

# Smith-Lemli-Opitz Syndrome

## Case Report

R. H. A. RUVALCABA, ALBERT REICHERT, and DAVID W. SMITH

*From Rainier School, Department of Institutions, Buckley, Washington; and the Department of Pediatrics, University of Washington, Seattle, Washington*

To date, 11 cases with the Smith-Lemli-Opitz syndrome of failure to thrive and mental retardation, plus anomalies of the face, hands, feet, and genitalia have been reported (Smith, Lemli, and Opitz, 1964; Gibson, 1965; Blair and Martin, 1966; Dallaire and Fraser, 1966; Pinsky and DiGeorge, 1965). The purpose of this paper is to describe one more case which, in addition, presented evidence of anomalous brain structure and abnormal carbohydrate metabolism.

### Case Report

This 5½-year-old Caucasian boy (Fig. 1) was the first-born child of a 19-year-old mother and a 21-year-old father. The parents were not related and there was no family history of congenital anomalies or known hereditary diseases. A 2-year-old female sib is normal except for a 'pigeon-toe' deformity.

**Pregnancy.** The mother had diathermy treatments to the back during the first two months. She was immunized with a smallpox vaccination and typhoid injections between the third and fourth month, and was admitted to hospital because of hypertension during the last month. The weight gain was 8.2 kg. (18 lb.) during the gestation of 43 weeks. The child was born by normal delivery. The birth length was 50 cm., with a birthweight of 2330 g.

**Postnatal course.** He had a poor suck and severe projectile vomiting during the first six months of life. Pyloric stenosis was suspected but could not be shown. He failed to thrive, the increments of height and weight being consistently below the third centile. Mental retardation was suspected at an early age. Three psychological evaluations performed at 2 3/12, 3 2/12, and 4 2/12 years showed mental ages of 1, 1, and 2 3/12 years, respectively. At 5 9/12 years of age the mental age was estimated to be 2 3/12 years. Acquired diseases included pneumonitis and a non-specific febrile erythematous illness.

**Physical examination.** At 5 9/12 years his height was 100.5 cm., with a height age of 3 7/12. His weight of 31.5 kg. represented a weight age of 3 3/12 years. His head circumference was 46.5 cm., below 3 SD from the mean for age (Watson and Lowrey, 1962). His skin was mottled and he had scanty blond curly hair. The frontal area was narrow, with mild plagiocephaly. He had broad and short nostrils, inner epicanthal folds, moderate ptosis of the eyelids, and intermittent right esotropia. The nasal bridge was broad, with an interpupillary distance of 5 cm., and the canthal index was 39. The auricles were asymmetrical;

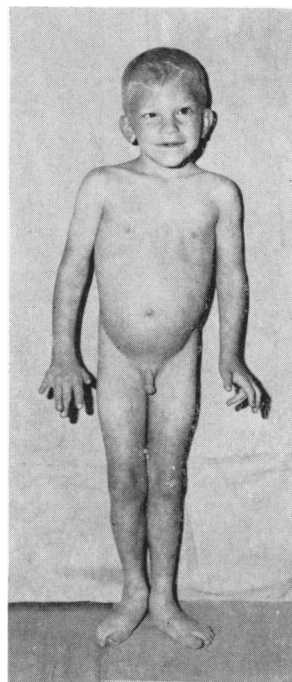


FIG. 1.—The patient at 6½ years of age.

the left measuring 5.7 cm. in length, and implanted at a 15° angle away from the perpendicular, whereas the right was 5.4 cm. and was at a 2° angle. The mandible was small. The central and lateral incisor teeth were located above the occlusal plane and angulated labially. The neck was short. The chest showed moderate pectus excavatum. There were deep sacral dimples, and a pre-anal dimple. The penis measured 3 cm. and was bound down by chordee. The testicles were not palpable.

He showed functional preference for the left upper extremity. The muscular tone was normal. He had asymmetry of the fingers, the fifth finger being unusually short and the third and fourth relatively long, and the right thumb was hypoplastic. There was partial syndactyly between the fourth and fifth fingers. The thenar eminences were flat. He had poor function of the fifth fingers and a non-functional right thumb. There was moderate metatarsus-adductus. The toes were asymmetrical, the fifth toes being hypoplastic and the third toes having a somewhat plantar origin. There was partial syndactyly of the 2nd-3rd toes.

**Dermatoglyphs.** The dermal ridge pattern of the fingers showed one whorl, 7 ulnar loops, one radial loop (on the left thumb), and one vestigial pattern (2nd finger of the left hand). The left palmar axial triradius was distally placed. There were bilateral plantar furrows.

**Laboratory examination and diagnostic tests.** Chromosomal studies performed from culture of peripheral cell leucocytes showed a normal male karyotype.\*

Urinalysis, blood urea nitrogen, serum calcium and phosphorus, and total protein, CSF cells, protein and sugar, as well as urine for amino acid screening (one-dimensional thin-layer chromatography) were normal. Routine peripheral blood cell counts were normal. The 24-hour urine 17-hydroxycorticosteroid determination was 0.7 mg., and the plasma value was 25 µg./100 ml. After a 4-hour intravenous infusion of 40 units of ACTH, the plasma value for 17-hydroxycorticosteroids increased to 47 µg./100 ml. The thyroxine plasma level by column chromatography was 4.4 µg./100 ml. as iodine.† The serum immunoglobulin level determined by the immunodiffusion assay technique (Fahey and McKelvey, 1965) showed: IgG 2020 mg./100 ml., IgA 400 mg./100 ml., and IgM 430 mg./100 ml.‡, and blood group isohaemagglutinins and antibody response to typhoid vaccine showed no abnormality.

