Nephropathy in Townes-Brocks syndrome (SALL1 mutation): imaging and pathological findings in adulthood

Stanislas Faguer1,2, Adèle Pillet3, Nicolas Chassaing4, Marion Merhenberger3, Pauline Berndet-Monrozies3, Joëlle Guitard1 and Dominique Chauveau1,2

1Service de Néphrologie et Immunologie clinique et Centre de référence des maladies rénales rares, CHU Rangueil, 2INSERM unite 563, CHU Purpan, 3Service de Néphrologie, HTA, dialyse et Transplantation multi-organe, CHU Rangueil and 4Service de Génétique médicale, CHU Purpan, Toulouse, France

Abstract

Background. Townes-Brocks syndrome (TBS) is a rare autosomal dominant disease, resulting from mutation in the developmental gene SALL1. The phenotype encompasses malformations of limbs (triphalangeal thumbs and pre-axial polydactyly), intestine (anal stenosis) and ears (dysplastic ear with perception hearing loss). Renal involvement (hypodysplasia, multicystic kidneys or unilateral absence) is observed in almost half of patients and may progress to end-stage renal failure in childhood.

Methods. Herein, we report two adult patients diagnosed with TBS at age 28 and 35.

Results. Both exhibited severe chronic renal failure and kidney hypodysplasia by imaging studies while focal and segmental glomerulosclerosis (FSGS) was demonstrated in one case.

Conclusion. Regular assessment of glomerular filtration rate is mandatory throughout life in all TBS patients.

Keywords: adulthood; kidney development; nephropathy; SALL1; Townes-Brocks syndrome

Introduction

Townes-Brocks syndrome (TBS) is a rare autosomal dominant disease (MIM107480) of unknown prevalence. Diagnosis was first established in a family with five affected relatives belonging to two generations and father-to-son inheritance [1]. Some key features are easily recognized at birth, including imperforated or stenotic anus, external ear anomalies (preauricular ear tags and overfolding of ear helices), pre-axial polydactyly and tripalangeal thumbs and possibly congenital heart disease [2]. Sensorineural and/or conductive hearing loss warrants early detection in childhood. TBS results from mutations in the developmental gene SALL1 that encodes for a zinc-finger transcription factor [3]. Sporadic cases related to new mutations account for nearly half of all TBS cases [4]. Within affected families, phenotypic heterogeneity has been described [5].

Renal involvement has been reported in patients with mutation of SALL1 but precise morphological and pathological features are not described. Herein, we report two adult patients with TBS and renal failure diagnosed at ages 28 and 35. In addition, we extensively describe histopathological features of renal involvement.

Patient 1

After an uneventful pregnancy, the male proband was born with multiple congenital abnormalities: imperforated anus requiring surgery, limb malformation (unilateral pre-axial polydactyly of one hand and contralateral tripalangeal thumb, right overlapping toes and syndactily of the third and fourth left toes) and bilateral dysplastic external ears (microtia and dysplastic ear) with bilateral moderate hearing loss. Neonatal findings were suggestive of conductive abnormalities. Despite early hearing fitting, mild learning difficulties were evidenced later in childhood (without behavioural anomalies) with subsequently suited counselling. The patient had no affected relative.

At age 30, proteinuria was incidentally discovered on urinary dipstick. Five years later, the patient was referred for hypertension. The characteristics of renal involvement at presentation included increased serum creatinine [145 µmol/L, glomerular filtration rate (GFR), estimated by simplified MDRD, 70 mL/min] and proteinuria (1 g/day) without haematuria. Liver tests showed a moderate increase in alanine-aminotransferase and aspartate-aminotransferase titres (60 UI/L and 45 UI/L, respectively) without any evidence for viral (B or C) or alcohol hepatitis. Abdominal ultrasonography and magnetic resonance imaging (MRI) of the urinary tract disclosed left kidney hypoplasia (8.4 cm) with diffuse reduction of cortical thickness, while the right kidney had a normal size (10.2 cm). A few bilateral cortical cysts, ranging in size from 10 to 13 mm, were also detected (see Figure 1). Corticomedullary differentiation was unremarkable. The urinary tract was normal.
and imaging studies did not detect additional abnormalities of liver, spleen and pancreas.

