

Oligomeganephronia

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Abstract

Oligomeganephronia is characterized by a severe developmental defect of both kidneys (without urinary tract malformation) and by the following histopathologic features: low number of nephrons, hypertrophic glomeruli with diameters twice the normal size, hypertrophic tubules, thickening of Bowman's capsule and variable abnormalities of the glomerular basement membrane; electron microscopy also reveals irregular thickening and fusion of epithelial cell foot processes. Both kidneys are symmetrically affected, except when associated with unilateral agenesis. Monopapillary kidney is also a variant of oligomeganephronia. The symptoms of affected patients depend in part upon the age at presentation. Birth weight is often below the normal mean. During the neonatal period, patients may present with one or more of the following manifestations: pneumothorax, feeding problems, metabolic acidosis, urinary sodium loss, high plasma creatinine and urea concentrations. During the first year of life, the usual symptom is persistent anorexia with vomiting, associated in more than 50% of the cases with failure to thrive. Patients below the age of 1 year may also exhibit growth retardation independent of renal function abnormalities. After the age of 1 year, the initial presenting abnormality is often proteinuria discovered incidentally on routine urinalysis. In other patients, the disease may be discovered because of impaired growth, or polyuria and polydipsia. Renal failure can result in anemia and secondary hyperparathyroidism. Most reported cases have not been associated with a genetic disorder, even though a number of case reports support a possible genetic component. Management of oligomeganephronia is only supportive.

Keywords

Oligomeganephronia, renal hypoplasia, growth retardation, proteinuria.

Disease name and synonyms

Oligomeganephronia

Oligonephronic renal hypoplasia

Diagnosis criteria/definition

Oligonephronic renal hypoplasia or oligomeganephronia was first described in 1962 [1,2]. It is characterized by a severe developmental defect of both kidneys (without

urinary tract malformation) and by the following histopathologic features:

- low number of nephrons - The kidneys of patients with oligomeganephronia have only 20-25 % of the normal total number of nephrons;
- hypertrophic glomeruli - the diameter of glomeruli is twice the normal size (250-325 μm versus 100 to 150 μm);
- hypertrophic tubules - affected tubules are both longer (4 times the normal length) and larger (15 times the normal volume for age without dysplasia) than normal [2];
- other - thickening of Bowman's capsule and variable abnormalities of the glomerular basement membrane are seen [2]. Electron microscopy also reveals irregular thickening and fusion of epithelial cell foot processes [3].

Both kidneys are symmetrically affected, except when associated with unilateral agenesis [4,5]. Monopapillary kidney is also a variant of oligomeganephronia [6].

Although this disorder has principally been reported in the French literature [1,7], oligomeganephronia has also been described in other geographical areas [8-10].

Differential diagnosis

The term "renal hypoplasia" is used to describe congenitally small kidneys resulting from a defect in development. It is important to understand that similar macroscopic and (in some areas) microscopic features may be observed with renal "atrophy".

However, renal atrophy and hypoplasia can be differentiated by the clinical history, the association with urinary tract malformation, and a close histologic examination of the whole kidney (if available).

- Atrophy is acquired, as in reflux nephropathy with scars. Histologic examination shows areas of atrophic tubules with sclerotic glomeruli and (occasionally) areas of subnormal parenchyma with hypertrophied nephrons.

- Renal hypoplasia, an inherited disorder, results from either simple hypoplasia or oligomeganephronia, which are due to a low or high degree of a quantitative defect of the renal parenchyma, respectively. Renal dysplasia is a different disorder that is characterized by the presence of primitive tubules or cartilage on renal biopsy.

Prevalence

It is unknown, but autopsies series have shown that approximately 2.5% of children have small kidneys without necessarily having clinical manifestations [11].

Etiology

Oligomeganephronia is thought to result from developmental arrest of the metanephric renal blastema between the 14th and 20th weeks of fetal life. For example, histologic examination of two cases of oligomeganephronia with contralateral renal agenesis, an 18-week fetus and a preterm infant, revealed markedly smaller metanephric blastemas [13]. Additional findings included fewer glomeruli/gram of parenchyma and severe hypertrophy combined with lower numbers of nephrons.

Several animal models of the disease, outlined below, have shed light on possible predisposing factors for the development of oligomeganephronia.

- Mild oligomeganephronia can be induced in rats by the administration of gentamicin during pregnancy [13].

- A genetic murine model of reduced renal mass with dominant inheritance was found in irradiated mice with ROP (Ragged, Oligosyndactylism [*OS gene*], and Pintail) [14]. Heterozygous ROP mice with the *Os/+* genotype have half the number of nephrons of homozygous *+/+* wild-type animals. They also have hypertrophy of glomeruli and epithelial cells in the proximal tubules and collecting tubules, findings that are similar to those of human oligomeganephronia.

Most reported cases of oligomeganephronia in humans have not been associated with a genetic disorder. Vascular abnormalities, for example, have been proposed as being causative in several cases of oligomeganephronia affecting only one of two homozygous twins [10,15]. In those cases, a placenta vascular shunt at a critical developmental period may have impaired kidney development. Other types of vascular accidents might also be involved, including disseminated intravascular coagulation or embolization of necrotic zones followed by the death *in utero* of the twin fetuses [16]. In addition, intrauterine growth restriction may be associated with the formation of fewer nephrons [17,18].

