Smith-Lemli-Opitz Syndrome

Case Report

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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.

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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 pector
muscles. There were deep sacral dimples, and a pre-anal
dimple. The penis measured 3 cm. and was bound down by
together. 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 were moderate metatarsus-adductus. The toes
were asymmetrical, the fifth toes being hypoplastic and
the third toes having a somewhat planter 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 planter furrows.

Laboratory examination and diagnostic tests.
Chromosomal studies performed from culture of
peripheral 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-hydroxycorticoid 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-hydroxycorticoids 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
isoheamagglutinins 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 ad-
ministration 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
hyperglycaemia 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 crypt-
orchidism, hypospadias, and/or orchidoe 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
or 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
Cyto genetics Service Laboratory, Department of Public Health
and Institutions, Rainier School, Buckley, Washington.
† Performed by Bio-Science Laboratory, California.
‡ 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>
<thead>
<tr>
<th>Table</th>
<th>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)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malformation</td>
<td>Frequency From Past Reports</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>11/11</td>
</tr>
<tr>
<td>Hypertonicity</td>
<td>5/9</td>
</tr>
<tr>
<td>Hypotonicity</td>
<td>2/9</td>
</tr>
<tr>
<td>Broad nasal tip with anteverted nostril</td>
<td>10/10</td>
</tr>
<tr>
<td>Ptosis of eyelid</td>
<td>7/8</td>
</tr>
<tr>
<td>Broad maxillary alveolar ridges</td>
<td>6/7</td>
</tr>
<tr>
<td>Strabismus</td>
<td>5/8</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>9/9</td>
</tr>
<tr>
<td>Auricle slanted or low set</td>
<td>5/8</td>
</tr>
<tr>
<td>Cleft uvula and/or palate</td>
<td>4/10</td>
</tr>
<tr>
<td>Flexed hand, index over third</td>
<td>3/9</td>
</tr>
<tr>
<td>Simian crease</td>
<td>7/9</td>
</tr>
<tr>
<td>Whorls, 9 or more</td>
<td>4/6</td>
</tr>
<tr>
<td>Distal axial triad</td>
<td>2/7</td>
</tr>
<tr>
<td>Syndactyly 2nd-3rd toe</td>
<td>9/10</td>
</tr>
<tr>
<td>Asymmetrical short finger</td>
<td>3/8</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>1</td>
</tr>
<tr>
<td>Wide-spread nipples</td>
<td>1</td>
</tr>
<tr>
<td>Calcaneo-varus</td>
<td>1</td>
</tr>
<tr>
<td>Metatarsus adductus</td>
<td>3/7</td>
</tr>
<tr>
<td>Dislocated hip</td>
<td>1</td>
</tr>
<tr>
<td>Deep sacral dimple</td>
<td>2/5</td>
</tr>
<tr>
<td>Pre-anal dimple</td>
<td>2/4</td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td>1</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>9/9</td>
</tr>
<tr>
<td>Hypospadias or chordee</td>
<td>9/9</td>
</tr>
</tbody>
</table>

plastic thymus was found at necropsy in one case (Smith et al., 1964). The present patient appears to have 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.

**References**


Gibson, R. (1965). A case of the Smith-Lemli-Opitz syndrome of
Smith-Lemli-Opitz Syndrome


The following articles will appear in future issues of this Journal:

Review Article: Virus Infections and Respiratory Disease of Childhood. By P. S. Gardner.
Familial Congenital Adrenal Hypoplasia. By W. S. Uttley.
Control of Enuresis with Imipramine. By D. Shaffer, A. J. Costello, and I. D. Hill.
Familial Congenital Adrenal Hypoplasia. By N. V. O'Donohoe and P. D. J. Holland.
Congenital Atrial Flutter. By Bryan J. McDonagh.
Intrauterine Growth Rate in Relation to Anorectal and Oesophageal Anomalies. By F. Cozzi and A. W. Wilkinson.
Association of Hypoglycaemia with Symptoms in the Newborn. By A. D. Griffiths.