Proteinuria, hypertension and chronic renal failure in X-linked Kallmann’s syndrome, a defined genetic cause of solitary functioning kidney

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Abstract

Background. Anosmia and hypogonadotrophic hypogonadism are the classic features of X-linked Kallmann’s syndrome, a disorder caused by mutations of KAL, a gene expressed during kidney and brain development. About a third of patients have a solitary functioning kidney, but little is known about their renal morbidity.

Methods. We studied seven patients aged 22–35 years with X-linked Kallmann’s syndrome and a solitary functioning kidney.

Results. Two patients developed significant proteinuria associated with mild to moderate arterial hypertension in the second to third decades of life. In one, proteinuria and renal impairment preceded the appearance of hypertension, and the disorder progressed to chronic renal failure. The remaining five patients had normal plasma creatinine concentrations and no significant proteinuria although four had borderline systolic and/or diastolic hypertension. In two sets of patients from the same kindreds, there was a striking discordance for the occurrence of renal morbidity.

Conclusions. All patients with X-linked Kallmann’s syndrome should be screened for renal malformations, and those with solitary kidneys require life-long follow-up to detect hypertension, proteinuria and renal failure.

Key words: hypertension; Kallmann’s syndrome; proteinuria; renal failure; solitary functioning kidney

Introduction

The term ‘renal malformation’ encompasses various developmental aberrations [1]. In the most extreme type, renal agenesis, the kidney is absent [2]. In an autopsy study of 9200 individuals dying of incidental causes, unilateral agenesis was noted in seven [3], whereas another, radiological, series identified no renal tissue unilaterally in 0.3% of 682 adult controls [4]. Unilateral renal agenesis is often associated with absence of the ipsilateral ureter and with malformations of the urinary tract attached to the solitary functioning kidney, including duplication and obstruction of the ureter as well as vesicoureteric reflux [5]. Bilateral renal agenesis is an order of magnitude less common than unilateral disease [6] and presents with the Potter’s sequence (oligohydramnios, lung hypoplasia and neonatal renal failure).

Nephrogenesis is controlled by genes which enhance or inhibit precursor cell growth [1]. Gene expression, and hence kidney development, can be perturbed by at least three types of events: mutations, urinary flow obstruction and chemical teratogens [1]. Several multi-organ malformation syndromes affecting the kidney have defined genetic bases. These include the renal–coloboma syndrome, in which renal hypoplasia and vesicoureteric reflux is caused by mutations of the PAX2 transcription factor gene [7], and the branchio-oto-renal syndrome, in which diverse malformations of the kidney and urinary tract are caused by mutations of EYA1, a gene coding for a nuclear factor which may limit apoptosis [8]. X-linked Kallmann’s syndrome is another such inherited disorder which incorporates renal malformations [9].

Anosmia and hypogonadotrophic hypogonadism are defining features in patients with Kallmann’s syndrome and occur because of defective migration of olfactory and gonadotrophin-releasing hormone neurons from the nasal placode into the precursor of the forebrain: this is associated with failure of olfactory bulb development [10]. KAL gene [Xp22.3] mutations cause the X-linked form of the syndrome [9,11,12]. It has been established recently that about one-third of patients with this disorder have a solitary functioning kidney with presumed
contralateral renal agenesis [9,13], but little is known regarding the potential for renal morbidity in these individuals. We now draw attention to the fact that, at least in some patients with X-linked Kallmann’s syndrome, the solitary functioning kidney can be accompanied by proteinuria, hypertension and renal failure.

**Patients and methods**

We studied seven patients from four X-linked Kallmann’s kindreds [9,13] with solitary functioning kidneys as assessed by 99mTc-technetium-dimercaptosuccinic acid (DMSA) scan, a test delineating renal parenchyma. In addition, ultrasound scans had failed to detect contralateral kidneys. The patients’ current renal status (blood pressure, plasma creatinine and proteinuria) is shown Table 1, and case histories are given below. All were treated with testosterone replacement since their teenage years.

**Kindred A**

The endocrine and genetic aspects of this family have been described by Pike et al. [14] and Bouloux et al. [15]. Patients 1 and 2 are cousins. Two other family members (the brother and a maternal uncle of patient 1) also have Kallmann’s syndrome but have two functioning kidneys on DMSA scans [13]. These patients also have X-linked ichthyosis with steroid sulfatase deficiency. They have a contiguous gene defect with deletion of 6–7 megabases on Xp22.32 incorporating KAL and steroid sulfatase loci.

