Teaching Point
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An uncommon genetic syndrome with acute renal failure in a 30-year-old diabetic patient

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Case

AB is a 31-year-old man who has had type 1 diabetes since the age of 7 years, severe visual impairment and hypoacousia. In August 1998 he was referred to a nephrologist because of progressive impairment of renal function. At his last evaluation by the diabetologist, his serum creatinine, previously 1.5–1.7 mg/dl, had risen to 2.4 mg/dl. During his first nephrological evaluation 5 days later, the patient reported oligoanuria beginning approximately 18 h earlier. On physical examination, the patient, who manifested a modest intellectual deficit, appeared co-operative and in good clinical condition. His blood pressure, reported as normal in the past, was 130/85 mmHg. Cardiac and pulmonary assessments were normal, and oedema was absent. A moderate bladder globus was present.

The only symptoms the patient reported were occasional dysuria and urgency during the last 3 months. Glycaemic control had been good recently (in the last year glycated haemoglobin had been in the 6.5–7.8% range) and was reported as having been generally good in recent years. Insulin therapy was standard (four daily injections), and home monitoring was adequate. The patient reported no other medication except some unspecified drugs taken occasionally for a severe depressive disorder. He also reported the diagnosis of bilateral optic atrophy as the cause of his visual impairment.

A contemporaneous measurement of serum creatinine, urea and electrolytes revealed creatinine at 3.8 mg/dl, BUN 76 mg/dl, Na 138 mEq/l, and K 4.8 mEq/l. An ultrasound study was immediately performed, and showed marked bilateral dilatation of the upper urinary tract and ureters, and bladder distension. A urologist was consulted and a bladder catheter, inserted without apparent obstruction, drained about 1.5 l of clear urine. Biochemical and microscopic urinalysis showed urinary density of 1005, proteinuria +, haemoglobin +, few red blood cells and 2–3 white blood cells per high-power field.

The patient was hospitalized in the urology ward. Within 1 week his serum creatinine decreased to 1.5 mg/dl; however, ultrasound study showed that dilatation of the urinary tract remained unchanged. Urography confirmed a marked, diffuse and bilateral dilatation of upper and lower urinary tract (Figure 1).

Urethroscopy revealed no urethral valves and a normal bladder; urodynamic studies diagnosed detrusor sphincter dyssynergy. Two attempts to eliminate the use of the catheter were fruitless. The patient was discharged with instructions for intermittent self-catheterization. Urinary output was in the range of 1.5–2.5 l/day.

Two years after the acute event, the patient’s serum creatinine was 1.2 mg/dl, his last creatinine clearance was 58 ml/min, proteinuria 0.08 g/24 h, and diuresis ranged from 2 to 3 l/24 h. The ultrasound picture was unchanged; the neurological picture had worsened progressively and the patient is currently bedridden.

Discussion

AB has the Wolfram syndrome, named after the diabetologist who first described it in 1938. The condition is also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness) [1]. This uncommon genetic syndrome is usually considered to have an autosomal recessive inheritance—the alternative hypothesis of a mitochondrial genome abnormality is still matter of discussion [2]. In the Wolfram syndrome, an array of signs and symptoms related to neuronal degeneration is reported, including urinary tract dysfunction, usually with dilatation [3,4].
The prevalence of the disease has been estimated to range from 1 in 770,000 in the UK to 1 in 68,000 in Lebanon; the carrier frequency was estimated as 1 in 354 in the UK study, and perhaps more interestingly, as occurring in $4.58 \times 10^{-1}$–$1 \times 10^{-5}$ patients with type 1 diabetes [5,6]. The prevalence of Wolfram syndrome, as is usual for autosomal recessive inheritance, is higher in some ethnic groups with high rates of consanguinity as in Turkey or Lebanon [4,6].

Usually considered as a disorder of the paediatric age group, the syndrome is now also being diagnosed increasingly in adults, because of the genetic heterogeneity and to the late onset of some complications. This is how it occurred in our case, where severe visual impairment developed after the age of 20, together with a duration of diabetes that suggested diabetic retinopathy [3,5] (Table 1).

The hallmarks of the syndrome are diabetes mellitus, which is usually the first sign of the disease (median age at diagnosis 6–10 years), followed by optic atrophy (median age at diagnosis 11 years); diabetes insipidus of hypothalamic origin is diagnosed during the third decade of life in up to 75% of cases [3]. Other signs of neuronal degeneration, in the central and peripheral nervous systems, may complicate the picture; among these signs are deafness, olivo-ponto-cerebellar ataxia, behavioural disturbances, severe depression, hypogonadism and anosmia [3,5,6].

