**ABSTRACT.** Congenital syphilis continues to occur despite the advances in testing of pregnant women in many countries and the availability of penicillin since 1943. This is a report of a child with multiple systemic manifestations of congenital syphilis. This is one of the few cases of survival with pituitary involvement from congenital syphilis and the first noted case in which diabetes insipidus developed. Institution of routine testing in all countries might have prevented the severe manifestations of syphilis seen in this child. Pediatrics 2002;109(4).

**URL:** http://www.pediatrics.org/cgi/content/full/109/4/e63; congenital syphilis, diabetes insipidus, hypopituitarism.

**CASE REPORT**

The patient was a full-term Saudi Arabian male infant born to a gravida 3 para 3 female who had prenatal care in her native country. The prenatal course and pregnancy were uncomplicated; however, syphilis testing was not included as standard of obstetrical care. The patient’s birth weight was 2.8 kg. He was reported to feed poorly from birth and had copious rhinorrhea, which at times was bloody. He had gradually decreasing activity. On several visits to the pediatrician, the patient received a diagnosis of viral upper respiratory tract infections and was treated supportively without the administration of antibiotics. At 3 months of age, the patient was noted to be edematous and to have a new cardiac murmur. Accordingly, he was referred to a pediatric cardiologist. When he was admitted to the local hospital, the infant was lethargic and without spontaneous movement and cried when touched.

When he was admitted to the local hospital, the infant was lethargic and without spontaneous movement and cried when touched. His rectal temperature was 38.1°C. The heart rate was 160 beats/min, and the systolic and second heart sounds were normal. There was a grade 3/6 systolic ejection murmur at the upper sternal border radiating to the neck, back, and both axillae. Both the liver and the spleen were palpable 5 cm below the costal margins. The extremities were cold with a capillary refill of 6 seconds. Lymph nodes were palpable over the groin area and both axillae. Laboratory data are shown in Table 1. An echocardiogram of the heart showed mild left-ventricular hypertrophy, left atrial and left ventricular dilation, and peripheral pulmonary artery stenosis.

Radiographs of the long bones showed symmetrical periosteal reactions of the upper and lower extremities with sclerotic lines in the distal metaphyses. These findings were suggestive of congenital syphilis, and diagnostic evaluation revealed positive Venereal Disease Research Laboratories and Treponema pallidum hemagglutination assay (TPHA) tests (former not quantified). Abdominal ultrasound showed increased echogenicity of the renal cortex consistent with nephropathy, in addition to homogeneous enlargement of the liver and spleen.

Both parents had a positive TPHA. The patient was treated with penicillin intravenously at 50 000 U/kg every 8 hours. He was transfused with packed red blood cells for his severe anemia over 5 occasions. He received replacement thyroid hormone for his hypothyroidism, which was presumed to be central. The rhinorrhea cleared with antibiotics, but he continued to have low-grade fevers, generalized edema, difficulty feeding, and diffuse pain. He was transferred to the Children’s Hospital of Pittsburgh on day 10 of penicillin therapy because of concerns that his clinical status was deteriorating despite appropriate therapy. On examination, he was febrile to 39°C rectally and tachypneic at 52 breaths/min. His head circumference was 38 cm (below the 5th percentile for his age), and his height was 5 kg (25th percentile). His length was 53 cm (below the 5th percentile). The rest of his examination was similar to that noted in Saudi Arabia with the exception that his rhinorrhea had cleared. He continued to be irritable when passively moved, with little spontaneous movement. A quantitative rapid plasma reagin (RPR) test obtained 11 days into therapy was 1:32 768. The mother’s RPR quantitative titer was reactive at 1:1024. Human immunodeficiency virus enzyme-linked immunosorbent assays were negative for both the patient and the mother.

The patient had abnormalities of multiple organ systems secondary to his underlying syphilis: radiographs showed diffuse periostitis and demineralization of his long bones (Fig 1A). Pathologic fractures were observed involving bilateral tibias, proximal humeri, and distal ulnar metaphyses (Fig 1B). His extremities were casted for comfort and showed realignment of his fracture sites at hospital day 21 (after 21 days of antibiotics). On day 32, his extremities showed some bony healing.

The patient had respiratory insufficiency with tachypnea and a supplemental oxygen requirement until hospital day 17. The chest radiograph showed a mild hazy opacity of the left lung. His respiratory status slowly improved on antibiotic therapy and oxygen. His severe anemia prompted 2 additional packed red blood cell transfusions. An echocardiogram showed normal anatomy with a moderately dilated left atrium probably attributable to the severe anemia. There was good systolic function.

The patient had evidence of a syphilitic glomerulonephritis with nephrotic syndrome. He had gross hematuria with red blood cell casts. His urine showed a protein-to-creatinine ratio of 9.3 (normal: <0.2), with a concurrent serum albumin of 2.7 g/dL. After 21 days of treatment, urine-protein to urine-creatinine ratio

