Exceptional Case

Whole gene deletion of the hepatocyte nuclear factor-1β gene in a patient with the prune-belly syndrome

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Introduction

Prune-belly syndrome is characterized by a triad of congenital anomalies: a deficiency or an absence of abdominal wall musculature, dilatation of the urinary tract and bilateral undescended testes. The complete syndrome is only present in males [1]. There are other associated conditions including pulmonary hypoplasia, renal hypoplasia, cardiac and orthopaedic anomalies, imperforate anus and intestinal malrotation and malfixation [2]. The complete prune-belly syndrome has an incidence of about 1 in 40 000 live births [3]. The aetiology of the syndrome is unknown and no consistent genetic, environmental, infectious or teratogenic factors have been identified [2]. There are two aetiological theories; the first theory proposes that severe bladder outlet obstruction early in gestation is only relieved after irreversible damage has occurred. The second theory proposes a primary defect in mesenchymal development early in gestation [1].

Hepatocyte nuclear factor-1β (HNF-1β) is a member of the homeodomain-containing superfamily of transcription factors. It is important in the tissue-specific regulation of gene expression in a number of organs including the kidney, pancreas, liver, genital tract and gut [4]. HNF-1β is also involved in the early embryogenesis of these organs [5]. Heterozygous mutations and whole gene deletions of the HNF-1β gene cause multi-system disease in man. Renal disease, typically renal cysts, is the most consistent phenotype but a wide spectrum of renal developmental disorders have been described [6,7]. Diabetes is the most common extra-renal phenotype. Diabetes is usually present in the early adulthood with a median age of 20 years (range 15 days to 61 years) and is associated with pancreatic atrophy and asymptomatic exocrine dysfunction [6,8]. The renal cysts and diabetes (RCAD) syndrome is used to describe the most common HNF-1β phenotype [9]. Other clinical features of the HNF-1β phenotype include genital tract malformations, abnormal liver function tests, hyperuricaemia and gout [9].

We present a case of complete prune-belly syndrome associated with a whole gene deletion of the HNF-1β gene. This extends the description of the HNF-1β phenotype.

Case report

A male patient was noted from birth to have a markedly distended and pendulous abdomen. At the age of 6 it was noted that his abdominal musculature was almost absent. An intravenous pyelogram showed a large shadow on the right side consistent with a hydronephrotic kidney, but no dye was excreted. There was a left hydronephrotic kidney and a large soft tissue swelling arising out of the pelvis consistent with a distended bladder. Cystoscopy confirmed a grossly distended bladder. It was noted that he tended to pass large volumes of urine infrequently. He was treated by encouragement to frequent urinary voiding, which achieved adequate drainage such that his bladder was impalpable.

He remained well until the age of 26 when he had an episode of painless haematuria. On clinical examination his testes were noted to be absent from the scrotum and this was confirmed by the ultrasound. Further assessment by IVP, ultrasound and renal isotope scan confirmed bilateral hydronephrosis more marked on the right than the left, gross dilatation of the right ureter and moderate dilatation of the left ureter. A repeat cystoscopy showed his bladder to be of very high capacity, the ureteric orifices could not be identified and his bladder neck was thought to be normal. He was not felt to have evidence of bladder outflow obstruction. At this stage he was labelled with the prune-belly syndrome.

He represented at the age of 42 years with pain on the right side of his back and groin. Urine cultures were positive for gram-positive cocci and anaerobes. He was catheterized...
but there was no residual urine in his bladder. A CT scan showed an absence of abdominal wall muscles, bilateral hydronephrosis as before and calculi in the right kidney (Figure 1a and b). His pancreas was noted to be atrophied. His creatinine was raised at 456 µmol/l (reference range 60–120 µmol/l) with a urea of 29.9 mmol/l. His creatinine fell to 310 µmol/l after antibiotic treatment for urinary sepsis. Random blood glucose was elevated at 10 mmol/l. The subsequent fasting glucose level of 8.7 mmol/l confirmed the diagnosis of type 2 diabetes. His BMI was 38 kg/m². There was no family history of diabetes or renal disease. It was also noted that he had had recurrent attacks of gout from the age of 37 years.

Over the next 8 years there was a progressive deterioration in his renal function in association with recurrent urinary tract infections despite prophylactic antibiotic treatment. By the age of 50 his creatinine had risen to over 1500 µmol/l and he commenced haemodialysis.

On the basis of his developmental urinary tract abnormalities, early onset gout, type 2 diabetes and pancreatic atrophy he was screened for abnormalities in the HNF-1β gene. Direct sequencing of the nine coding exons, as well as intron and exon boundaries of the HNF-1β gene, was carried out as previously described [6]. This failed to identify a change from the normal sequence. A multiple ligation-dependent probe amplification (MLPA) assay was then used to detect partial or whole HNF-1β gene deletions [7]. This identified a heterozygous deletion that had deleted all the exons of the HNF-1β gene. Genotyping based on the position of the informative microsatellites on chromosome 17 showed that the deletion was no larger than 3.2 Mb. His parents were subsequently screened and neither had
the heterozygous deletion of the HNF-1β gene, which had therefore occurred spontaneously in this patient.