A percutaneous, US-guided biopsy of the left kidney was performed. Among 11 glomeruli, typical FSGS was observed in 3 and complete sclerosis in 2. The tubulointerstitial compartment was normal except for a few inflammatory cells around sclerotic glomeruli. Electron microscopy failed to disclose electron-dense deposits or any tubular and glomerular abnormality (data not shown).

Cerebral MRI was normal. Fundoscopy disclosed mild hypertensive retinopathy, while thorough ophthalmologic examination was otherwise normal. Echocardiography was normal except for moderate, hypertension-induced, circumferential hypertrophic cardiomyopathy. Finally, auditive tests disclosed moderate bilateral neurosensitive hearing loss. Both the proband's parents were examined. None disclosed phenotypic anomalies of TBS. The two brothers could not be examined. In spite of negative family history, genetic testing for SALL1 mutation was performed after informed consent of the proband. Sequencing analysis disclosed a frameshift mutation (insertion) in exon 2 (c.981_982insTGGC) which is predicted to produce a non-functional truncated protein (p.Asn328TrpfsX28). Relatives declined genetic testing.

**Patient 2**

The male proband was born after an uneventful pregnancy. Anteriorly placed anus with anal stenosis and testicular ectopy were respectively diagnosed at ages 3 and 6. Both of them required surgery. Imaging studies performed, at age 3, detected left kidney agenesis and bladder diverticulae without vesico-ureteral reflux. Given that serum creatinine was normal at age 14, the renal follow-up was no longer sustained.

At age 28, the patient was referred for foot gouty arthritis. Clinical examination disclosed bilateral thumb ulnar deviation without polycystactyly and dysplastic ears. X-ray of the hands demonstrated triphalangeal right thumb (see Figure 2). Blood tests showed stage 4 chronic renal failure (serum creatinine 375 µmol/L; GFR assessment by inuline clearance 19 mL/mn). Blood pressure was <140/90 mmHg and there was no haematuria. Proteinuria reached 4 g/day. US and CT scan without contrast media demonstrated left kidney absence and a small-sized right kidney (10 cm) with three cysts (diameter <10 mm) and a bladder diverticulae (see Figure 1). A renal biopsy was not performed. Liver and pancreas were normal. Audiometry was not performed.

Although his relatives could not be examined, the patient reported no feature suggestive of TBS in his family. After informed consent, genetic testing was performed and disclosed a frameshift mutation (insertion-deletion) in exon 2 (c.1451_1458delACAGGTTCinsT) that is predicted to produce a non-functional truncated protein (p.Asn484IlefsX7). Genetic counselling was provided.

**Discussion**

SALL1 is one of the four mammalian homologues of the Drosophila region-specific homeotic gene spalt [6]. Recent reviews have underlined the pivotal role of Sall1 in mouse kidney development [7–11]. It is expressed in embryonic kidney mesenchyme-derived structures [12,13]. Sall1 controls the expression of major kidney development genes including Gdnf, Pax8 or FoxD1, all required for proper ureteric bud invasion [9,10]. Sall1-null mice present with kidney agenesis, severe dysgenesis or bilateral renal hypoplasia leading to early death within 24 h after birth [8]. Histological examination shows disorganized cortical structure, shrunken glomeruli, proximal tubular necrosis and multiple cysts. Note that heterozygous mice have no renal abnormality.

The two cases reported here illustrate the implication of SALL1 in kidney disease that may be encountered in adulthood. Renal presentation was not specific. However, unilateral hypoplasia and solitary kidney with a few renal cysts are suggestive of a developmental disorder, and extra-renal findings were vital clues for its hereditary basis, with TBS as a unifying hypothesis. Moreover, given a fairly typical extra-renal phenotype, both patients might well have been given a TBS diagnosis at birth (patient 1) or in childhood (patient 2).

