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Annotations

Multiple causes of human kidney malformations

Anatomy of human nephrogenesis

The human kidney derives from two parts of the metanephros, its embryonic precursor. The first of these is the ureteric bud, which branches into the collecting ducts containing K^+ secreting principal and H^+ handling intercalated epithelia, and also forms the urothelium of the calyces, renal pelvis, ureter, and bladder trigone. The second is the renal mesenchyme, which differentiates into nephrons comprised of glomeruli, proximal tubules, and loops of Henle. The human metanephros appears at 5 weeks of gestation, the first glomeruli form by 9 weeks, and nephrogenesis is complete by 34 weeks.[1 2]

Variety of human kidney malformations

The term 'renal malformation' encompasses a mixed bag of developmental aberrations, all of which involve anatomical or major structural anomalies which are present at the time of birth.[1 2] In the most extreme example, called renal agenesis, the kidney is absent. Renal dysplasia describes an organ comprised of undifferentiated and metaplastic cells: these organs may be tiny (renal aplasia) or can distend the abdomen (the multicystic dysplastic kidney). A hypoplastic kidney is small and has fewer nephrons than normal: these nephrons may be grossly enlarged in oligomeganephronia.

This classification is ultimately based on histopathology, yet in clinical practice it is unusual to have the luxury of viewing renal biopsy material from these children. The diagnoses on discharge summaries are often best guesses based on a detailed review of the clinical history combined with radiological appearances.

Table 1 Multiple causes of human renal malformations

Teratogens
Dietary agents, for example vitamin A
Metabolites, for example glucose
Drugs, for example angiotensin enzyme converting inhibitors
Obstruction of fetal urinary tract
Anatomical obstruction, for example urethral valves
Physiological obstruction, for example neurogenic bladder
Primary genetic defects
Transcription factors, for example *PAX2* mutation in renal-coloboma syndrome
Growth factor signalling, for example *FGFR2* mutation in Apert's syndrome
Cell adhesion molecules, for example *KAL* mutation in X linked Kallmann's syndrome
Miscellaneous, for example mutation of peroxisomal protein in Zellweger syndrome

Other familiar malformations include the ectopic, duplex, and horseshoe kidney and these organs may include both dysplastic and normal tissues. Associated malformations of the urinary tract include agenesis, duplications, and obstruction of the upper (for example hydronephrosis) or lower (for example posterior urethral valves) tract, as well as vesicoureteric reflux. Human renal malformations are the major causes of end stage renal failure in children less than 5 years of age.[3] As the techniques of dialysis and transplantation continue to be refined, there are increasing numbers of infants with renal malformations entering programmes for the treatment of renal failure.

Some of the varieties of polycystic kidney disease may present at birth. These disorders include autosomal recessive polycystic kidneys and the disorder resulting from contiguous deletion of the TSC2 (tuberous sclerosis 2) and PKD1 (an autosomal dominant polycystic kidney disease) genes. These entities are, however, best considered as disorders of terminal epithelial differentiation and the gross structural steps of nephrogenesis (for example nephron formation and collecting duct morphogenesis) are complete. Therefore they will not discussed further in this paper, although details can be found elsewhere.[4–7]

Renal malformation as a dynamic process

This classification of renal malformations is a rather dry system based on pathological end points. Yet we now know, based on a wealth of animal experiments, that normal kidney development is a highly dynamic and tightly controlled programme of cellular events comprising: (a) cell proliferation; (b) cell death by apoptosis (about 50% of cells formed in the developing kidney are destined to die before birth); (c) morphogenesis or the acquisition of three dimensional form (for example the formation of a nephron tubule from undifferentiated cells or the branching of the collecting ducts); and (d) differentiation into specific cell types including diverse epithelia, mesangial cells, and endothelia.[7]

These processes are controlled and mediated by the temporal and spatial expression in the developing kidney of genes coding for molecules which generally fall into a few classes: (a) transcription factors which orchestrate the expression of other genes; (b) growth factors which act in paracrine or autocrine fashion; (c) survival factors which prevent apoptosis; and (d) adhesion molecules which hold cells to one another or anchor them to adjacent matrices.[8–10]