Discussion

We have identified a heterozygous whole gene deletion of the HNF-1β gene in this patient. This is the first case of prune-belly syndrome in which a genetic aetiology has been confirmed. The HNF-1β deletion has occurred spontaneously and includes the same deleted region that has previously been reported. Previous studies have reported a high prevalence for spontaneous HNF-1β gene deletions in patients with developmental disorders of the kidney [10].

The patient we describe has the typical features of the complete prune-belly syndrome. He has abdominal distension noted from birth with the absence of abdominal wall muscles and cryptorchidism. He has dilatation of the urinary tract and a high capacity bladder without evidence of obstruction. Chronic urinary sepsis has contributed to the decline in his renal function to the point where he requires haemodialysis.

The most obvious abnormality in the prune-belly syndrome is the thin, lax, protruding abdominal wall apparent in the newborn infant [3]. Prenatal ultrasound may detect the presence of a foetus with a severely distended abdomen. Abnormalities of the urinary tract are the major determinants of survival in these patients. There is a 20% chance of stillbirth or death in the neonatal period from renal dysplasia and associated pulmonary hypoplasia. A further 30% will develop urosepsis and/or renal failure in the first 2 years of life [1]. In the surviving patients, long-term prognosis is dependent on their degree of renal dysfunction. Renal dysplasia and damage from recurrent infections contribute to renal dysfunction. The kidneys typically have malformations including hydronephrosis, dilated and blunted calyces and malrotation, even if renal function is normal [1].

Cryptorchidism is seen in all the cases of complete prune-belly syndrome. The testicles are usually small and located high in the abdomen above the level of the iliac vessels. There are often developmental abnormalities of the epididymis and vas deferens. Even after orchiopexy the testes may have an influence on the phenotype. One gene mutation carriers [13].

We have identified a heterozygous whole gene deletion of the HNF-1β gene in this patient. This is the first case of prune-belly syndrome associated with a deletion of the HNF-1β phenotype—nor were the kidneys hypoplastic.

Studies in mice have shown HNF-1β expression in the epididymis, vas deferens and seminal vesicles, which are all derived from the embryonic Wolffian duct and in the prostate and testes [4]. In man, atresia of the vas deferens, epididymal cysts and rarely infertility due to asthenospermia have been described in HNF-1β mutation carriers [13]. Cryptorchidism has not previously been reported.

Our patient also has early-onset type 2 diabetes and gout, both of which are features of the HNF-1β phenotype but not of the prune-belly syndrome [9]. His BMI is 38 that would be an additional risk factor for type 2 diabetes. However, there was evidence of pancreatic atrophy on CT scan. Patients with HNF-1β mutations typically have a BMI <30 and usually have pancreatic atrophy visible on CT scans [6].

The prune-belly syndrome affects other organ systems in 65–73% cases. Significant pulmonary problems only occur in the neonatal period. Cardiac anomalies are present in up to 10%, including patent ductus arteriosus, atrial and ventricular septal defects and tetralogy of Fallot. Gastrointestinal problems are present in >30% patients at autopsy including malrotation and atresia. Orthopaedic problems such as talipes and congenital dislocation are less common [1]. Although HNF-1β is expressed in the lung and gut there have been no reports of lung or gastrointestinal disorders as part of the phenotype. Our patient did not have involvement of the lungs, heart, gut or limbs. It is possible to speculate that abnormalities in the HNF-1β gene may be involved in the subset of patients with the complete prune-belly syndrome without involvement of these other organ systems.

The abnormalities or the complete absence of abdominal wall muscles in the prune-belly syndrome together with abnormalities of musculature within the urinary tract have not previously been described in patients with HNF-1β mutations. HNF-1β is not known to be expressed in muscle. It is possible that other genes present within the deleted region may have an influence on the phenotype. One gene within this region is LHX1, a limb homeodomain gene known to be important for the renal development in the mouse [14]. The obstructive theory of aetiology for the prune-belly syndrome suggests that in utero obstruction of the bladder results in bladder distension, ureteral dilatation, hydronephrosis and atrophy of the abdominal wall muscles. However, some patients have a complete lack of abdominal wall muscles suggestive of a congenital absence rather than atrophy. Also, the bladder lacks the hypertrophy and hyperplasia normally present with obstruction. The alternative theory proposes a deficiency of mesenchyme which develops into abdominal wall and urinary tract muscles [1,2].

In conclusion, we present the first case of complete prune-belly syndrome associated with a deletion of the HNF-1β gene. This is an extension of the previously described HNF-1β phenotype.

Conflict of Interest Statement. None declared.
References


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