Kidney and urinary tract involvement is not rare in TBS: in two paediatric series including 17 and 29 individuals, respectively, renal anomalies were found in 59 and 62% of the cases and early impairment of renal function in 41 and 56% [14,15]. The renal phenotype is heterogeneous and includes renal hypo- or dysplasia, multicystic kidneys, bilateral vesico-ureteral reflux (VUR), unilateral agenesis, posterior urethral valves or meatal stenosis [16–19]. Such
heterogeneity is reminiscent of similar findings in other developmental disorders, including mutation of *TCF2* or *PAX2* (see Table 1). Recently, the possibility that renal involvement related to *SALL1* mutation may be an isolated finding was demonstrated in 1 of 99 children with renal hypoplasia [20].

Long-term prognosis of renal involvement in TBS patients remains largely unknown. The risk of developing renal failure and the slope of renal decline are lacking. To our knowledge, almost 150 cases of TBS patients have been quoted in the literature [2,4,14,15,19–21]. Renal failure was recognized in at least 59 of them, including 8 who reached end-stage renal disease (ESRD) between 1 and 23 years of age [4,14,16,19,22]. Among the two largest series reported so far, totalling 61 TBS individuals from 33 unrelated families, only 3 (5%) reached ESRD (age unknown) and were subsequently transplanted [14,19]. However, at the last follow-up, only 18/61 (29%) were adults and late renal decline cannot be ruled out, as exemplified by patient 2, who had normal serum creatinine as a teenager but developed severe chronic renal failure in his fourth decade.

In contrast to paediatric nephrologists, adult nephrologists are not familiar with kidney involvement related to developmental genes. Hence, they may fail to make an accurate diagnosis and to pursue subsequent genetic counselling in young adult patients seeking care for chronic renal failure of obscure origin. The question is, when to suspect and how to diagnose a developmental gene disorder in adult patients. First, consider that there is increasing evidence that late-onset renal failure may be associated with slow renal decline, as evidenced by *TCF2/HNF-1β* nephropathy, where the mean loss of GFR in adulthood averaged 2 mL/min/year [23]. Secondly, patients presenting renal hypoplasia or urinary tract malformation perform thorough family analysis. Although small kindred (for autosomal recessive disorders) or neomutation (for autosomal dominant trait) may hamper Ariane’s thread, even subtle extra-renal abnormality in first-degree relatives should be sought. Third, careful clinical evaluation should focus on

