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Cholesterol and Bile Acid Replacement Therapy in Children and Adults With Smith-Lemli-Opitz (SLO/RSH) Syndrome

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Tint et al. [N Engl J Med 1994, 330:107–113], working with blood samples from the Smith-Lemli-Opitz syndrome (SLOS) patients of Irons and Elias showed the biochemical basis of this disorder to be a cholesterol biosynthesis defect [Irons et al., Lancet, 1993, 341:1414]. Based on this finding, clinical protocols for cholesterol and bile acid replacement therapy were established in a few centers including the University of Pittsburgh. We report our experience with bile acid and/or cholesterol replacement therapy in six patients with SLOS, now aged 3–27 years, with a confirmed biochemical diagnosis. Levels of plasma cholesterol and 7-dehydrocholesterol were correlated with periodic clinical evaluations over 8–27 months of therapy. There was a marked improvement in the growth of all the children. There was also an increase in the plasma cholesterol level in all the children and an overall increase in their percent sterol as cholesterol. Subjective improvement was also noted in their development. Although there was no significant change in the plasma cholesterol level of the older patients, there was a marked improvement in their behavior and in their quality of life. Am. J. Med. Genet. 68:315–321, 1997.

KEY WORDS: Smith-Lemli-Opitz syndrome; multiple congenital anomalies syndrome; cholesterol; 7-dehydrocholesterol; bile acids; autosomal recessive; multiple congenital abnormalities/mental retardation syndrome

INTRODUCTION

The Smith-Lemli-Opitz (SLO/RSH) syndrome, first reported by Smith et al. in 1964, is an autosomal recessive disorder (McKusick # 270400) of multiple congenital anomalies with extreme range of variability. It comprises characteristic craniofacial anomalies, cardiac malformations, renal aplasia/dysplasia, genital anomalies, Hirschsprung disease, syndactyly/polydactyly, and mental and severe growth retardation [Smith et al., 1964; Curry et al., 1987]. The incidence of this defect in North American Caucasians is between 1 in 20,000 to 1 in 40,000 liveborn infants [Lowry and Yong, 1980], making it a relatively common autosomal recessive disorder. It was previously diagnosed on the basis of clinical criteria only. Recently, very high levels of 7-dehydrocholesterol (cholesta-5,7-dien-3β-OL) were reported in five patients with SLOS [Irons et al., 1993; Tint, 1993; Tint et al., 1994], thus making this a true metabolic malformation syndrome. We present clinical and biochemical data obtained on six patients (5 females and one male; ages 3–26 years) who have been on a regimen of bile acid and/or cholesterol replacement for at least 11 months.

CLINICAL AND BIOCHEMICAL FINDINGS

Patient 1

A.M. (Fig. 1), previously reported as the first patient with a biochemical diagnosis leading to a clinical diagnosis [Nwokoro et al., 1994] was a 3,660 g product of a term pregnancy to a 27-year-old G1 woman. The pregnancy was complicated by amniotic fluid leak and decreased fetal activity. At birth the patient had hypotonia, relative microcephaly, bilateral cataracts, lateral displacement of the inner canthus, wide nasal root, small nose with anteverted nares, high narrow palate, absence of a sucking reflex, wide short neck with loose skin folds, flat chest, widely spaced nipples, left bridged simian crease, edema of the hands, hypoplastic labia, left 5th hammer toe, and bilateral 2–3 toe syndactyly. The family history was unremarkable and the marriage was nonconsanguineous. The infant failed to thrive and had vomiting episodes. With evolving manifestations suggestive of an underlying metabolic defect, she had an extensive metabolic investigation. Her chromosomes were normal (46,XX), and she had normal

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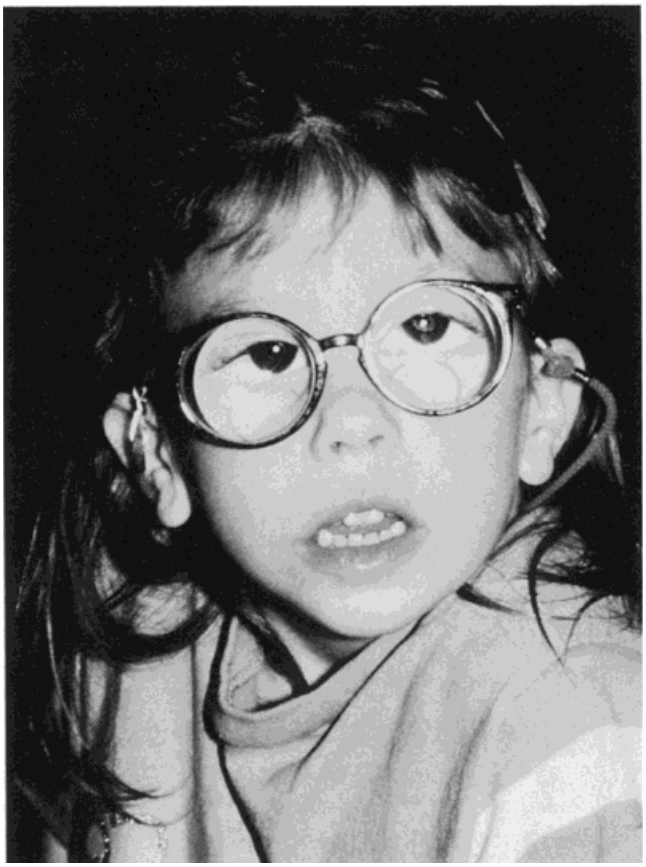

Fig. 1. A.M. at age 44 months.

