Tolvaptan use in a patient with TSC2 - PKD1 contiguous gene deletion syndrome – a case report

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Case Report

Keywords: Tolvaptan, Tuberous sclerosis, Polycystic, Contiguous gene deletion, Case report

Posted Date: April 8th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-4222104/v1

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Additional Declarations: The authors declare no competing interests.
Abstract

The TSC2 gene is contiguous to the PKD1 gene on chromosome 16. A large deletion in this region is associated with a clinical phenotype involving features of tuberous sclerosis and polycystic kidney disease (TSC-PKD CGD). While Tolvaptan use in patients with autosomal dominant polycystic kidney disease is well established, it is less so in those TSC-PKD CGD syndrome. Here, we report a case of Tolvaptan use in a 23 year old woman diagnosed with TSC - PKD CGD using micro-array testing. She had a known diagnosis of tuberous sclerosis, but renal imaging had shown enlarged polycystic kidneys and no angiomyolipomas. Following a rapid decline in kidney function, micro-array testing was arranged, which confirmed a large deletion involving the TSC2 and PKD 1 genes respectively. She was subsequently commenced on Tolvaptan therapy, which has been well tolerated, without significant side effects. After 12 months of therapy, the rate of decline in kidney function is slower in comparison to the pre-Tolvaptan phase.

Introduction

Polycystic kidney disease (PKD) is the commonest monogenic kidney disorder, with a reported incidence of 1:1000 live births. It is typically characterized by progressively enlarged cystic kidneys, hypertension and decline in kidney function. In the UK, it is the primary kidney diagnosis for over 10% of those receiving kidney replacement therapy (KRT) [1].

The underlying pathogenic mechanism involves reduced expression or function of Polycystin. This disrupts several intracellular pathways resulting in cell proliferation and fluid secretion. This leads to cyst development, predominantly in the distal tubules. While several pathogenic gene variants have been associated with PKD, the PKD 1 variant is the commonest; accounting for up to 80% of cases [2]. It is located on chromosome 16, in juxtaposition to the TSC2 gene which codes for the protein Tuberin. A mutation in this TSC gene leads to tuberous sclerosis, a multi-systemic disorder characterised by non-cancerous tumours including angiomyolipomas or cystic lesions in the kidneys.

Large deletions involving the TSC2 and PKD1 genes, known as the TSC2 PKD1 contiguous gene deletion (TSC2 PKD1 CGD) syndrome and was first described by Brooke- Carter et al [3]. This is associated with more severe clinical phenotype and is typically characterised by early onset, enlarged polycystic kidneys and other features of tuberous sclerosis. Patients with TSC2-PKD1 CGD tend to have rapidly progressive chronic kidney disease and develop end-stage kidney disease (ESKD) at an earlier age than those with the PKD1 gene variant.

Tolvaptan, a vasopressin-2 receptor antagonist, has been shown to reduce renal cyst growth and consequently decline in kidney function in those with PKD [4]. It is approved for use in those with progressive disease. However, evidence of use in those with TSC2-PKD1 CGD is limited, with one published case report [5]. We report a case of Tolvaptan use in a young woman diagnosed with TSC - PKD CGD.
Case report

A 23-year-old woman had been under follow up in the nephrology clinic, with a known diagnosis of tuberous sclerosis. She had typical clinical features including epilepsy, cerebral astrocytomas, facial angiofibromas, retinal hamartomas and a mild learning disability. However, she did not have the typical renal angiomyolipomas. An MRI of the kidney showed bilateral enlarged polycystic kidneys (Fig. 1) with a total kidney volume of 1689 mls. Her kidney function was preserved up until 20 years of age. Subsequently, her kidney function declined rapidly, (Fig. 2) with new onset hypertension. There was no history of recurrent urinary tract infections, visible haematuria, abdominal pain, nephrolithiasis or proteinuria. There was no significant family history. Her medications included Sodium valproate, Adcal D3, Ferrous sulphate and Amlodipine.

The decline in kidney function prompted discussions about Tolvaptan eligibility, on suspicion of a contiguous gene deletion syndrome involving the TSC2 and PKD1 genes. Multiplex ligation-dependent probe amplification (MPLA) and array comparative genomic hybridisation (aCGH) testing were therefore arranged from a blood sample, after obtaining informed consent. MPLA testing confirmed the presence of a heterozygous contiguous gene deletion encompassing exon 30–41 of the TSC2 gene and the whole of the PKD1 gene.

She was commenced on Tolvaptan therapy after appropriate counselling, at an initial sub-therapeutic dose of 15mg/ day. This has been titrated to 60 mg/day, based on tolerability. She has been on Tolvaptan therapy for 12 months, with an average daily oral fluid intake of 3 litres. Other than polyuria, there have been no other significant side-effects including acute liver injury or hypernatraemic dehydration. Table 1 shows her baseline investigations and Fig. 2 shows the trend in her kidney function before and after the onset of Tolvaptan. The annualized rate of decline in estimated GFR prior to the onset of Tolvaptan was – 10.7 (– 7.34 to – 14.33) ml/min/year. This was lower after 12 months of treatment [– 9.6 (– 6.92 to – 12.29) ml/min/year].
### Table 1
Investigations pre and post Tolvaptan