### Table 1. Development disorders with autosomal dominant or sporadic inheritance and renal involvement

<table>
<thead>
<tr>
<th>Gene</th>
<th>Common kidney phenotype</th>
<th>Additional urogenital findings</th>
<th>CRF</th>
<th>Extra-renal symptoms</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>SALL1</em></td>
<td>Hypo- or dysplasia, multicystic kidneys, vesico-ureteral reflux, unilateral agenesis</td>
<td>Posterior urethral valves, meatal stenosis</td>
<td>Yes</td>
<td>External ear anomalies, hearing loss, tripalangeal thumb, pre-axial polydactyly, anal stenosis or imperforation, cardiopathy</td>
<td>Townes-Brocks syndrome</td>
</tr>
<tr>
<td><em>TCF2</em></td>
<td>Hypo- or dysplasia, multicystic or paucicystic kidneys, vesico-ureteral reflux, unilateral agenesis</td>
<td>Hyperechogenic kidneys, pelvic dilatation, ectopic kidney chromophobe cancer (?)</td>
<td>Yes</td>
<td>Maturity diabetes of the young type 3, pancreas hypoplasia, liver cytolysis, genit al tract malformation</td>
<td>TCF2-related nephropathy</td>
</tr>
<tr>
<td><em>PAX2</em></td>
<td>Hypo- or dysplasia, multicystic kidneys, vesico-ureteral reflux, unilateral agenesis</td>
<td></td>
<td>Yes</td>
<td>Optic disc coloboma, microphthalmia, perception hearing loss</td>
<td>Renal-coloboma syndrome</td>
</tr>
<tr>
<td><em>EYA1</em></td>
<td>Hypoplasia, vesico-ureteral reflux, unilateral agenesis</td>
<td></td>
<td>Yes</td>
<td>Hearing loss, auricular malformations, branchial arch remnants</td>
<td>Branchio-oto-re nal syndrome</td>
</tr>
<tr>
<td><em>SIX5</em></td>
<td>Hypoplasia, unilateral agenesis</td>
<td>Nephrocalcinosis, renal artery dysplasia</td>
<td>Yes</td>
<td>Neonatal cholestasis, vertebral anomalies, pulmonary stenosis, mental and growth retardation, posterior embryotoxon</td>
<td>Alagille syndrome</td>
</tr>
<tr>
<td><em>SALL4</em></td>
<td>Hypoplasia</td>
<td>Ectopic kidney, horseshoe kidney</td>
<td></td>
<td>Duane anomaly, tripalangeal thumb, ear anomalies, radial defect, limb anomalies</td>
<td>Okihiro syndrome</td>
</tr>
<tr>
<td>?</td>
<td>Hydronephrosis, vesico-ureteral reflux</td>
<td>Intravesical ureter stenosis, posterior urethral valves</td>
<td>Rare</td>
<td>Peculiar faces and gestures while smiling and crying</td>
<td>Ochoa syndrome</td>
</tr>
<tr>
<td>?</td>
<td>Dysplasia, hydronephrosis</td>
<td>Urethral or bladder neck obstruction, megaceystis</td>
<td>Yes</td>
<td>Dysplasia of the abdominal muscle</td>
<td>Prune Belly sequence</td>
</tr>
<tr>
<td>?</td>
<td>Hydropnopia, uni- or bilateral agenesis</td>
<td>Ectopic kidney</td>
<td>Rare</td>
<td>Vertebral defect, absent vagina or uterus</td>
<td>MURCS association</td>
</tr>
<tr>
<td>?</td>
<td>Dysplasia, unilateral absence, vesico-ureteral reflux, pelvi-ureteric junction obstruction</td>
<td>Ectopic kidney, hypospadias, persistent urachus</td>
<td>Rare</td>
<td>Vertebral and cardiac anomalies, tracheo-oesophageal fistula, anal stenosis, radial dysplasia</td>
<td>VATER association</td>
</tr>
</tbody>
</table>

CRF: chronic renal failure.
discrete extra-renal symptoms that may provide clues for syndrome-specific features and a unifying diagnosis, as exemplified by Newman et al. [22]. Lastly, in the case of apparently unrelated findings, ask the geneticist to search for specific syndromes in specialized databases [for instance, the London Medical Data Base (www.lmdatabases.com)]. It should be recognized that the complete TBS phenotype, as reported in our two patients, allows for a straightforward clinical and molecular diagnosis, even in adulthood. However, partial phenotypes have been reported, for instance, isolated bilateral renal hypoplasia (see above) [20] and isolated external ear anomaly [24]. The true frequency of incomplete TBS remains unknown.

Data on renal histopathology are extremely rare in TBS: in one adult patient, with the heterozygous c.1819delG SALL1 mutation, a diagnosis of thin basement membrane nephropathy with focal glomerulosclerosis was recognized [21]. In childhood, pathological findings are restricted to a single infant with TBS and severe cardiac involvement. Renal pathology showed focal cortical disorganization, tubular dilatation, dysplastic area with primitive duct layering with mesenchymatous cells and foetal glomeruli persistence [25]. In our patient, microscopic examination showed non-specific FSGS. Electron microscopy rules out a primary basal membrane abnormality. FSGS is not unexpected given (1) a high amount of proteinuria (4 g/day) suggestive of glomerulopathy was reported by Reardon et al. in a female patient who reached ESRD at age 47 [4] and (2) similar glomerular findings are found in patients with branchio-oto-renal syndrome (BOR syndrome) [26]. Note that the promoter of Sall1 is regulated by Six1 and Eya1 [27], the genes involved in BOR syndrome. Not unexpectedly, the spectrum of renal involvement in BOR and TBS syndrome overlaps, encompassing renal agenesis, hypoplasia or dysplasia and vesico-ureteral reflux [28]. These features suggest a common pathological mechanism.