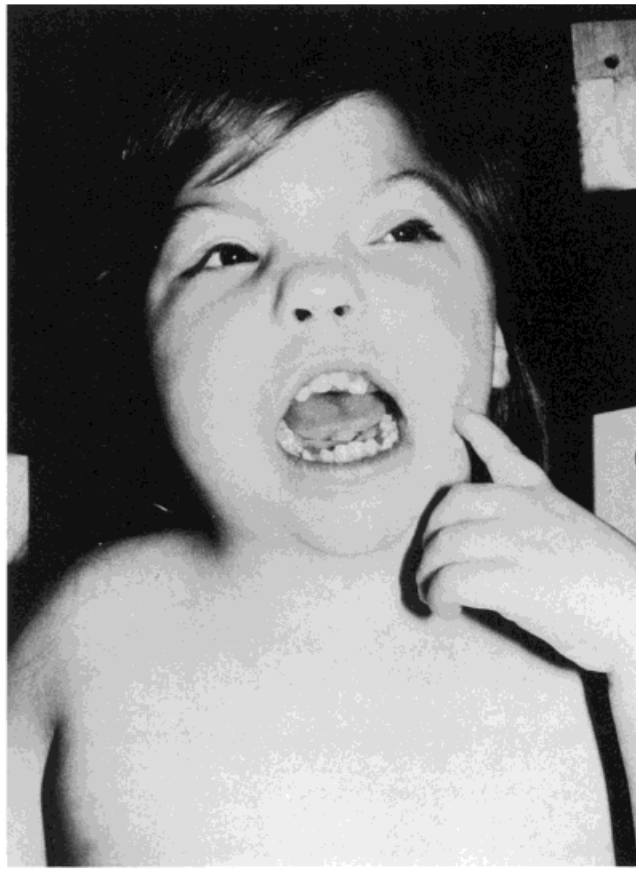

Fig. 2. H.S. at age 44 months.

blood and urine amino acid levels, normal very long chain fatty acids, normal lysosomal enzymes, mild sialyloligosaccharidiuria, and abnormal urinary bile salts. The last finding led to plasma sterol quantification by Dr. Tint, which showed a marked increase in 7-dehydrocholesterol (7-DHC) and a markedly decreased cholesterol level. Subsequent medical history included severe failure to thrive, gastrostomy-tube placement, gallstones, mildly elevated serum transaminases, fundoplication for gastroesophageal reflux, recurrent otitis media, surgical excision of cataracts, extreme irritability, tactile defensiveness, severe photosensitivity, skin rash, ligation of patent ductus arteriosus, right strabismus, and, per cranial MRI, a short corpus callosum, abnormal gyral pattern, and frontal lobe atrophy.

Cholesterol replacement therapy was initiated at age 11 months and bile acid supplementation was added 6 months later.

Now 44 months old, she is a healthy, pleasant toddler who walks with assistance, is moderately developmentally delayed, and is dependent on gastrostomy tube alimentation. She is presently only on supplemental cholesterol (77 mg/kg/day) without supplementary bile acids.

Patient 2

H.S. (Fig. 2) was the 2,480 g term product of an uneventful pregnancy to a 28-year-old G1 woman. Delivery was vaginal vertex, and there was meconium aspiration. H.S. had microcephaly, a narrow forehead, cataracts, anteverted nares, high arched palate with posterior cleft palate, narrow long chest with low-set nipples, ulnar deviation of the fingers with thumb hypoplasia, abnormal palmar creases, and bilateral 2–3 toe syndactyly. A diagnosis of SLOS was made by age 2 weeks and chromosomes were normal (46,XX). The family history was unremarkable and the marriage was nonconsanguineous. Her course has included severe failure to thrive with placement of a gastrojejunostomy tube at age 3 months, irritability, tactile defensiveness, photosensitivity, skin rash of limbs, obstructive sleep apnea, recurrent sinusitis and otitis media, moderate developmental delay, gastroesophageal reflux with fundoplication and pyloroplasty, seizure disorder, periodic elevation of plasma transaminase levels, and a cranial MRI that showed delayed myelination and decrease of white matter volume with ventriculomegaly. Cholesterol replacement therapy was initiated at age 1 year, and bile acid supplementation was added 6 months later. Presently she receives only cholesterol (125 mg/kg/day).