It is interesting to observe the multicystic dysplastic kidney with these perspectives in mind. Serial ultrasound scans performed prenatally and postnatally have shown that some of these organs can increase to a massive size, then subsequently regress and even involute completely.[11] Detailed examination of these organs shows that epithelial cells lining the cysts resemble undifferentiated ureteric bud branches and have a high rate of proliferation which is correlated with the expression of PAX2, a potentially oncogenic transcription factor, and BCL2, a survival molecule.[12 13] Preliminary evidence, based on gene expression patterns, also suggests that soluble paracine signalling molecules, such as hepatocyte growth factor and insulin-like growth factor II, may drive the expansion of these cysts.[14 15] Conversely, tissue around these cysts has a high rate of apoptosis, or programmed cell death, which is associated with a lack of BCL2 and PAX2 expression and a failure to differentiate into functioning nephrons.[13 16]

Hence we can begin to correlate phases of growth and involution with cellular events and the aberrant expression of master nephrogenesis genes. Furthermore, an understanding of the dynamics which underlie these malformations now allows us to envisage potential treatments, especially the administration of growth factors which prevent apoptosis and enhance normal differentiation into nephrons. The deregulated expression of these genes, although intriguing, is likely to be a secondary event and the question remains: what are the primary causes of human kidney malformation? From first principles, I suggest that there will be three answers (table 1): teratogens, physical obstruction of the urinary tract, and sporadic or inherited mutations of genes expressed in the developing kidney.

Teratogens

A wide variety of agents has been implicated as renal teratogens based on animal studies[17] and one of the best studied is vitamin A. When administered to mice in large doses just before the formation of the metanephros, this vitamin causes massive apoptosis in the renal mesenchyme followed by the involution of the organ to cause renal agenesis.[18] Other experiments suggest that ethanol is teratogenic for the urinary tract later in gestation and this substance also induces premature cell death.[19] In humans, both glucose (that is, a mother with diabetes) and angiotensin converting enzyme inhibitors (that is, drugs used for maternal hypertension and now contraindicated) are recognised renal teratogens.[17 20] It is unusual to elicit a history of exposure to known teratogens from the parents of children with renal malformations, but it remains possible that 'occult' exposure is important. For example, one study has suggested that the incidence of various malformations, including those of the kidney, was increased with a daily intake vitamin A over levels as low as 10 000 IU.[21]

Table 2 Examples of human renal malformations associated with genetic defects

Associated with syndromes
Apert's syndrome*
Bardet-Biedl syndrome†
Branchio-oto-renal syndrome*
Campomelic dysplasia*
DiGeorge syndrome†
Kallmann's syndrome (X linked type)*
Meckel's syndrome†
Renal-coloboma syndrome*
Simpson-Golabi-Behmel syndrome*
Smith-Lemli-Opitz syndrome†
Zellweger syndrome*
Non-syndromic
Renal aplasia and dysplasia
Primary vesicoureteric reflux

* Defined mutation.
† Locus known, but gene not yet known.
For the exact types of renal malformation in each disorder, please refer to references 2, 7, and 42.

Key messages

- The next decade will see further progress in defining genetic causes of human renal malformations; in cases where the mutation is inherited this may lead to prenatal diagnosis very early in gestation
- Appreciation of the biology of malformed kidneys is beginning to suggest therapeutic options to alter aberrant developmental processes
- The possibility that low grade exposure to tetatogens can cause renal malformations requires further investigation, but may have major health implications

Physical obstruction of the urinary tract

It has long been recognised that a significant minority of kidney malformations in girls, and perhaps half of all malformations in boys, are associated with physically obstructed lower urinary tracts at the level of the pelviureteric junction, ureter, or urethra.[1 2 22] Obstruction in the last third of gestation is associated with hydronephrosis, poor renal parenchymal growth, and subcortical cysts. Kidneys associated with obstruction in early gestation are usually dysplastic. Bilateral obstructive fetal nephropathy causes oligohydramnios with lung hypoplasia and severely affected infants die after birth from respiratory or renal failure. Although prenatal surgical decompression is technically feasible, there are few controlled clinical studies assessing the potential beneficial effects on lung and kidney development.