Involvement of the urinary tract is estimated to occur in up to 90% of patients [4]. The pathogenesis of this complication was initially attributed to the high urinary output, in the presence of a functional obstacle; however, other authors advance the hypothesis that urinary dysfunction is also due to neuronal degeneration at various levels of the urinary tract. The changes reported are variable, but diffuse and huge urinary tract dilatation is frequent and usually bilateral [4,7].

Interest in this syndrome was recently enhanced by the mapping of the gene [2] and by the report of a high frequency of carriers with diabetes mellitus or psychiatric disorders [6,8].

Table 1. Patterns of end-organ damage considered in the differential diagnosis of the renal disease of AB, based on data available at hospitalization

<table>
<thead>
<tr>
<th>Organ damage</th>
<th>Comment</th>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 diabetes</td>
<td>Onset at early age (7 years); good metabolic control</td>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>Severe visual impairment</td>
<td>Diabetes-related: time of onset; diagnosis of optic atrophy</td>
<td>Severe visual impairment Optic atrophy</td>
</tr>
<tr>
<td>Deafness</td>
<td>The disease may be unrelated to diabetes; juvenile progressive deafness is, however, a rare disease—it may point to a different syndrome</td>
<td>Deafness</td>
</tr>
<tr>
<td>Acute renal failure due to neurogenic bladder</td>
<td>Diabetes-related: time of onset; concomitant blindness absence of vascular or nervous involvement; alternative explanation for visual impairment</td>
<td>Urinary tract dilatation Neurogenic bladder</td>
</tr>
<tr>
<td>Depression</td>
<td>Diabetes related: possibly more common in diabetics, relationship to other problems unusual aggressive pattern; possible relationship to mental impairment</td>
<td>Depression</td>
</tr>
<tr>
<td>Other</td>
<td>Mild mental deficit, not in keeping with diabetes, possibly suggestive of another syndrome</td>
<td>Mental impairment</td>
</tr>
</tbody>
</table>

Fig. 1. Urogram shows diffuse bilateral dilatation of upper and lower urinary tract.
The Wolfram syndrome is seldom encountered in clinical practice, but is regularly cited in two widely used classifications in internal medicine: diabetes mellitus, where it is reported as an exception to the autoimmune origin of type 1 diabetes, and diabetes insipidus, where it is considered as an example of selective neuronal degeneration [9].

The features of the Wolfram syndrome may make the differential diagnosis of diabetes with long-term complications, an interesting challenge in such cases as the one here reported, with complications occurring at an adult age. In fact, in patients with long-lasting diabetes, the discovery of the renal manifestations of the syndrome is usually made together with the staging of other signs of end-organ damage; the patterns of ocular, peripheral, and possibly central nervous involvement may overlap with those of diabetes mellitus, as they did in this case, and result in misleading interpretations of the renal and urological involvements (Table 1). (A previous diagnosis of the Wolfram syndrome made by paediatricians was not remembered by the patient, nor was available to us at his hospitalization.)

The discrepancies in the pattern of multi-organ damage, together with the presence of other problems unrelated to diabetes (deafness, mild mental deficit, severe depression), and in the absence of hypertension or vasculopathy—usual hallmarks of end-organ damage due to diabetes, prompted the search for a different unifying explanation.

Electronic databases may be precious tools for diagnosing complex or uncommon syndromes. On Medline (1966 to February 2002, week 4) our search strategy leading to a ‘best guess’ of Wolfram syndrome combined clinical data in the same order in which they appeared in the patient, from type 1 diabetes (exp diabetes mellitus or diabetes.mp: 161 176 citations), optic atrophy (3175 citations), deafness (17 548 citations), to neurological bladder (1760 citations), and retrieved only five papers.

The Wolfram syndrome, or DIDMOAD, is mentioned in all five papers retrieved in the last search combination, which included the main clinical features found in our patient. The syndrome accounted for 107 of 281 papers in the first combination, of diabetes and optic atrophy, and was the main diagnosis in 80 of 109 papers, when deafness was also added.

Teaching points

1. The differential diagnosis of end-organ damage due to diabetes may be difficult, because of, among other things, the late referral of diabetic patients with renal disease. The examination of the concomitance of commonly observed end-organ damage may offer a rapid analytical scheme.
2. Renal failure in long-term diabetic patients who also have problems not related to diabetes (deafness, mild mental deficit, severe depression) may be caused by a genetically determined Wolfram syndrome.
3. Patients with the Wolfram syndrome are now likely to live long enough to become patients of internists rather than only of paediatricians [10].
4. Electronic databases are precious tool for obtaining a speedy diagnosis, especially in cases, such as ours, of uncommon syndromes with multi-organ involvement.

References

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