Now 44 months old, she is a well-nourished, sociable, alert microcephalic child who is making slow developmental progress. She is developmentally delayed, moves by rolling herself across the floor, and becomes weepy at the sound of other children crying. She is

frightened by loud noises such as sirens, food mixer, and vacuum cleaner.

Patient 3

C.K. was the 2,500 g term product of an uncomplicated pregnancy to a 28-year-old G3 P2 mother. Presentation was breech, but delivery was vaginal vertex. At birth she had hypotonia, a weak cry, ptosis, protruding maxilla, cleft of the posterior palate, hypoplastic mandible, short index fingers, finger deformities, bilateral 2–3 toe syndactyly, and ambiguous genitalia. She failed to thrive and was hospitalized for 20 days for feeding difficulties and hyperbilirubinemia.

SLOS was suspected, as there had been an older sister with multiple congenital anomalies, including microcephaly, cleft of the soft palate, cataracts, flexion contractures of the hands and fingers, radial deviation of the wrists, and bilateral 2–3 toe syndactyly. This sister had an unusual continuous cry, was extremely irritable and spastic, and died at age 4 $^{3}/_{12}$ years. Also, there were three affected paternal first cousins, one of whom died at age 6 weeks (Fig. 3). The marriage was nonconsanguineous. C.K.'s other history has included photosensitivity, tactile defensiveness, especially of her feet, hypogonadotropic hypogonadism, mild elbow and knee contractures, sensitivity to bass sounds, multiple maxillofacial surgeries, and severe kyphoscoliosis with Harrington rod placement. She walked independently at 8 years and her highest functioning level at a chronologic age of 19 years was at the 3-year level. Her chromosomes were normal (46,XX). Cholesterol replacement therapy (1 g/day) was initiated when she was 25 years old. Until age 26 years, she lived with her parents and is now in a sheltered group home. She is moderately to severely mentally retarded, very pleasant and sociable, has a vocabulary of 10 words, including two 2-word phrases, and loves to sing and listen to music.

Patient 4

D.K. is the paternal first cousin of patient 3 (Fig. 3). He was the 2,600 g term product of an uncomplicated pregnancy to a 31-year-old G3 P2 woman whose first-born son had multiple congenital anomalies, microcephaly, upturned nares, cleft of the soft palate, receding chin, micropenis, undescended testes, club foot, and bilateral 2–3 toe syndactyly. He died at age 6 weeks of pneumonia. The marriage was not consanguineous. At birth, D.K. had hypotonia, apparently lowset ears, ptosis, epicanthal folds, cleft of the soft palate, prominent maxilla, micrognathia, cryptorchidism, micropenis with hypospadias, bilateral 2–3 and 3–4 toe syndactyly and club foot. The diagnosis of SLOS was made in infancy. He had a weak suck and severe failure to thrive with milk intolerance and was hospitalized neonatally for failure to thrive. He did not require a feeding gastrostomy tube. His chromosomes were normal (46,XY). Laboratory findings included low plasma triglycerides and mildly elevated serum transaminases. He also manifests microcephaly, severe mental retardation, self-abusive behavior, short stature, photosensitivity, tactile defensiveness, redundant mitral valve with intermittent murmur, marked kyphoscoliosis with bulging right thoracic cage and thoracolumbar surgical fusion with Harrington rod placement, Nissen fundoplication at age 16 years for gastroesophageal reflux and severe esophagitis, followed 2 years later with a repair of periesophageal hernia and a repeat Nissen fundoplication, contractures of the elbows and knees, marked atrophy of limb muscles, pronation deformity of both feet, left hydrocele, right inguinal testis, hooded penis with first-degree hypospadias, and hypogonadism. His cholesterol replacement therapy (1 g/day) was initiated at age 18 years.

Now 20 years old, he is well nourished, happy, and sociable when not stressed and walks with molded shoes. He is not toilet-trained and lives in a community living facility.

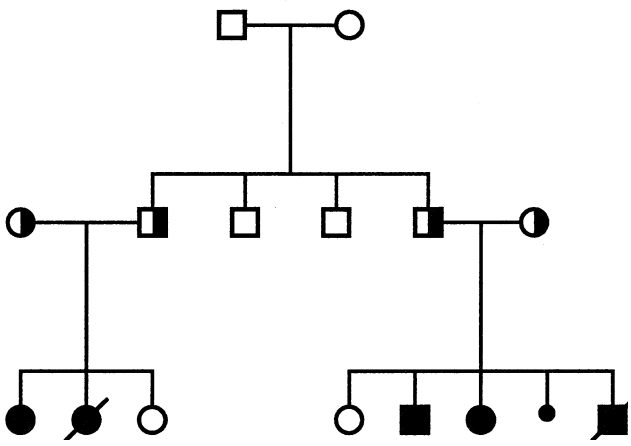

Fig. 3. Pedigree of C.K. family.