Preliminary data suggest that the experimental obstruction of murine kidneys in the neonatal period causes enhanced cell death by apoptosis, as well as aberrant patterns of expression the BCL2 survival factor, transforming growth factor β1, angiotensin II, and epidermal growth factor.[23] All these molecules have been functionally implicated in metanephric growth in various other experiments using organ culture or transgenic mice. It will be interesting to see whether these same molecules can be implicated in the pathogenesis of renal dysplasia, a phenotype which can be generated in animals, such as sheep, by ureteric obstruction much earlier during development.[24]

Mutations

Mutations of genes expressed in nephrogenesis can occur spontaneously in mice or be created by the genetic engineering of early murine embryos; an increasing number of genes (currently about 10) has been found to be essential for normal nephrogenesis.[7–10] Important lessons with considerable implications for human disease include the fact that a single mutation can cause a range of renal malformations, with particular phenotypes appearing to depend on the mouse strain (that is genetic background), hence suggesting the presence of modifying genes.[25] We also know that in certain cases the deficiency of a particular gene can be compensated for by the expression of another molecule with similar functions.[26 27] The same phenotype (for example agenesis, dysplasia) can result from the mutation of very different genes, perhaps indicating that the developing kidney has a limited number of ways of reacting to 'molecular lesions'. In the same way, diverse primary insults to the adult kidney tend to lead to a final common pathway of glomerular and interstitial

fibrosis. Finally, mouse models have shown that nephrogenesis genes are usually expressed in other organs where they are sometimes critical for normal development.

The same genes which have been implicated in mouse nephrogenesis are likely to be important in human development, an excellent example being the *PAX2* transcription factor gene.[28] The ablation of a single *PAX2* allele in mice causes impaired metanephric growth and fewer nephrons than normal as well as megaureter, a finding consistent with gross vesicoureteric reflux. These animals are also blind, due to maldevelopment of the retina, another site of embryonic PAX2 expression. There is a human syndrome which is strikingly similar to these mouse models, namely the renal-coloboma syndrome. This comprises blindness due to optic nerve colobomas, and renal failure and hypertension associated with vesicoureteric reflux and small, malformed kidneys. This resemblance was noted by a New Zealand based laboratory where workers described heterozygous mutations of *PAX2* in patients with this syndrome.[29] These mutations most likely result in haploinsufficiency (that is a partial lack of functional protein) and they can arise de novo or be inherited in an autosomal dominant manner. Various research groups are now searching for mutations of genes such as *PAX2* in non-syndromic cases of human vesicoureteric reflux; this common disorder is often inherited in a dominant manner.[30 31] *PAX2*, or a similar gene, might also be implicated in the rare families reported with inherited non-syndromic kidney aplasia and dysplasia.[32]

Congenital malformation syndromes are individually often rare, but collectively account for considerable morbidity and even mortality in young children. Many affect the kidney in a way which can be mild or which can dominate the clinical course. Some clearly have a genetic basis and loci have been defined. For example, renal malformations occur in Bardet-Biedl syndrome (loci at 11q, 3p, 16q, and 15q), Meckel's syndrome (17q), and DiGeorge syndrome (22q). In addition, specific mutations in some of these syndromes have been clarified (table 2): the *eyes absent* gene, a putative transcription factor expressed in renal mesenchyme in branchio-oto-renal syndrome[33]; *SOX9*, a transcription factor expressed in embryonic collecting ducts in campomelic dysplasia[34]; *FGFR2*, a receptor for fibroblast growth factor receptor 2 in Apert syndrome[35]; *GPC3*, a gene encoding an extracellular proteoglycan in Simpson-Golabi-Behmel syndrome[36]; *KAL*, a gene encoding another cell signalling molecule in X lined Kallmann's syndrome[37]; mutation of a peroxisome assembly gene in Zellweger syndrome[38]; mutation of a cholesterol biosynthesis gene in Smith-Lemli-Opitz syndrome[39]; *FAA*, a gene implicated in DNA repair in a variety of Fanconi's anaemia[40]; and *WT1*, a transcription factor gene mutated in Denys-Drash syndrome.[41] There are over 100 varieties of inherited syndromes with kidney malformations, so there is plenty of scope for further research in this field![2 42]

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Can measures of infant habituation predict later intellectual ability?