Whether Sall1 is expressed in glomeruli in mice remains unclear. Using in situ hybridization with Sall1 antisense riboprobe on embryological sections Buck et al. showed that Sall1 is expressed in glomeruli, [13]. On the other hand, Nishinakamura et al. found no glomerular expression of Sall1 in a transgenic model [8]. In humans, SALL1 is expressed in glomeruli in the embryo, but not after birth. Since FSGS could be induced by glomerular hyperfiltration in hypoplastic kidneys with reduced nephron number, we consider it as a non-specific finding.

TBS is an autosomal dominant trait (transmission risk of 50%), with almost complete penetrance. However, neomutation occurs in 30% of cases [15]. In addition, germline mosaicism has been proven in two unrelated cases [15,29]. Finally, SALL1 mutations are not identified in 17 to 36% of patients with typical TBS, suggesting genotype heterogeneity [15,30]. The molecular mechanism leading to TBS in patients with SALL1 mutation is not fully understood. Interestingly, haploinsufficiency does cause a mild TBS phenotype as recently demonstrated by Borozdin et al. in five patients with heterozygous deletion of SALL1 [29]. Mice carrying heterozygous deletion have peculiar phenotype, while constitutional expression of mutant allele of Sall1 (1277–1278delGA) in a mouse leads to TBS-like developmental defects, suggesting that truncated Sall1 proteins have a dominant-negative effect [11]. Furniss et al. have provided an elegant explanation why haploinsufficiency causes milder phenotypes than mutation in the 5’ region [25]. mRNA transcripts from the latter escape nonsense-mediated decay; hence truncated SALL1 protein acts in a dominant-negative manner giving rise to a more severe phenotype.

In conclusion, our findings enlarge the number of developmental genes involved in late-onset, dominantly inherited, nephropathy. Making a diagnosis of SALL1-related TBS has two practical implications: (1) renal function should be yearly checked throughout life and (2) genetic counselling is mandatory, given the 50% risk of transmission and phenotypic variability within families. Further studies are needed to determine the true incidence of SALL1 mutations in nephropathies of unknown origin in adulthood.
Silent recovery of native kidney function after transplantation in a patient with membranous nephropathy

Bernard Descœudres¹, Olivier Giannini², Markus Aschwanden³, Thomas Eugster⁴, Helmut Hopfer⁵, Michael J. Mihatsch⁵, Juerg Steiger¹ and Michael Mayr¹

¹Clinic for Transplantation Immunology and Nephrology, University Hospital Basel, Basel, ²Nephrology and Internal Medicine Services, Ospedale Regionale Beata Vergine, Mendrisio, ³Clinic for Angiology, University Hospital Basel, ⁴University Vascular Center Aarau/Basel, University Hospital Basel and ⁵Institute for Pathology, University Hospital Basel, Basel, Switzerland

Abstract

Recurrence of membranous nephropathy (MN) is frequently seen after transplantation. However, there are no published data about the course of MN in the native kidneys after transplantation. Disease progression in almost all cases is assumed to be the ‘natural’ course after transplantation. We report on a patient suffering from end-stage renal disease due to MN. Eight years after transplantation, nephrectomy was performed due to chronic rejection and unexpectedly, partial recovery of native kidney function was noted. As far as we know, there is no other similar case reported in the literature. The potential impact of the immunosuppression, especially of calcineurin inhibitors, is discussed.

Keywords: calcineurin inhibitors; kidney transplantation; membranous nephropathy; recovery of renal function

Background

Of all patients who receive a kidney transplant, 20–40% have glomerulonephritis as the cause of renal failure [1]. In patients with membranous nephropathy (MN), a recurrence rate of 30% is reported [2]. The management of recurrent MN is based on anecdotal reports and extrapolation of data on the management of native kidney MN. Spontaneous remissions, responses to, and failures with immunosuppressive treatment have all been reported. However, there are no published data about the course of MN in native kidneys after transplantation suggesting that further disease progression is the ‘natural’ course after transplantation. We report on a patient suffering from end-stage renal disease due to MN with unexpected recovery of native kidney

Correspondence and offprint requests to: Michael Mayr, Clinic for Transplantation Immunology and Nephrology, University Hospital, Petersgraben 4, 4031 Basel, Switzerland. Tel.: +41-61-265-25-25; Fax: +41-61-265-24-10; E-mail: mmayr@uhbs.ch

© The Author [2009]. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org