Patient 5

S.K. is the younger sister of D.K. (Fig. 3). She was the 2,784 g product of a term pregnancy to a 33-year-old G5 P3 AB1 woman. At birth she had hypotonia, microcephaly, low-set soft ears, anteverted nares, posterior cleft palate, left simian crease, right bridged simian crease, ulnar deviation of fingers, low set thumbs, ambiguous genitalia (absent labia minora and absent vaginal opening), 2–3 and 3–4 toe syndactyly and foot deformities. SLOS was diagnosed neonatally. Her peripheral blood chromosomes were normal (46,XX). She failed to thrive, required hospitalization but did not need a feeding gastrostomy tube. She walked with assistance at age 6 years. She also has photosensitivity, tactile defensiveness, self-abusive behavior inflicted by her teeth and nails, short stature, microcephaly, moderate to severe mental retardation, insomnia, 30° left lumbar scoliosis, two Harrington rod placement procedures, and severe pes planovalgus deformity despite surgical corrections. She is not toilet-trained and wears a bilateral, double metal upright ankle foot orthosis with valgus correction T-straps. Her cholesterol therapy (1 g/day) was initiated at age 16 years. Now 18 years old, she is a well-nourished, sociable, happy, and manageable young woman who lives in a community living facility home. She has a vocabulary of five words, and loves to sing and listen to music.

Patient 6

K.E. (Fig. 4) was the 3,048 g product of a 42-week pregnancy to a 24-year-old G2 AB1 woman. The pregnancy was complicated by oligohydramnios noted at term. Delivery was by Cesarean section for failure of labor to progress and absent amniotic fluid. The infant had a weak cry and meconium-stained cord and fingers, was malformed and hypotonic. She had microcephaly, congenital posterior polar cataracts, gingival hyperplasia, micrognathia, ambiguous genitalia, congenital dimples of elbows and back, radial deviation of fingers, bilateral upper and right lower limb postaxial polydactyly, bilateral 2–3 toe syndactyly, ambiguous genitalia, long segment Hirschsprung disease, and bowel malrotation. At age 2 weeks, she had a colostomy, Nissen fundoplication for gastroesophageal reflux, and a gastrostomy-tube placement. The family history was unremarkable, and the marriage was nonconsanguineous. She developed intolerance to several infant formulas and was hospitalized for severe failure to thrive. At age 4 ½ years, she weighed 5.8 kg, unchanged since age 1½ years. Although phenotypically female her karyotype was (46,XY) with gonads present in the inguinal canal. She had seizures at 5 months, hypertension from birth until age 5 months, a history of dumping syndrome, elbow and knee contractures, metatarsus adductus deformities and valgus deformity of both feet, patent ductus arteriosus, unexcised right cataract, hypogonadotropic hypogonadism and cranial MRI findings of microcephaly, partial agenesis of the corpus callosum, small cerebral hemispheres, colpocephaly, and cerebral atrophy. Her bone age was significantly delayed. Cholesterol replacement therapy (85 mg/kg/day) was begun at age 4¾ years.

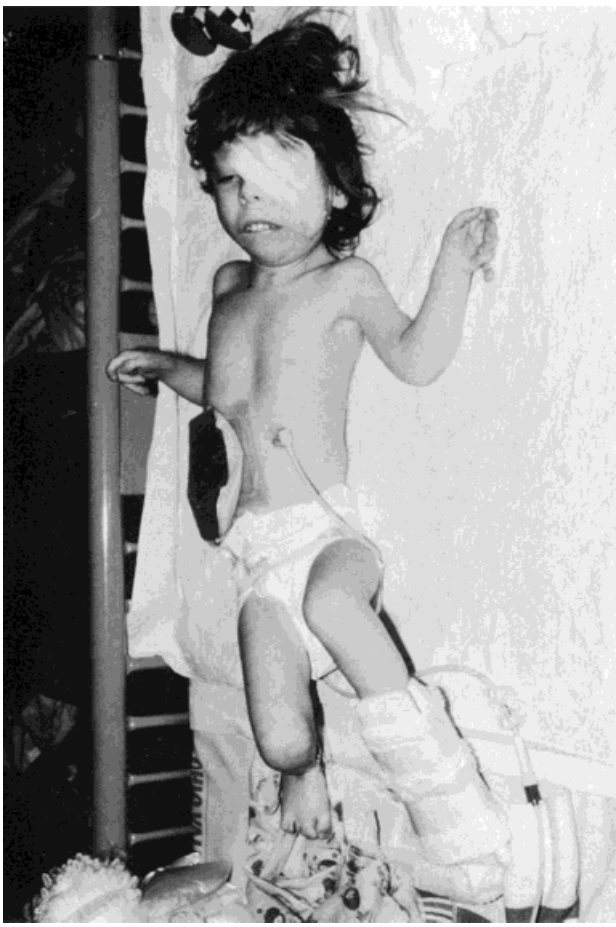

Fig. 4. K.E. at age 4 years and 8 months.