By the end of the 1970s, about 50 years of research had shown fairly clearly that prediction coefficients from measures of infant behaviour to later measures of intelligence in childhood were so low as to indicate that, except in extreme cases such as severe subnormality, the early measures had no predictive validity.[1 2] From about this time, however, researchers began to question the nature and validity of the infant tests on which these findings were based. It was argued that the 'mental scales' on these tests primarily measured perceptual and motor development, rather than mental or cognitive growth, and there is little reason to expect measures of such abilities to predict later IQ.[3 4]

Accordingly, the search began for cognitive or information processing measures of infant performance which might more reasonably be considered to tap abilities that are similar to, and may be predictive of, the abilities measured by the childhood intelligence tests. A major focus of this research has been on measures of visual information processing and attentiveness, and it has become clear that a moderate degree of predictability may be possible, leading some to the view that the 'promise of greater predictive accuracy using recognition memory and habituation rate represents one of the most exciting contemporary fields of inquiry'.[5]

Problems with standardised infant tests

One of the best known and most widely used tests of infant development is the Bayley scales of infant development (BSID). In the second edition of these scales published in 1993, many items on the mental development index appear to measure perceptual-motor rather than mental or cognitive development. At 4 months the items include: #36 'eyes follow rod'; #44 'uses eye-hand coordination in reaching'; and #45 'picks up cube'. At 12 months the items include: #73 'turns pages of book'; #79 'fingers holes in pegboard'; and #97 'builds tower of three cubes'. By 2 years of age such seemingly perceptual-motor items are fewer in number and they have been replaced with a preponderance of items that would generally be considered more mental or 'cognitive': verbal comprehension, recall of geometric forms, and comparison of masses. From about 2 years of age the predictive validity of the BSID increases.[2 6] Similar comments apply to other well known tests of infant development, such as the Griffiths' scales.[7]

Several studies have introduced programmes in which infants at risk of intellectual retardation have been given educational intervention designed to enhance their cognitive development. At the end of the first year these groups did not seem to differ from non-intervention control groups.[8 9] A likely interpretation of these findings is that the mental scales used to evaluate the effectiveness of these programmes were simply not measuring mental or cognitive growth and there is therefore a great need for a valid test of infant cognitive development.

Visual information processing

Control of attention, memory formation, and the ability to process information quickly and efficiently have traditionally been conceived of as being central to mature cognitive functioning.[10 11] In the search for predictors of later intelligence a major focus has been on measures of visual information processing and attentiveness as these appear to be measuring these abilities: 'attentiveness reflects not only the detection of information but also the ongoing processing of that information and the status of the relation between the new information and the child's existing knowledge'.[12] Measures of habituation to visual stimuli in particular have been seen as potential predictors of later intelligence.

Habituation is an aspect of learning in which repeated presentations of a stimulus result in decreased responsiveness. When an infant is placed in an otherwise homogeneous environment and shown a visual stimulus the stimulus will initially attract the infant's attention, but as time passes the infant's attention will wane (as measured by reduced looking). Habituation refers to this decrement in visual attention and measures of this decrement reflect memory formation (of the now familiar stimulus), and therefore the processing of information from the stimulus, and may also be an indication of infants' ability to inhibit attention to the familiar stimulus.[13]

For several other reasons measures of habituation have been seen as potential predictors of later intellectual functioning: (a) there are interage differences in speed of habituation, with older infants taking less time to reach a criterion of habituation than younger infants,[14] and there are also intra-age differences; (b) infants who habituate in shorter times have been found to process information more rapidly and more efficiently than 'long lookers'[15]; and (c) infants 'at risk' for cognitive delay or handicap habituate less effectively than non-risk infants matched for age.[16–18]

Psychometric considerations

There are many different habituation procedures and many different dependent measures that can be drawn from them.[19] An important enterprise is to establish the psychometric adequacy of these measures, particularly by examining their test-retest reliabilities. Those measures that give the best reliabilities are likely to be the best potential predictors because if a measure does not correlate with itself it is unlikely to correlate well with other concurrent or future measures.

Several groups of workers have assessed the short and long term reliability of various measures of habituation in the first year after birth[20–22] and the results are both encouraging and discouraging. What is encouraging is that measurements at points close in time (separated by a few days or weeks) tend to give reliability estimates in the range r = 0.40–0.60, but what is discouraging is that measurements separated by a month or more tend to yield lower estimates, with r values in the range 0–0.20. Thus these infant measures tend to have low test-retest reliabilities and this will inevitably limit the maximum predictive correlations that might be found.

Predictive validity of visual information processing

Three measures can be distinguished which have some predictive power: (a) visual recognition memory (preferences for a novel stimulus after a brief look at a 'familiarised' stimulus); (b) the time taken to reach a criterion of habituation and associated measures (such as the duration of the longest single or peak look); and (c) the duration of individual fixations to visual stimuli, independent of habituation. There are many studies that have reported predictive correlations and several reviews of these studies are available.[3 19 23] The measures predicted are