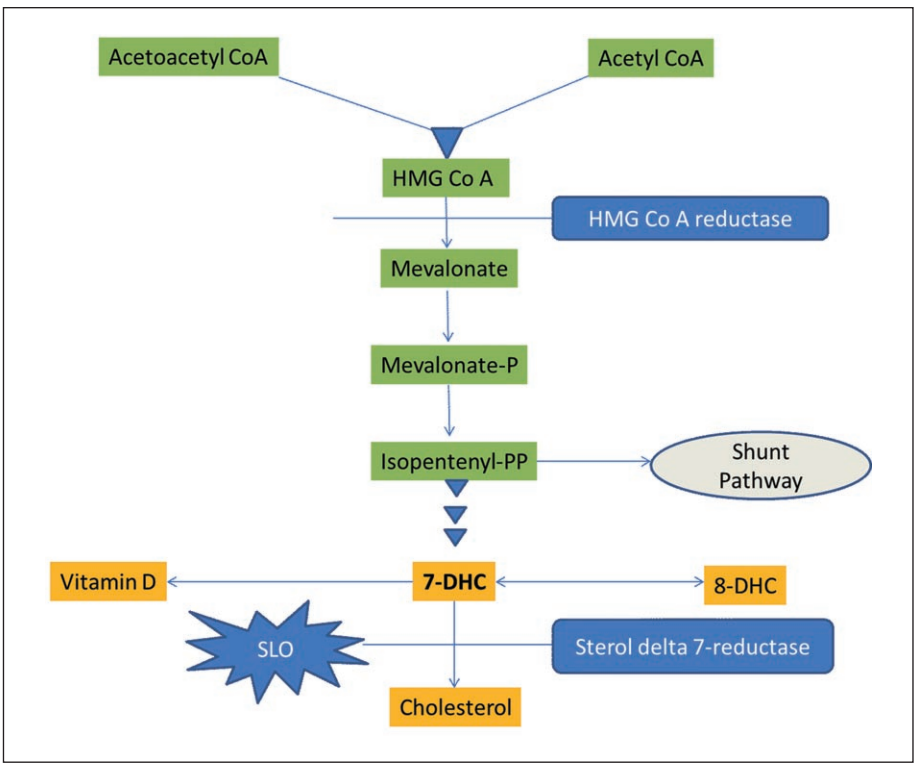

Figure 2 The diagram showing the biosynthesis of cholesterol.

What are the Biochemical Defects in SLOS?

Children with SLOS have defect in the last step of biosynthesis of cholesterol. Deficiency in enzyme 7-dehydrocholesterol delta-7-reductase activities would lead to reduction of cholesterol and accumulation of the cholesterol precursors 7-DHC and 8-dehydrocholesterol (8-DHC) (Figure 2). This contributes to the unique sterol profile in SLOS.

How is the Diagnosis Established in SLOS?

The diagnosis of SLOS relies on clinical suspicion and detection of elevated serum concentration of 7-DHC. Serum concentration of cholesterol may be in the normal range in approximately 10% of affected individuals, making it an unreliable test for screening and diagnosis. In 1998, the gene 7-dehydrocholesterol reductase (*DHCR7*) encodes the enzyme 7-dehydrocholesterol delta-7-reductase that reduces 7-DHC to cholesterol was discovered to be the causative gene of SLOS. It is so far the only gene that causes SLOS.[2] Sequence analysis of *DHCR7* detects approximately 96% of cases.[3] Carrier detection is possible if the pathogenic variants in the family are known. Carriers are asymptomatic. In the old day, prenatal testing for pregnancies at risk is only possible by using amniotic fluid or tissue from chorionic villus sampling for biochemical testing of elevated 7-DHC. Currently, prenatal diagnosis or even preimplantation genetic diagnosis can be offered to at risk couples if the known pathogenic variants have been identified in those families.

What Are the Management Issues for SLOS?

Management of SLOS required multi-disciplinary approach, which included pharmacological interventions, e.g. cholesterol supplementation and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG CoA reductase inhibitors), physical/occupational/speech therapies and dietitian support. Neonatal cholestatic liver disease responds well with cholesterol and/or bile acid therapy.

HMG CoA reductase inhibits the cholesterol pathway proximal to the enzymatic defect in SLOS and increases the expression of hypomorphic *DHCR7* alleles.[4] It was relatively safe and improved the dehydrocholesterol-to-total sterol ratio biochemically in patients with SLOS.[5]

Acknowledgement

We would like to thank the patient and the family for their contribution.

References

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