Now 5⅓ years, she requires a gastrostomy tube, is developmentally delayed, and is neither ambulatory nor toilet-trained. Since the initiation of the therapy, she has steadily gained weight (2.1 kg in 6 months), made slow progressive psychomotor development, is more alert and interactive, loves hand bells, and loves to sing. Her favorite activity is to get on her knees and elbows and rock backwards and forwards.

The children have improved (motor and social development) and, although nonverbal, are attempting to pronounce some words. All six patients have prominent alveolar ridges, pre-treatment abnormal urinary bile acids, normal vitamin A, D, E and K levels, and the older children have prominent lips.

TREATMENT

A month after the biochemical diagnosis of SLOS in Patient 1 (low serum cholesterol and abnormally elevated 7-DHC), an attempt was made to alter her metabolic status by giving her exogenous cholesterol (20–40 mg/kg/day) followed 6 months later by the addition of bile acids in the form of chenodeoxycholic acid (7 mg/kg/day) as described previously by Irons et al. [1994] and cholic acid base (15 mg/kg/day). Her cholesterol intake was gradually increased to 85 mg/kg/day. At age 32 months, her cholic acid was discontinued because of severe diarrhea and at age 43 months, her chenodeoxycholic acid was discontinued. She has been on supplementation therapy for a total of 33 months.

Patient 2 has also been on replacement therapy for 33 months. However, chenodeoxycholic acid therapy was discontinued after 12 months because significant elevation of her plasma transaminases. Her cholic acid base was discontinued when she was 40 months old, and her cholesterol replacement therapy is presently at 125 mg/kg/day level.

Patients 3–5 have been on cholesterol replacement therapy (1 g/day) for 24 months with the exception a 2-month period when they received ursodeoxycholic acid supplementation. Patient 6 has been on cholesterol replacement therapy (gradually increased to 85 mg/kg/day) for 8 months. She has never tried bile acid replacement therapy. Results from these studies are shown in Figures 5–10.

During this study every attempt was made to correlate plasma neutral sterol levels with each patient's clinical status. Although plasma cholesterol level increased steadily in the SLOS children, it rapidly decreased during intercurrent illness and, except for a brief period in patient 1, the levels have yet to approach the normal age appropriate levels (Fig. 8). Patient 2 has had many episodes of diarrhea, otitis media, sinusitis, and seizures after the initial 12 months of therapy. Her

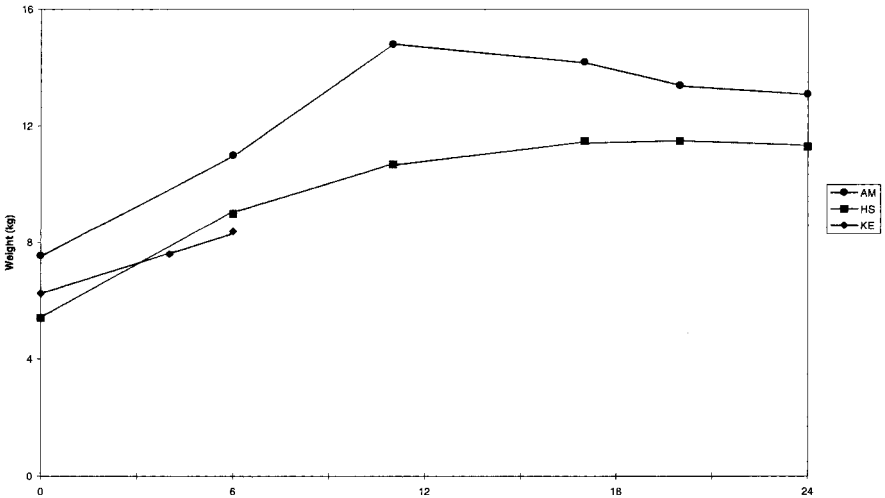

Fig. 5. Weight of SLOS children while on replacement therapy.

