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Primary Hypogonadism in Two Siblings With Wolfram Syndrome

Wolfram syndrome is a rare autosomal recessive condition consisting of diabetes mellitus and optic atrophy, often associated with diabetes insipidus, neurosensory hearing loss, and/or urinary tract abnormalities. More than 100 cases have been described since Wolfram's report in 1938; several recent articles review the syndrome and reported findings (1–3).

Signs of hypogonadism have frequently been found in association with Wolfram syndrome (4–7). Hypogonadism in Wolfram patients has been attributed to hypothalamic dysfunction, and serum gonadotropin levels have been consistently low or normal (7,8). However, several recent reports have suggested that hypogonadism may be on a primary basis and not due to hypothalamic dysfunction (2,3). We report the cases of two brothers with classic Wolfram syndrome, both of whom showed evidence of progressive primary testicular failure.

The first case was a 28-yr-old man who developed insulin-dependent diabetes mellitus (IDDM) at age 4 yr. Impaired vision was first noted at age 10 yr. At age 15 yr, examination showed visual acuity of 20/80 and moderate pallor of the disks bilaterally. An audiogram showed hearing loss at 6000 and 8000 Hz bilaterally. Laboratory data included follicle-stimulating hormone (FSH) 42.7 IU/L (normal 4–25 IU/L) and luteinizing hormone (LH) 11.2 IU/L (normal 7–24 IU/L). At age 19, a testicular biopsy showed partial fibrosis and atrophy of the seminiferous tubules with absence of spermatogenesis. Leydig cells were normal. Testosterone was prescribed, but the patient discontinued use on his own in <1 yr. At age 21 yr, FSH was 111 IU/L, LH was 23 IU/L, and testosterone was 6.1 nM (normal 10.4–41.6 nM). By age 25 yr, the patient had developed an atonic bladder and was performing self-catheterizations. Evaluation at this time revealed FSH was 136 IU/L and LH was 188 IU/L. Buccal smear cytology was sex-chromatin negative.

The second case, a 24-yr-old man, who was the younger brother of the first patient, also developed IDDM at age 4 yr. At age 10 yr, he was found to have visual acuity of 20/100 with optic atrophy bilaterally. An audiogram showed neurosensory hearing loss in the range of 3000–8000 Hz bilaterally. FSH was 1.2 IU/L, and LH was 5.0 IU/L. When evaluated at age 20 yr, the patient complained of marked polyuria in the face of excellent blood glucose control (HbA_1 6.2%). Diabetes insipidus was suspected; he had dramatic improvement in polyuria with chlorpropamide treatment. Laboratory evaluation showed LH was 23 IU/L (normal <18 IU/L) and testosterone was 8.1 nM (normal 9.0–38.8 nM).

Both patients demonstrate the criteria for Wolfram syndrome, including diabetes mellitus, optic atrophy, and neurosensory hearing loss. An atonic bladder is also present in the older brother, and diabetes insipidus is suspected in the younger brother. Both patients have also been shown to develop hypogonadism that was primary and not due to hypothalamic dysfunction, as suspected in most previous reports. This association has only recently been described, and it is possible that other Wolfram patients with hypogonadism presumed to be hypothalamic may actually have primary gonadal failure.

The cause of Wolfram syndrome is unknown. The most frequently cited hypothesis is that the manifestations of Wolfram syndrome, including diabetes mellitus, could be due to a neuronal degenerative process (specifically in the hypothalamus) (1). It follows that hypogonadism in affected patients would be attributed to hypothalamic dysfunction. As more Wolfram patients with hypergonadotropic hypogonadism are found, it seems less likely that hypothalamic degeneration is solely responsible for the many reported manifestations of the disease. Much more information is needed to better define Wolfram syndrome and its etiology.

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Residential Treatment Program for Children With Diabetes Mellitus

This study describes a residential treatment program for children with poorly controlled diabetes. The program was established in March 1984 by the Sunair Home for Asthmatic Children in Tujunga, California, and was a cooperative effort with the Division of Endocrinology and Metabolism at Childrens Hospital of Los Angeles. School-aged children with diabetes were admitted if they had extremely poor diabetic control and chaotic family structure. A retrospective evaluation of this program was performed with the first 16 patients admitted.

MATERIALS AND METHODS

Residential treatment program. The Sunair Home was a nonprofit, 38-bed residential health facility with an on-site staff consisting of around-the-clock licensed nurses, child-care workers, social workers, nutritionists, and clinical psychologists. The diabetes-management protocol included 4 blood glucose determinations/day (Chemstrip bG, Bio-Dynamics, Indianapolis, IN) and 2–3 insulin injections/day. Insulin-dose adjustment was accomplished by the patients with supervision by on-site nurses. HbA_{1c} was measured by a column assay (Bio-Rad, Richmond, CA) at monthly intervals.

There was an intensive diabetes-education program, consisting of 2–3 h of classes/wk for each child and 1 h/wk for each family. An individualized psychosocial treatment program was designed for patients and families. Psychosocial assessments were derived empirically from professional observations and interviews. A self-help program similar to that proven useful for improving compliance by asthmatic children was utilized (1). Statistical analysis was performed with Student's *t* test. Results are expressed as means ± SE.

Patient profile. The patient group consisted of 9 boys and 7 girls, 8–17 yr of age (mean 12.9 yr). Mean duration of diabetes was 3.9 yr (range 1–10 yr). Patients had a mean of 5 diabetes-related hospitalizations during the preceding year (range 2–14). All children came from families with significant psychosocial problems and had low self-esteem.

RESULTS

At Sunair Home. The mean length of stay in residential treatment was 6.0 ± 0.8 mo (range 3–11 mo). Mean insulin dosage was 1.44 ± 0.14 U/kg on admission compared to 0.83 ± 0.06 U/kg on discharge ($P < .005$). Mean fasting blood glucose was 244 ± 17 mg/dl on admission and 110 ± 6 mg/dl after 2 mo of confinement ($P < .005$). Mean HbA_{1c} was 10.4 ± 0.7% on admission (normal 3–6%) and decreased to 6.59 ± 0.25% at discharge ($P < .005$). No patient had ketoacidosis or required hospitalization for diabetes management. All children had inadequate knowledge of diabetes and its management on admission. At discharge, all children except one passed written diabetes tests (75% of answers correct). Psychosocial function improved during placement. All children complied with the self-help program and felt they had improved self-esteem.

After discharge from Sunair Home. At a mean of 5.8 mo (range 3–14 mo), mean insulin dosage was 0.95 ± 0.06 U/kg (not significantly greater than the value during placement); fasting glucose level increased to 250 ± 7.8 mg/dl ($P < .005$ compared with placement value) and HbA_{1c} increased to 9.15 ± 0.8 ($P < .005$ compared with placement value). Seven hospitalizations for diabetic ketoacidosis had occurred in 5 patients. All children except 1 passed diabetes-knowledge tests. After discharge, 13 of the 16 children admitted that they were not adherent to the diabetes-management protocol with regard to blood testing and insulin injection.

DISCUSSION

This experience indicates that residential treatment can improve the metabolic status of children with poorly controlled diabetes (2). Our results support the previous finding that improved patient understanding of diabetes and meticulous attention to its management, coupled with an intense psychosocial intervention, can lead to metabolic stability even in a group of children previously classified as having brittle diabetes (3). After discharge from Sunair Home, there was return of poor metabolic status and compliance, despite main-