Patient 1 was born on April 4, 1972. Blood pressure had been documented from the age of 15 years (Figure 1). Levels in his late teenage years were normal (100–120/65–70 mmHg) but he was noted to have mild diastolic hypertension (90 mmHg) at 23 years and was treated with an angiotensin-converting enzyme inhibitor (Quinapril, 5 mg/day). Plasma creatinine was first measured at 17 years and was elevated at that time (130 μmol/l; normal <120 μmol/l). Values rose progressively to 209 μmol/l at the age of 23, corresponding to a creatinine clearance of 36 ml/min, when he was started on antihypertensive treatment. However, plasma creatinine continued to rise, with a value of 270 μmol/l at 25 years (Figure 1). Dipstick-positive proteinuria [2+ to 4+] was documented between 19 and 25 years (Figure 1), with a recent total urinary protein excretion of 1.4 g/day (normal <0.2 g/day), and a urinary albumin/creatinine ratio of 210 mg/mmol (normal <6.8). Plasma albumin, complement and immunoglobulin levels were normal, as was his anti-nuclear factor (ANF) titre. Mid-stream urine (MSU) showed no bacterial growth, red or white cells. Hence renal impairment and proteinuria appeared to precede significant hypertension in this individual (Figure 1).

Patient 2, the cousin of patient 1, was born in December 4, 1974. At the age of 4 years, he was investigated for a small penis and undescended testes. At that time, he was also noted to have gonadotrophin deficiency and ichthyosis, and his blood pressure was normal (100 mmHg, systolic). We reviewed his renal status when he was 23 years old (Table 1). He had borderline systolic and diastolic hypertension (140/90 mmHg), with normal plasma creatinine and no evidence of increased excretion of protein. MSU was normal. Hence, there was a striking discordance between this patient and his cousin, patient 1, with regard to renal morbidity.

**Table 1. Renal status of Kallmann’s syndrome patients with solitary functioning kidneys**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Blood pressure (mmHg)*</th>
<th>Plasma creatinine (μmol/l)</th>
<th>Proteinuria (dipstick)</th>
<th>Albuminuria (Alb/Creat) (mg/mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls Young adults</td>
<td>&lt;140/90</td>
<td>&lt;120</td>
<td>0/+</td>
<td>&lt;6.8</td>
</tr>
<tr>
<td>Patient 1</td>
<td>24</td>
<td>120/75*</td>
<td>275</td>
<td>++ + +</td>
</tr>
<tr>
<td>Patient 2</td>
<td>22</td>
<td>140/90</td>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>Patient 3</td>
<td>31</td>
<td>100/70</td>
<td>96</td>
<td>0</td>
</tr>
<tr>
<td>Patient 4</td>
<td>29</td>
<td>170/115*</td>
<td>126</td>
<td>++ +</td>
</tr>
<tr>
<td>Patient 5</td>
<td>23</td>
<td>145/80</td>
<td>82</td>
<td>0</td>
</tr>
<tr>
<td>Patient 6</td>
<td>31</td>
<td>145/80</td>
<td>79</td>
<td>0</td>
</tr>
<tr>
<td>Patient 7</td>
<td>35</td>
<td>130/95</td>
<td>86</td>
<td>0</td>
</tr>
</tbody>
</table>

*Mean of two readings; *on regular treatment with ACEI; °on treatment with ACEI but poor compliance.
Kindred C

Patients 5 and 6 are half-brothers (they share a mother) and have typical X-linked Kallmann’s syndrome. The maternal uncle also had X-linked Kallmann’s syndrome.

Patient 5 was born on November 6, 1974. When we reviewed him at the age of 23 years, he had borderline systolic hypertension (145/80 mmHg) with normal plasma creatinine, and no evidence of increased urinary albumin excretion (Table 1). There was no excessive tubular proteinuria (RBP/creatinine 7 μg/mmol, NAG/creatinine 13 U/mmol). MSU was normal.

Patient 6 was born on September 22, 1966. When reviewed at the age of 31, he had borderline systolic hypertension (145/80), other parameters being normal (Table 1). MSU was normal.

Kindred D

This patient has typical features of Kallmann’s syndrome.

Patient 7 was born on September 3, 1961. At the age of 15 he was investigated for abdominal pain and was found to have a single functioning kidney on the right with a left ureteric stump identified on cystoscopy. When we reviewed him at the age of 35 years (Table 1), he had borderline diastolic hypertension (130/95 mmHg), normal plasma creatinine and urinary albumin excretion and no evidence of excessive tubular proteinuria. An ultrasound and intravenous pyelogram showed a hypertrophied right kidney with normal calyces as well as contrast in the distal extremity of a left ureter (Figure 3): in view of the blind-ended ureteric stump, this dye is likely to represent reflux from the bladder. No renal tissue could be identified on the left by ultrasound, DMSA or MAG3 isotope scans. An indirect isotope study

Fig. 1. Decline in renal excretory function in patient 1. Open circles denote 1/plasma creatinine and closed circles refer to proteinuria.