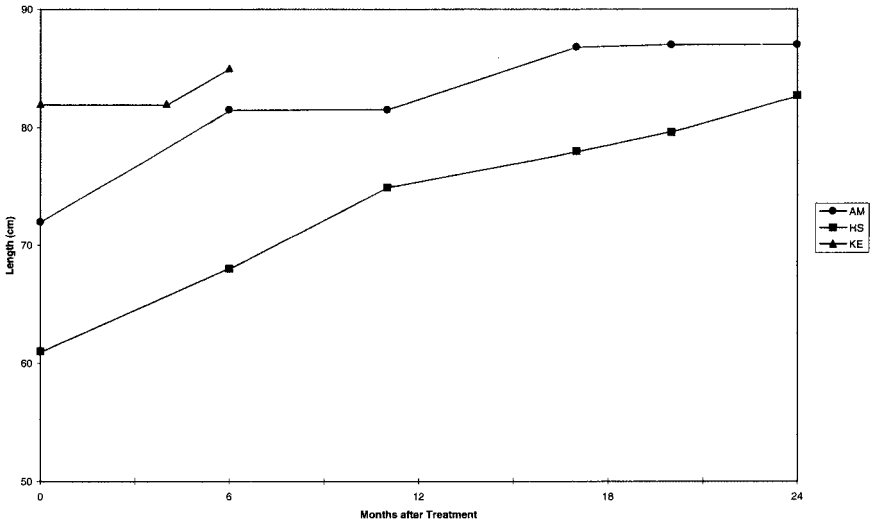

Fig. 6. Length of SLOS children while on replacement therapy.

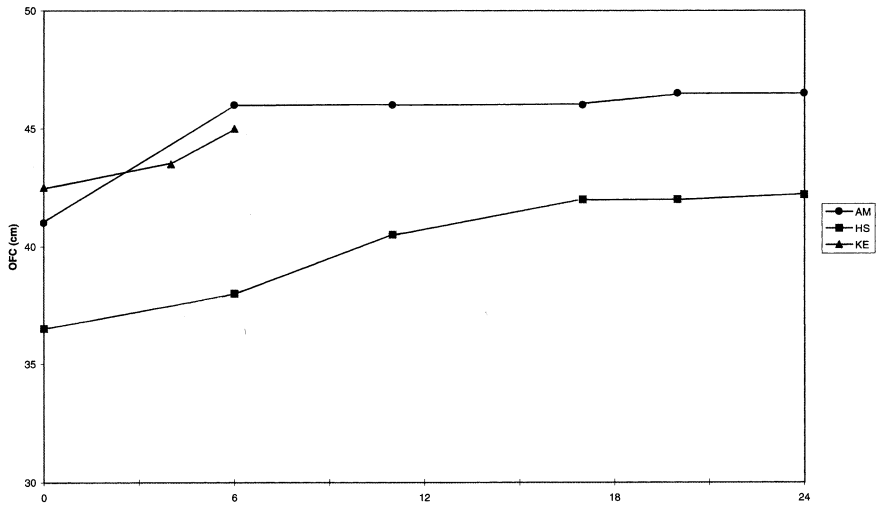

Fig. 7. OFC of SLOS children while on replacement therapy.

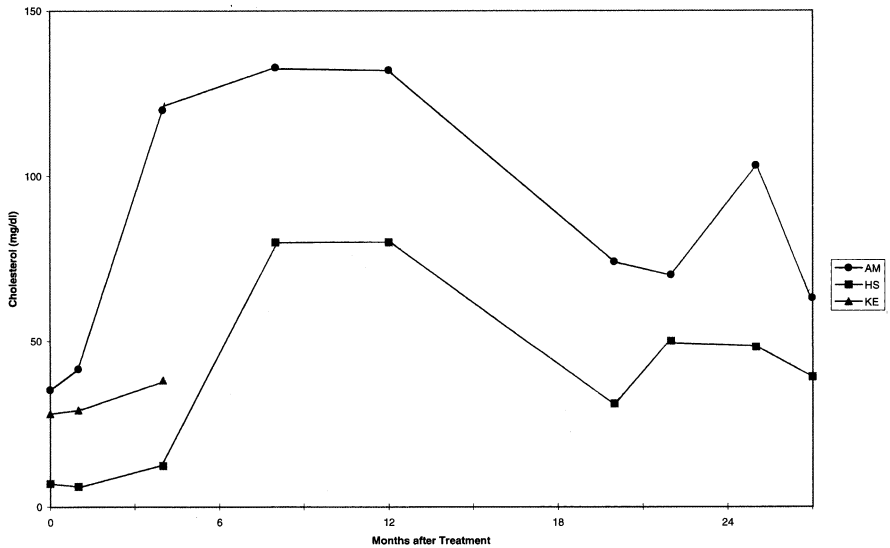

Fig. 8. Plasma cholesterol levels in children with SLOS during the first 27 months of replacement therapy.