In some patients, however, a mutation in the *PAX-2* gene, a transcription factor that underlies normal renal development in the mouse, is responsible for isolated oligomeganephronic renal hypoplasia [19]. In a preliminary study of 15 patients with oligomeganephronia, three had heterozygous *PAX-2* mutations, two with a single base-pair insertion and one with a six base pair deletion.

A number of case reports also support a possible genetic component in human disease. For example, oligomeganephronia has been reported in two siblings [20]. In addition, oligomeganephronia has been observed in

association with certain genetic disorders including:

- branchio-oto-renal syndrome [21]
- acrorenal syndrome [22,23]
- deletion of chromosome 4p [24]
- tapetoretinal dystrophy [25]
- deafness with amblyopia [26]
- coloboma-renal syndrome (due to mutation in the *PAX-2* gene) [27]

Clinical manifestations

The symptoms of affected patients depend in part upon the age at presentation. The birth weight is often below the normal mean. During the neonatal period, patients may present with one or more of the following:

- pneumothorax
- feeding problems
- metabolic acidosis
- urinary sodium loss
- high plasma creatinine and urea levels. During the first year of life, the usual symptom is persistent anorexia with vomiting, associated in more than 50% of the cases with failure to thrive. Patients below the age of 1 year may also exhibit growth retardation independent of renal function abnormalities.

After the age of 1 year, the initial presenting abnormality is often proteinuria discovered incidentally on routine urinalysis. In other patients, the disease may be discovered because of impaired growth, or polyuria and polydipsia. Renal failure can result in anemia and secondary hyperparathyroidism.

Natural history of renal function

As observed in a large series of patients [28], both the absolute glomerular filtration rate (GFR) and the GFR corrected for surface area rapidly increase during the first months of life in affected patients. After this early period, renal filtration continues to increase but at a slower pace. Although the maximal GFR may be reached within the first year of life in the most severe cases, it is attained between 3 and 6 years of age in most patients.

The maximum GFR varies widely, ranging between 6 and 100 mL/min per 1.73m². The older the age at which the maximum GFR is reached, the higher the GFR eventually becomes and the later the time at which the patient develops end-stage renal failure. There is also a good correlation between the GFR at 1 year and the highest GFR eventually observed; there is, however, no correlation between the GFR and kidney size. It is therefore necessary to wait until at least 1 year of age to obtain a more reliable prognosis.

Once the maximum GFR is reached, renal function remains at this level for a variable length

of time, which depends, in part, upon the absolute level of renal function. For example, patients with maximum filtration rates of 40 mL/min or more may experience stable renal function for at least 4 years.

Unfortunately, once begun, deterioration of renal function progresses at a constant rate. The onset of proteinuria precedes this decrease by several years. Initially, proteinuria is lower than 0.5 g per day, but increases with progressive decrease of renal function. The degree of proteinuria is higher when the functional loss is more than 5 mL/min per year. This process eventually leads to end-stage renal failure. Progressive renal insufficiency, which is associated with focal glomerulosclerosis, is thought to be due at least in part to the hyperfiltration and increased glomerular size (which also increases the stress on the glomerular capillary wall) of the markedly hypertrophied glomeruli. This process is similar to that seen with other forms of nephron loss and may be slowed by antihypertensive therapy, particularly with an angiotensin-converting-enzyme (ACE) inhibitor (see below).

Although the lower number of nephron is similar in the vast majority of patients with oligomeganephronia, changes of renal function vary from patient to patient. The reasons for these differences remain unclear. Several hypotheses have been proposed, including mutations in the ACE gene (as has already been shown in several nephropathies) [29,30].

Renal pathology in patients with renal failure

Histologic examination of the kidneys of patients with oligomeganephronia who develop renal failure reveals progressive focal and segmental glomerular sclerosis and interstitial fibrosis, which in turn leads inexorably to nephron obsolescence. Similar lesions are observed in rats who have undergone five-sixths nephrectomy [31].

Kidneys with only end-stage function removed from patients at the time of transplantation are very small and have a lower number of papillae. In this context, histologic examination enables the clinician to confirm or diagnose oligomeganephronia, and reveals unusual numbers, sizes and characteristics of nephrons [28].

- The number of glomeruli is markedly lower than normal and varies from 2 to 6 depending, in part, upon the area of the kidney examined. By comparison, the normal number is at least 10.

- There is a relatively high proportion of permeable glomeruli. The diameters of these glomeruli are increased to over 300 nm and often reach 400 nm; adjacent proximal tubules are also similarly hypertrophied.

- Segmental sclerosis and hyalinosis of glomeruli are consistently observed [28,32].

Diagnostic methods

Renal ultrasonography or intravenous urography (IVU) in children with oligomeganephronia reveals small kidney size (20-75% of normal) [33,34]. Affected kidneys are also hyperechogenic on ultrasonography.

Although serial sonography shows an increase of absolute kidney size over time, this increase is smaller than that observed in normal children. There appears to be no relationship between initial kidney size and the evolution of renal function with time. Visualization of the urinary tract also does not reveal any malformations, including the absence of renal cavity distension or of massive vesicoureteral reflux.

Treatment

Management of oligomeganephronia is supportive, and includes maintaining fluid and electrolyte balances and treating progressive renal insufficiency. As noted above, ACE inhibitors may be given in an attempt to slow the progression to end-stage renal failure.

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