Fig. 2. DMSA scans on brothers in kindred B. In (A), patient 3, the right kidney is absent, while in (B), patient 4, the left kidney is absent with a diminished signal in the upper pole of the solitary functioning organ.
mesonephric duct [13], which also gives rise to the ureter and collecting ducts. An extension of this study noted a solitary kidney in nine of 27 X-linked patients (33%) [9]. The solitary kidney which occurs can be large or ‘hypertrophied’ [17], a normal response to the absence of a contralateral organ. Wegenke et al. [17] reported a case of X-linked Kallmann’s syndrome with a solitary but duplex renal tract: the upper renal moiety was attached to a dilated ureter, while the lower part connected to a separate ureter with vesicoureteric reflux. We are also aware of an unreported kindred with proven vesicoureteric reflux (W. Heale, personal communication). Finally, Levy et al. [22] reported two females with anosmia and hypogonadism with vesicoureteric reflux, but these patients probably represent a phenocopy of the Kallmann’s syndrome unlinked to the X chromosome, and Quinton et al. [9] failed to find renal agenesis in non-X-linked patients with anosmia and hypogonadism.

In the current report, we have added to previous observations by measuring blood pressure, plasma creatinine and protein excretion in seven individuals with Kallmann’s syndrome and a solitary functioning kidney. Two patients were found to have developed moderate proteinuria in the second and third decades of life: this was associated with mild to moderate arterial hypertension. In one individual (patient 1), proteinuria and renal impairment appeared to precede significant hypertension and the disorder was associated with a progressive renal failure. The remaining five patients had normal plasma creatinine concentrations and no evidence of gross proteinuria or microalbuminuria. Four, however, had borderline systolic and/or diastolic hypertension. In two affected brothers from the kindreds A and B, there was a striking discordance for the occurrence of renal morbidity. Since all the patients we studied were young adults, further follow-up is necessary to establish the final number of individuals who develop proteinuria or renal impairment. It is of note that an uncle with Kallmann’s syndrome in kindred B required treatment for end-stage renal failure, although the details of his nephropathy were unavailable for review.

**Discussion**

X-linked Kallmann’s syndrome constitutes a human genetic model of a solitary functioning kidney. Occasional reports of Kallmann patients with solitary kidneys appeared before 1985 [16–20], although it is of note that this association was not made in the ‘definitive’ report of the syndrome by Kallmann and colleagues in 1944 [21]. Kirk et al. [13] investigated 17 patients with X-linked Kallmann’s syndrome including patients with large deletions of the short arm of the X chromosome (encompassing the KAL and steroid sulfatase loci) as well as individuals with discrete KAL mutations. Using DMSA scans, 37% had one functional kidney and no ectopic organs were detected. This study also documented a male infant with the Potter sequence, compatible with bilateral renal agenesis, giving a total of 40% of patients with either un- or bilateral agenesis. Two patients also had an absent ipsilateral vas deferens, a structure derived from the mesonephric duct [13], which also gives rise to the ureter and collecting ducts. An extension of this study noted a solitary kidney in nine of 27 X-linked patients (33%) [9]. The solitary kidney which occurs can be large or ‘hypertrophied’ [17], a normal response to the absence of a contralateral organ. Wegenke et al. [17] reported a case of X-linked Kallmann’s syndrome with a solitary but duplex renal tract: the upper renal moiety was attached to a dilated ureter, while the lower part connected to a separate ureter with vesicoureteric reflux. We are also aware of an unreported kindred with proven vesicoureteric reflux (W. Heale, personal communication). Finally, Levy et al. [22] reported two females with anosmia and hypogonadism with vesicoureteric reflux, but these patients probably represent a phenocopy of the Kallmann’s syndrome unlinked to the X chromosome, and Quinton et al. [9] failed to find renal agenesis in non-X-linked patients with anosmia and hypogonadism.

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It is recognized that apoptosis-driven regression of multicystic dysplastic kidneys [23] can produce tiny remnants which, on occasion, cause arterial hypertension, probably via renin secretion [24]. Although such lesions may not be detectable by ultrasound or radioisotope scans, and hence would mimic renal agenesis, we know of no reports of multicystic dysplastic kidneys or such rudiments in Kallmann’s syndrome. However, direct inspection at laparotomy (or autopsy) would be necessary to exclude the latter possibility totally [24]. To our knowledge, there is only one published report of autopsy-proven unilateral agenesis in Kallmann’s syndrome [18]. However, Sainton [20] did comment on a eunuchoid male who was found to have unilateral renal agenesis at post-mortem: although the olfactory bulbs were not examined, this individual most likely had Kallmann’s syndrome [20]. In the current series, we noted that the urinary tract opposite the solitary...
functioning kidney was not completely absent in patient 7 because a blind-ending ureteric stump was detected at cystoscopy.