**Radiological studies.** The intravenous pyelogram showed no abnormality. The pneumoencephalogram

showed 'symmetrical generalized dilatation of the lateral and third ventricles and a smaller than usual cerebellum'. The skull films showed moderate flattening of the occipital bone. The bone age was commensurate with his chronological age. X-rays (Fig. 2) of the hands showed fusion of the proximal and central parts of the fourth and fifth metacarpals in a Y-shape; however, the fifth left metacarpal was rudimentary. The phalanges of the right thumb were hypoplastic. Those of the feet showed subluxation of the distal phalanges of the fourth and fifth toes.

**Carbohydrate studies.** Alteration in the ability to maintain euglycaemia was detected in this case during an institutional screening for hypoglycaemia (Ruvalcaba, Reichert, and Kelley, 1967). Following a 24-hour fast, the patient was lethargic, sweating, and pale, at which time the venous sugar value by the Somogyi and Nelson method (Nelson, 1944) was 40 mg./100 ml. Blood sugar values after overnight fasting ranged from 63 to 88 mg./100 ml. The blood sugar response to standard intravenous tests with glucose, epinephrine, glucagon, and insulin was considered to be within normal limits. A test for detection of ketogenic hypoglycaemia (Colle and Ulstrom, 1964) showed ketonuria 12 hours after administration of the ketogenic diet; after 24 hours the patient was lethargic and sweating, with a blood sugar value of 33 mg./100 ml. At this time there was no glycaemic response to glucagon, suggesting depletion of glycogen stores.

### Comments

The pattern of malformation detected in this patient bears close resemblance to the reported cases, with the symptoms first described by Smith *et al.* in 1964 (Table). This clinical entity has been characterized by: failure to thrive, mental retardation, severe vomiting in early life, growth retardation, microcephaly, broad tipped nose, with anteversion of the nostrils, broad alveolar ridges of maxillae, ptosis of eyelids, asymmetric short fingers, and syndactyly of second and third toes, with cryptorchidism, hypospadias, and/or chordee in the male.

Our patient was found to be hypoglycaemic after a prolonged fast. It is not possible to state whether this patient's mental retardation bears any relation to hypoglycaemia in early infancy or not, as the hypoglycaemia is only present after prolonged fast or ketogenic diet.

A second feature not previously described as a characteristic of the Smith-Lemli-Opitz syndrome is the presence of cerebral ventricular abnormalities. The pneumoencephalogram revealed generalized dilatation of the lateral and third ventricles and a smaller cerebellum than expected.

Severe infectious diseases have been described in some of the previously reported cases, and a hypo-

\* Performed by courtesy of H. C. Thuline, M.D., at the Joint Cytogenetics Service Laboratory, Departments of Public Health and Institutions, Rainier School, Buckley, Washington.

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‡ Performed by the Immunology Laboratories of the Department of Pediatrics, School of Medicine, University of Washington, Seattle, Washington.



FIG. 2.—X-ray at 6 years of age. Note the deformities of the fourth and fifth metacarpals and the hypoplasia of the phalanges of the right thumb.

TABLE

*Pattern of Malformations in the Smith-Lemli-Opitz Syndrome (Smith et al., 1964; Gibson, 1965; Blair and Martin, 1966; Dallaire and Fraser, 1966; Pinsky and DiGeorge, 1965)*

Malformation	Frequency From Past Reports	Present Report
Microcephaly .. .. .	11/11	+
Hypertonicity .. .. .	5/9	0
Hypotonicity .. .. .	2/9	0
Broad nasal tip with anteverted nostril .. .. .	10/10	+
Ptosis of eyelid .. .. .	7/8	+
Broad maxillary alveolar ridges ..	6/7	0
Strabismus .. .. .	5/8	+
Micrognathia .. .. .	9/9	+
Auricle slanted or low set .. .. .	5/8	+
Cleft uvula and/or palate .. .. .	4/10	0
Flexed hand, index over third .. .. .	3/9	0
Simian crease .. .. .	7/9	0
Whorls, 9 or more .. .. .	4/6	0
Distal axial triradius .. .. .	2/7	+
Syndactyly 2nd-3rd toe .. .. .	9/10	+
Asymmetrical short finger .. .. .	3/8	+
Polydactyly .. .. .	1	0
Wide-spread nipples .. .. .	1	0
Calcaneo-varus .. .. .	1	0
Metatarsus adductus .. .. .	3/7	+
Dislocated hip .. .. .	1	0
Deep sacral dimple .. .. .	2/5	+
Pre-anal dimple .. .. .	2/4	+
Inguinal hernia .. .. .	1	0
Cryptorchidism .. .. .	9/9	+
Hypospadias or chordee .. .. .	9/9	+

plastic thymus was found at necropsy in one case (Smith et al., 1964). The present patient appears to have an adequate capacity for immune response. He has normal IgA and IgM, raised IgG immunoglobulins, normal isohaemagglutinin titres, normal lymphocytes, and a good antibody response to the typhoid antigen injection.

### Summary

A new presumed case of the Smith-Lemli-Opitz syndrome is reported, showing two previously unreported features: (1) hypoglycaemia after prolonged fast and ketogenic diet, and (2) morphological anomalies of the brain. It is not known whether the above findings are usual components of this syndrome.

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