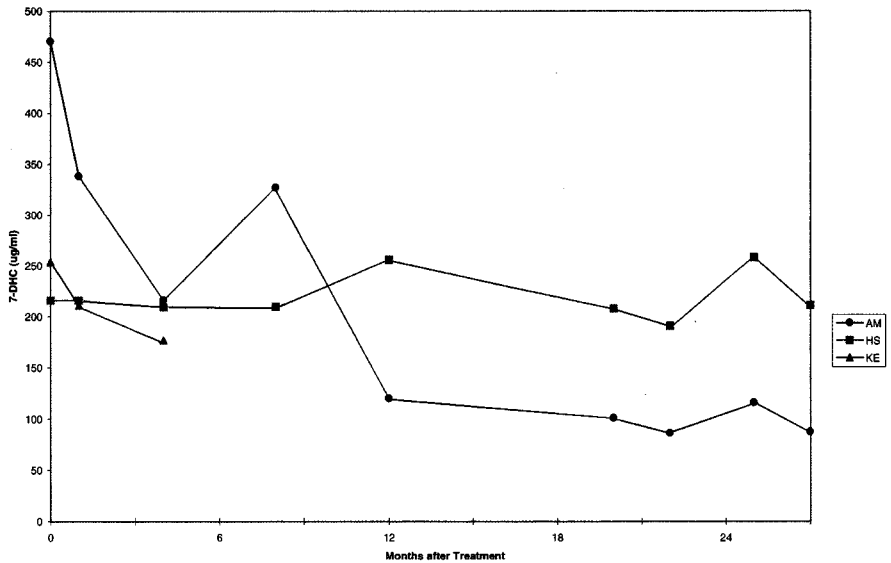

Fig. 9. Plasma 7-DHC levels in SLOS children during the first 27 months of replacement therapy.

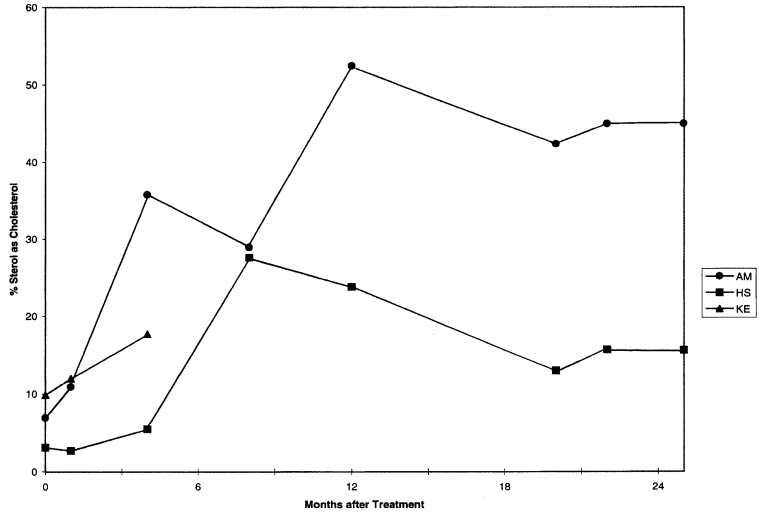

Fig. 10. Percent sterol as cholesterol in SLOS children during the first 27 months of replacement therapy.

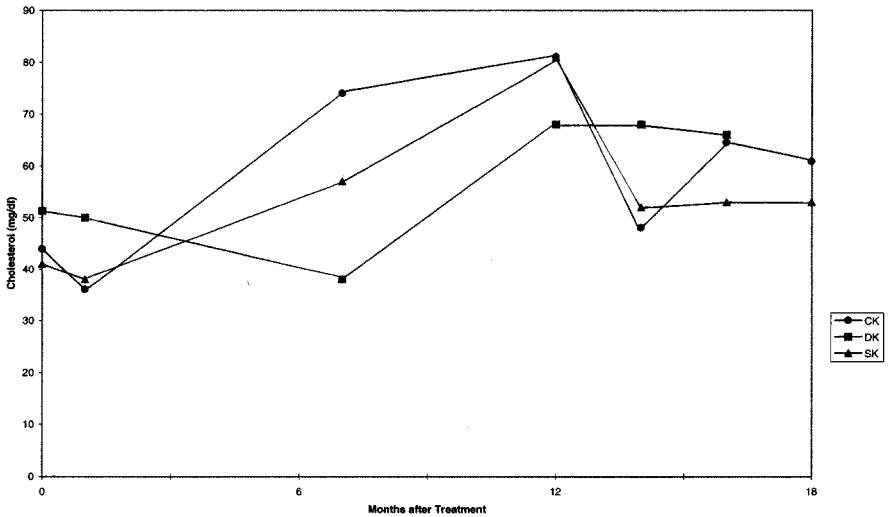

Fig. 11. Plasma cholesterol levels in SLOS adults during replacement therapy.