Reports of non-syndromic congenital solitary kidneys demonstrate that this condition is not always benign [2]. Thorner et al. [25] reported two such children who had proteinuria, renal impairment and glomerulosclerosis, while others described four children with congenital single kidney and proteinuria [26]. Kiprov et al. [3] found focal segmental glomerulosclerosis in seven solitary kidneys, and two of these patients developed chronic renal failure. A recent study reviewed 157 adults with unilateral renal agenesis and found hypertension in 47%, proteinuria in 19% and decreased renal function in 13% [27]. Arfeen et al. [28] described a 22-year-old woman with a congenital solitary kidney with proteinuria, renal failure and glomerulosclerosis; two of her four children also had a single kidney, but the genetic lesion in this kindred is unknown.

Perhaps these cases, as well as individuals with Kallmann’s syndrome and renal impairment, have ‘hyperfiltration damage’, an eventual decline in function of too few glomeruli which become hypertrophied and sclerosed [29]. Certainly, the creatinine clearance of 102 ml/min measured in patient 4 is evidence for an enhanced single nephron filtration rate, assuming that no more than a normal number of glomeruli were present in his solitary kidney. In future, it would be interesting to measure GFR and renal plasma flow in this and other patients to confirm hyperfiltration. Thus far, renal biopsy material is unavailable from our two proteinuric patients but we speculate that glomerulosclerosis might contribute to their proteinuria. Interestingly, glomerulosclerosis has been documented in children with oligomeganephronic renal hypoplasia: these individuals are born with significantly fewer nephrons than normal [30].

Another explanation for renal damage in patients born with single functional kidneys is that such organs may be attached to abnormal lower urinary tracts which predispose to renal damage [5]. In fact, one of our patients (patient 4) had a DMSA scan compatible with focal scarring from vesicoureteral reflux. However, none gave a history of urinary tract infection, and recent MSUs showed no growth.

The pathogenesis of many defects in X-linked Kallmann’s syndrome involves aberrant development. When KAL was expressed in mammalian cells, protein was localized both on the cell surface and in conditioned medium [31]: hence the gene encodes a secreted molecule. It has four fibronectin type III repeats and has homology to neural cell adhesion molecule (N-CAM), suggesting adhesive roles, and there is also a ‘four disulfide core motif’ with homology to antiproteases. At 11 weeks of human gestation, KAL mRNA localized to the olfactory bulb [32], supporting the hypothesis that KAL enables migrating neurons to enter the brain and synapse at this site [10]. Low levels of KAL transcripts are detected in the human mesonephros and metanephros at 6 weeks gestation and continued to be expressed in the metanephric cortex at 11 weeks [32], supporting the contention that KAL is involved in nephrogenesis. Presently, there are no reported data to establish whether the gene is expressed at a significant level in the adult kidney. If KAL was expressed in mature organs as well as during embryogenesis, perhaps mutations might cause progressive renal disease as well as kidney malformations.

In this context, heterozygous Wilms’ tumour-1 mutations cause glomerulosclerosis in patients with the Denys–Drash syndrome [33] whereas homozygous null mutations cause renal agenesis in mice [34]; this gene is important in maintaining glomerular integrity as well as in nephrogenesis.

From these studies, there arise many questions about renal disease in Kallmann’s syndrome. First, why are only some patients affected by a malformation, even within a single kindred? Here, the action of modifying genes can be invoked, as described in genetically engineered mice with renal malformations [1]. Second, why is the malformation unilateral? Perhaps, in order to affect nephrogenesis adversely, there needs to be a second perturbation in a group of cells destined to form a kidney: this ‘second hit’ could be a somatic mutation in another nephrogenesis gene. Certainly, somatic mutations do occur in the kidney and contribute to cyst growth in autosomal dominant polycystic kidney disease [35]. Lastly, factors other than germline mutation must determine renal morbidity in patients with a single kidney, based on the discordance of proteinuria and renal impairment between individuals in a single kindred.

We suggest that all patients with X-linked Kallmann’s syndrome are screened for renal agenesis and, furthermore, individuals found to have solitary kidneys probably require life-long follow-up to detect proteinuria, hypertension and chronic renal impairment.

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