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Increased to 25 with a serum albumin of 3.6 g/dL. Serum comple-
ments were normal at 2 weeks of treatment, with C3 at 116
ng/dL (normal: 86–184 ng/dL) and C4 at 24 ng/dL (normal:
20–59 ng/dL).
Approximately 2 weeks after antibiotics and replacement thy-
roid hormone for hypothyroidism were initiated, diabetes insip-
dus developed with polyuria, diabetes insipidus, and cortisol and prolactin insufficiency, a diagnosis of hypopituitarism was entertained. 1-Desamino-8-
arginine vasopressin at 50
mg orally twice a day and cortisol at
0.45 g/dL; normal: 10–20 ng/mL, respectively. This suggested growth hormone
deficiency, although growth velocity in the first year is not depend-
ent on growth hormone. Evaluation of growth hormone defi-
ciency with clonidine stimulation tests (0–120 minutes) showed
levels of 0.3 to 1.2 ng/mL (normal: >10 ng/mL) at 19 months of
age. His fluid and electrolyte status was normal, and he was
euthyroid. The 1-desamino-8-
arginine vasopressin was discon-
tinued after his 12-month visit. He remains on therapy with cor-
tisol and levo-thyroxine. He is being allowed to outgrow his
cortisol dose. His thyroid replacement is adjusted with regard to
his free T4 level. Serial evaluations will be performed to determine the reversibility of these endocrine abnormalities. A repeat MRI at
19 months of age continued to show an empty sella turcica.
A repeat echocardiogram was completely normal. Develop-
mental evaluation by a developmental pediatric specialist re-
vealed his skills to be mildly delayed by 1 to 2 months, with mild
axial hypotonia without focal findings.

### DISCUSSION

Cases of congenital syphilis continue to occur de-
spite the advances in testing of pregnant women in
many countries and the availability of penicillin
since 1943. In the United States, the resurgence of
congenital syphilis seen since the late 1980s mirrors
the increase of cases of syphilis in adults,1 in part
from the sex-for-drugs practice during the cocaine
epidemic and from the rise in adult human immu-
nodeficiency virus infections.

Hossain et al2 reported the incidence of syphilis in
pregnant women in Saudi Arabia to be low (10
[0.8%] of 1186 women tested) in the 1980s. This is in
comparison with higher incidences in other regions,
such as 1.5% in Detroit, Michigan, in 1990 and 4% in Bolivia in 1996. Screening of outpatient populations in Saudi Arabia showed an overall prevalence of 2.7%, ranging from 0.9% in pregnant women to 12% in individuals seen in clinics of dermatology or venereal diseases.

*Treponema pallidum* is the causative agent of syphilis. Transmission is transplacental, occurring anytime during the pregnancy. A pregnant woman, in the first 4 years of untreated syphilis, has a >70% probability of transmitting the infection to her infant. The pathogenesis of syphilis is not well understood. As the bacteria invade tissues and blood vessels, a vigorous immune response unleashes activated macrophages to destroy many organisms. In the face of the host response, however, infection persists for life. Once the bacteria adhere to endothelial cells, mononuclear and plasma cells surround the affected cells and cause vasculitis. Gummas represent the maximal immunity to the treponemal organism. These are large granulomatous lesions, with a central necrotic region, consisting of plasma cells, lymphocytes, and monocytes. Gummas are often the cause of local destruction within an involved organ.

Untreated congenital syphilis usually presents by 3 months of age. Dorfman and Glasser described 7 infants (between 3 and 14 weeks of age) with delayed diagnosis of congenital syphilis, in part from lack of serologic testing of mothers and their infants at the time of delivery. Four had a characteristic rash, and the remaining 3 only had fever on presentation.

The child reported here had both common and uncommon findings of congenital syphilis. Because the pathogenesis of congenital syphilis is hematogenous spread of the treponemes, multiple organs can be affected. In this case, classic findings included snuffles, periostitis, pseudoparalysis, anemia, and thrombocytopenia. Less frequently seen but well-documented findings included renal disease. Most anemias are hemolytic, as opposed to our patient, who had evidence of bone marrow suppression secondary to malnutrition (with low reticulocyte counts and absence of red blood cell fragments on peripheral smear). In addition to having nephrotic syndrome, the primary renal manifestation of congenital syphilis, this patient had hemorrhagic glomerulonephritis. The hematuria and proteinuria persisted for several weeks and then gradually normalized over 3 months.

Another unusual feature in our patient was hypopituitarism. Syphilitic involvement of the pituitary gland was first noted in adults in 1858 and in autopo-
sies of congenitally infected infants in 1903. By 1914, pituitary disease was estimated to be present in 30% to 50% of autopsies of infants with fatal congenital syphilis. The authors speculated that death was most likely caused by untreated hypopituitarism. Berger et al postulated that with the hematogenous spread of the organisms in congenital syphilis, the pituitary gland may be affected secondarily from surrounding tissues (e.g., concurrent infection of the sella, dura, meninges, or adjacent brain tissue). Lesions of the pituitary included interstitial inflammation, fibrosis, and gummatas. These abnormalities were most often seen in the anterior region; pituitary insufficiency is manifested after 50% of the gland is destroyed. Although common in autopsies in the prepenicillin era, pituitary involvement of congenitally infected infants seems to be rare in the postpenicillin period.

Pituitary involvement is suggested by persistent hypoglycemia or abnormal growth in an infected infant. The pituitary gland of our patient could not be visualized on 2 MRIs. Manifestations of hypopituitarism in this patient included abnormal levels of thyroid hormone, growth hormone, cortisol, and prolactin, as well as the onset of diabetes insipidus. Diabetes insipidus did not become symptomatic until the hypothyroid state was corrected, possibly reflecting the essential role of thyroid hormones in excretion of free water.

Although the recommended duration of therapy of proven (or highly probable) congenital syphilis is usually 10 days, we opted for a longer duration in our patient. He had extensive involvement of multiple organs. He was still showing symptoms (diabetes insipidus and severe renal insufficiency) at day 14 of antibiotic therapy, and so the decision was to extend his antibiotic (penicillin) for 1 more week.

This is one of the few case reports of an infant with congenital syphilis surviving pituitary involvement and the first to describe diabetes insipidus. Institution of routine prenatal testing in all countries would have prevented the severe manifestations of syphilis seen in this child.

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