Genetic renal disease

Brief report

In utero nephropathy, Denys-Drash syndrome and Potter phenotype

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Abstract. We report an unusual case of Denys-Drash syndrome presenting in a newborn infant with end-stage renal failure of antenatal origin and Potter phenotype. DNA analysis showed a novel missense change in arginine 394 of zinc finger 3 of the WT1 gene. This mutation may lead to an earlier and more severe presentation of Denys-Drash syndrome. It may be of interest to look for this mutation in other Potter phenotype cases.

Key words: Denys-Drash syndrome – Newborn – Nephropathy – WT1 mutation – Potter phenotype

Introduction

Denys-Drash syndrome (DDS) consists of a typical nephropathy associated with ambiguous genitalia and predisposition to the development of Wilms tumour. Clinical diagnosis is very difficult, especially in karyotypic female infants who may not have ambiguous genitalia. However, because of the tumour risk, it is important to make the correct diagnosis. Renal failure usually develops after birth [1] and a diagnosis of DDS may be confirmed by demonstrating a mutation in the zinc finger region of the WT1 gene, the Wilms tumour predisposition gene, using DNA analysis [2]. Baird et al. [3] found no obvious correlation between the type of mutation and phenotypic expression. We report a case of DDS associated with end-stage renal failure of antenatal origin and a novel WT1 mutation.

Case report

A 30-year-old Caucasian woman, gravida 2 para 1, who has a healthy 14-year-old daughter, delivered an infant weighing 3.4 kg at 39 weeks’ gestation. There was no family history of note and the pregnancy was non-eventful. Early ultrasound scans performed at 12 and 19 weeks’ gestation were normal with no oligohydramnios. Onset of labour was spontaneous and severe oligohydramnios was noted when the membranes ruptured. The umbilical cord was very dry and snapped after delivery. The infant was in severe respiratory distress at delivery and required assisted ventilation.

Examination of the infant showed dysmorphic facies with low-set ears and a flat nose. The genitalia were ambiguous and consisted of a prominent clitoris/penis with a urethral opening at the ventral base of the shaft. There were two thick labial-scrotal folds but no palpable gonads. The infant had obvious multiple limb contractures which improved with physiotherapy.

A chest X-ray suggested pulmonary hypoplasia and showed a pneumothorax. An abdominal ultrasound scan showed large kidneys with increased echogenicity. Magnetic resonance imaging (MRI) of the abdomen and pelvis showed enlarged dysplastic kidneys with poor corticomedullary differentiation (Fig. 1) and neither uterus nor gonads were seen. A MAG3 dynamic renogram showed no renal function despite good perfusion. The karyotype was 46XY with no visible constitutional 11p13 deletion or rearrangement, and no other reported abnormalities.

A chest drain was inserted and the infant remained ventilated for 6 days. He remained anuric despite full intensive care support. A clinical diagnosis of DDS associated with Potter phenotype was suspected. DNA analysis showed a novel missense change in arginine 394 of zinc finger 3 of the WT1 gene. This mutation may lead to an earlier and more severe presentation of Denys-Drash syndrome. It may be of interest to look for this mutation in other Potter phenotype cases.

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made and peripheral blood was obtained from the infant and both parents and sent for DNA analysis, which confirmed the diagnosis.

Non-interventional care was advised in view of the poor prognosis. The infant received milk feeds throughout and died at the age of 15 days after spending 8 days at home with his parents. Consent for a postmortem examination was resolutely refused. The parents also refused to allow a renal biopsy.

DNA analysis

DNA was prepared from peripheral blood samples of the infant and both parents. These were analysed for alterations of sequence using restriction enzyme analysis and sequencing. The region studied was that most frequently found to be mutated in DDS cases. Zinc finger 3 (ZF3) of WT1, encoded by exon 9, was amplified by polymerase chain reaction using oligonucleotide primers (5’TGCAGAGACA TTGCAGGCA TGGCAGG3’ and 5’GCACTA TT-CCTTCTCTCAACTGAG3’, 92 ºC 60 s, 35 cycles for 64 ºC for 60 s and 72 ºC for 90 s). The resulting 350-base pair fragment was analysed for alterations of sequence using the restriction enzyme RsrII and by sequencing. ZF3 was studied, since amino acids 394 and 396 are most frequently mutated in DDS cases [2]. RsrII normally cuts in this region of the sequence, but fails to do so in the presence of the DDS mutation. Heterozygous mutations in these codons are represented by cut and uncut fragments. To identify the exact mutation the region was sequenced.

The infant was found to be heterozygous at the RsrII site in ZF3, while both parents showed the normal pattern. Sequencing revealed a novel heterozygous arginine to glutamine mutation at codon 394 (R394Q) (Fig. 2).

Discussion

Nephropathy is the most-consistent primary feature of DDS and is present in 95% of all reported cases [1]. Diffuse mesangial sclerosis has been proposed as the characteristic change in this syndrome [4], but other reports have failed to support this [5]. In the presence of nephropathy, MRI may demonstrate changes in the kidneys [6]. The infant presented here had end-stage renal failure in utero and this led to severe oligohydramnios which in turn led to pulmonary hypoplasia, positional limb contractures, and dysmorphic facies. These features are typical of Potter phenotype as described by Thomas and Smith [7]. MRI showed large dysplastic kidneys which is consistent with a DDS nephropathy [6]. The average age of onset of nephropathy in DDS is 1.37 (0.01–17) years [1], but there have not been any reports of nephropathy starting and progressing antenatally.

Wilms tumour has been reported in 74% of cases of DDS and presents at an average age of 1.65 (0.01–13) years [1]. MRI can usually identify Wilms tumour accurately in DDS but small tumours may not be visible [6]. The presence of Wilms tumour, although very unlikely, cannot be ruled out in this infant.

The genitalia in this infant were ambiguous, but the karyotype was 46XY. This is consistent with the majority of reported cases of DDS. There is a relative paucity of reported cases with a female karyotype, possibly because of underdiagnosis of the syndrome in phenotypic females with nephropathy [1].

The WT1 mutation described in this infant was an arginine to glutamine mutation at codon 394. This particular amino acid change has not been described before, al-