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Baseline</th>
<th>12 months post Tolvaptan</th>
</tr>
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<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>139</td>
<td>138</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>15.4</td>
<td>17.5</td>
</tr>
<tr>
<td>Creatinine (umol/L)</td>
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<td>241</td>
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<tr>
<td>GFR (CKD-EPI) (ml/min/1.73m²)</td>
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<td>23</td>
</tr>
<tr>
<td>Alanine Transaminase (iu/L)</td>
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<td>18</td>
</tr>
<tr>
<td>Alkaline phosphatase (iu/L)</td>
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<td>68</td>
</tr>
<tr>
<td>Bilirubin (umol/L)</td>
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<td>5</td>
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<tr>
<td>C-reactive protein (mg/L)</td>
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<td>&lt; 5</td>
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<tr>
<td>Urine osmolality (mosm/kg)</td>
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<td>121*</td>
</tr>
<tr>
<td>Urine specific gravity</td>
<td>1.015</td>
<td>1.005</td>
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<tr>
<td>Blood pressure (mm/Hg)</td>
<td>146/89</td>
<td>133/89</td>
</tr>
</tbody>
</table>

* After 2 months on Tolvaptan

### Discussion

Kidney cysts are not uncommon in people with tuberous sclerosis complex, affecting up to 32% of cases [6]. These are typically small, sparse and asymptomatic. In contrast, TSC2-PKD1 CGD is rare, accounting for 2.6% of all pathogenic variants involving the TSC2 gene [7]. It is characterized by a more severe renal phenotype, including early onset hypertension and ESKD. In a recent case series of persons with TSC2-PKD1 CGD, the age of onset of ESKD was 21.62 ± 12.87 years [8], which is substantially earlier than in patients with a PKD 1 pathogenic gene variant. Early diagnosis is therefore critical to the initiation of treatment strategies that may ameliorate deterioration. The diagnosis should be considered in the presence of typical features of tuberous sclerosis and early onset polycystic kidneys.

There has been one previous published case report of Tolvaptan use in a person with TSC2 PKD1 CGD, with some similarities to this case. Both cases were characterised by enlarged polycystic kidney disease, early onset progressive chronic kidney disease (CKD) and hypertension. Tolvaptan was well tolerated with similar side effect profiles. The initial dose was lower than recommended because of her concern about side effects. A cautious dose titration to 60mg daily was possible, once it was apparent that Tolvaptan was tolerable with normal liver function tests. There have also been no concerns about medication adherence. In contrast, genetic evaluation in the case reported by Guerra Torres et al identified a deletion
in exons 35–37 of the PKD1 gene and exon 41 of the TSC2 gene [5]. Our case was characterised by a much larger deletion involving the whole of the PKD1 gene. One may speculate that this explains the earlier onset of progressive CKD (33 years versus 23 years). However, a poor genotype-phenotype correlation has been reported in TSC2-PKD1 CGD cases [8].

It is thought that there is crosstalk between PKD and TSC genes. The Mammalian Target of Rapamycin (mTOR) complex pathway downregulates Polycystin 1, promoting cystogenesis [9]. That said, the pathogenetic mechanisms for cystogenesis differ between tuberous sclerosis and PKD. TSC cystogenesis is thought not to be mediated by vasopressin induced cAMP activation, as the cyst epithelia predominantly consist of α-intercalated cells. In contrast, PKD related cysts are lined by α-intercalated cells and principal cells, where Vasopressin 2 receptors (V2R) are predominantly expressed [10]. It is not known whether this holds true in TSC2-PKD1 CGD. Therefore, while mTOR inhibitors and Tolvaptan are recognised therapeutic agents in tuberous sclerosis and PKD respectively, there remains uncertainty about the therapeutic effects of these agents in people with TSC2 PKD1 CGD.

In this case report, there was a slower decline in her kidney function after commencing Tolvaptan therapy. It is noteworthy that the difference in the annual GFR slope before and after Tolvaptan is similar to that reported in the TEMPO 3.4 trial which compared Tolvaptan to placebo in PKD patients [4]. However, this is not a direct comparison, with the caveat that the observations are based on an individual case. A further limitation is the absence of serial imaging demonstrating slower cyst growth.

To conclude, Tolvaptan was deemed to be safe, tolerated and potentially therapeutic in this patient with TSC2-PKD1 CGD. Further corroborative evidence is required to establish the underlying mechanisms by which Tolvaptan exerts its effects in such cases. A prompt diagnosis may have allowed for earlier initiation of therapeutic strategies to ameliorate progressive disease. Typical clinical features of tuberous sclerosis in associated with early onset polycystic kidneys should therefore prompt genetic testing for TSC2-PKD1 CGD.

**Statements and Declarations**

**Conflicts of interest**

The authors have no conflicts of interest to declare. The authors did not receive support from any organization for the submitted work.

**Ethical approval**

Approval from the institutional board was not required for this case report.

**Data availability**

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.
Informed consent

Informed consent was obtained for the data used in this case report. Written informed consent for publication of the clinical details and clinical images was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Author contributions

All authors contributed to the conception and design of this case report. The first draft of the manuscript was written by Osasuyi Iyasere and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References


Figures

Figure 1

MRI of the kidneys showing enlarged polycystic kidneys
Figure 2
A plot of her estimated GFR trend before and after Tolvaptan