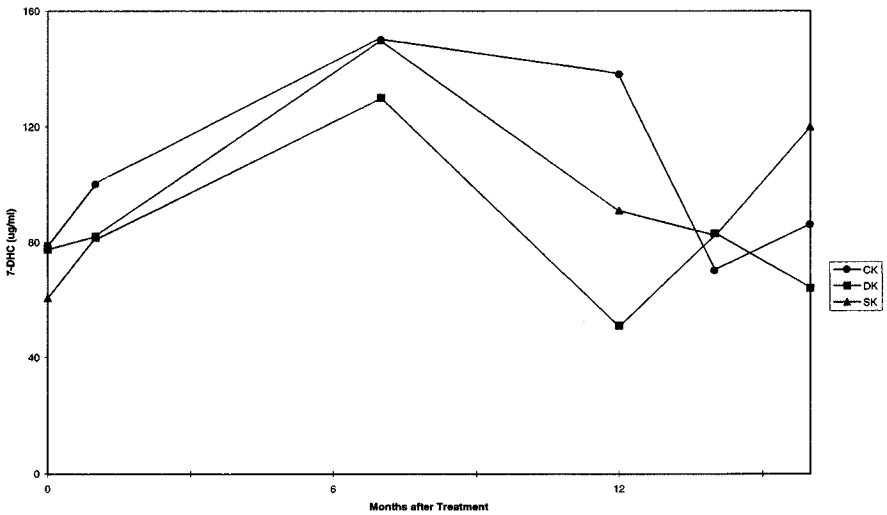

Fig. 12. Plasma 7-DHC levels in SLOS adults during replacement therapy.

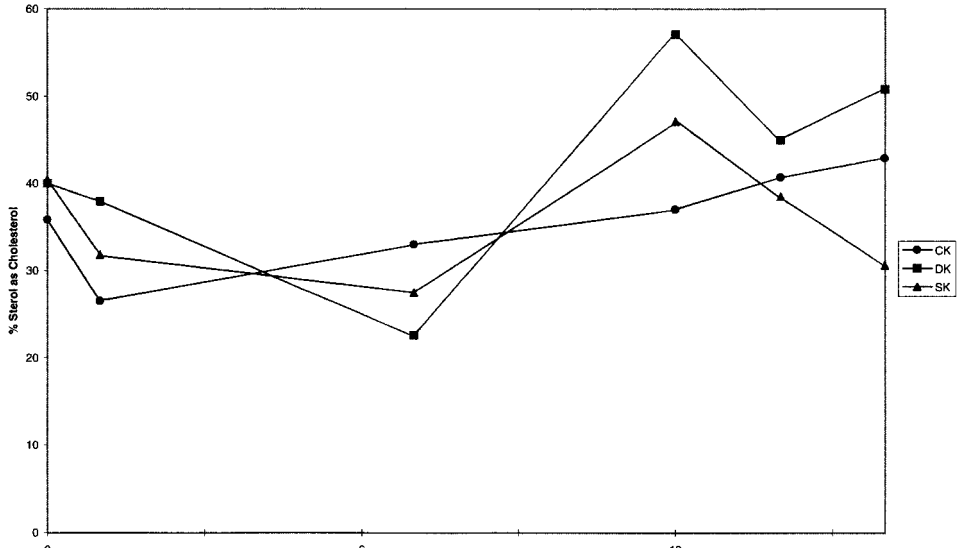

Fig. 13. Percent sterol as cholesterol in SLOS adults during replacement therapy.

condition has finally stabilized. In all SLOS children, the plasma 7-DHC levels increased with intercurrent illness. However, there was an overall increase in the percent sterol as cholesterol in the children (Fig. 10). Similar changes were not observed in the older patients (Fig. 13). Although the changes in their plasma cholesterol and 7-DHC levels are insignificant (Figs. 11, 12), there was marked improvement in their psychosocial status.

DISCUSSION

The six patients had the physical manifestations of SLOS, although this is not so obvious in the older patients. All patients had the biochemical characteristics unique to SLOS. In the children, cholesterol therapy improved their caloric intake, reduced the frequency of infection and their ability to overcome these infections, allowed them to make slow but progressive gains in psychomotor development, and resolved their skin exanthem, photosensitivity, and tactile defensiveness. There was a significant improvement in their disposition and sociability. It appears that early cholesterol replacement therapy improves the growth in these children, and the dietary intake of A.M. and H.S. has been reduced to maintain them at an acceptable weight for age. It is presently unclear whether this replacement therapy has any effect on the central nervous system of these children as there is presently no information on the transport of cholesterol through the blood-brain barrier of the human infant, child, or adult. We are in the process of accurately correlating the developmental status of these children by periodic comprehensive developmental assessment. Cholesterol therapy in the adult patients resulted in behavior alteration such as control of aggressive behavior, which manifested as frequent temper outbursts, trichotillomania, biting of hands, and self-inflicted facial and upper limb wounds by the use of the nails. There has been improvement in their tactile defensiveness, photosensitivity, skin exanthem, and a dramatic improvement in their appetite with associated weight gain that has resulted in the institution of diet control. They have become more sociable and now initiate direct personal contact such as hugging. There has been no evidence of toxicity of the replacement therapy in any of these patients. Cholic acid treatment was discontinued as there was no strong evidence of benefit to the children at this time. However, we think that a certain subgroup of SLOS patients will most likely benefit from added bile acid supplementation, but the criteria for identifying this population remain to be established.

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