Oligonephropathy: From a Rare Childhood Disorder to a Possible Health Problem in the Adult*

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Abstract

Recent data have shed significant new light on the structural and functional development of the kidneys, as well as on a rare congenital form of bilateral renal hypoplasia called congenital oligomeganephronia. In this renal disorder, few greatly enlarged and "hard-working" nephrons are found that will ultimately sclerose and lead to end-stage renal failure during early childhood. At the same time it has been recognized that the number of nephrons in the kidneys of various animal species and humans is correlated to renal mass. Therefore, premature babies and/or infants small for gestational age due to intrauterine malnutrition will be born with relatively small kidneys and a certain nephron deficit, a condition called congenital oligonephropathy. Extensive worldwide epidemiologic studies have now shown that these premature or SGA infants have a high incidence of cardiovascular disease, hypertension, hyperlipidemia, diabetes and renal failure in adulthood. Although the pathophysiologic mechanisms responsible for these complications of premature birth are not entirely understood, it has become clear that the described association may pose a possible health problem in the adult population. This review describes the background of COMN and CON as well as the evidence that has accumulated on the adult complications of the latter. In addition, some thoughts are presented on the importance of identifying subjects possibly affected by CON, such that early recognition may alter the ultimate outcome.

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In 1962 Habib et al. [1] described the renal pathology findings of a particular form of renal hypoplasia that was eventually called (congenital) oligomeganephronia [2]. A recent article reviewed this rare pediatric renal disorder on the basis of some 67 suspected cases of which 12 were proven by renal biopsy [3]. Most other publications report on single cases [4,5]. The clinical characteristics of COMN are few. Approximately 30% of the affected newborns are born prematurely or small for gestational age to mothers in their late twenties or early thirties, with a clear male preponderance (male:female ratio ~3:1). The disease is rarely familial and without major malformation of the kidneys or other organ systems, although a few reports describe COMN in twins [6], with hearing and ocular problems, mental retardation and limb abnormalities. All affected children develop progressive renal failure leading to end-stage renal disease, whether within months after birth or until early-mid adolescence. At birth the kidneys are very small (20–25 g), clearly indicating bilateral hypoplasia. The final diagnosis is made on the basis of renal pathologic findings described by Habib et al. and Broyer et al. [1,3], consisting of absent corticomedullary boundaries with only five to six pyramids and a few nephrons that are greatly enlarged (approximately two to three times normal size), often partly hyalinized. Interstitial renal fibrosis is a recurrent finding even at a very young age. Eventually focal segmental glomerulosclerosis evolves.

Several reasons rekindled interest in this rare congenital renal disease. Firstly, greater understanding of the factors involved in normal (and abnormal) nephrogenesis threw new light on the possible pathogenic mechanisms of COMN. Secondly, COMN is an experiment of nature that could validate the so-called hyperfiltration theory of renal damage. This theory is based on the notion that few (remaining) hard-working nephrons will eventually fail, resulting in progressive glomerulosclerosis (see below). In addition, new forms of congenital nephron deficit, lately termed congenital oligonephropathy, have been described and attributed to either genetic factors or acquired intrauterine events. Lastly, and most importantly, it has been recognized that humans born with relatively few nephrons have an increased incidence of a variety of important adult disease states associated with great morbidity and mortality.

In this review I will briefly address these four relatively new aspects evolving from the renewed recognition of COMN.

Renal embryology

In humans nephrogenesis starts at 5 weeks gestation. The kidney develops via two temporary, partly functioning stages (the pro- and mesonephros) into the primary final kidney, the metanephros. The latter will be formed from a tube, the so-called ureteric bud, and clusters of mesodermic/mesenchymal cells, the metanephric blastema. When these two structures meet, a vesicle is formed that transforms into an S-shaped body. At about 9 weeks of gestation, after in-growth of endothelial cells (precursors of small vessels), a primitive glomerulus develops. The urine-collecting system is formed by elongation and tree-like division of the ureteric bud ("branching"), whereas the cells of the metanephric mesenchyme transform into renal epithelial cells, a unique renal occurrence.

The first circumstantial evidence that a humoral factor was involved in nephrogenesis was presented by Grobstein in 1955 [7], when studying the very specific reciprocal signaling process(es) between the ureteric bud and the metanephric mesenchyme. This is still one of the keystones of understanding kidney development,

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SGA = small for gestational age

COMN = congenital oligomeganephronia

CON = congenital oligonephropathy

since only the bilateral meeting of the two above mentioned structures will induce formation of two metanephroi and ultimately two kidneys. Present knowledge indicates that renal embryology, including the primary inductive process between ureteric bud and mesenchymal blastema, is controlled and regulated by many genes (and gene products), including a variety of cytokines and growth factors with their specific receptors [8–12]. Obstruction of the fetal urinary tract is another important renal (mal)developmental factor [13]. Knockout animal models and/or antibodies against growth factors/cytokines and their receptors have been helpful in delineating the relative contribution of the factors to normal or abnormal kidney development. An in-depth description of these processes is beyond the scope of this text. Suffice it to point out that some or all of the above mentioned factors, together with the degree of apoptosis at the time of the primary induction of the metanephros, will ultimately control the number of nephrons to be formed. That number is normally between 400,000 and 1,400,000 per kidney, and not one million per kidney as previously thought. The preordained number of nephrons will remain relatively unchanged after birth since no significant postnatal nephroneogenesis occurs in humans. The incidence of an inborn nephron deficit, with or without intrauterine nephron enlargement (CON or COMN), is unknown. This is mainly due to the fact that few children and/or young adults with hypoplastic kidneys, even those with chronic renal failure, will undergo renal biopsy, and probably only a minority of the most severe forms will ultimately be detected – and then only in specialized medical centers interested in this disease entity.

Congenital oligonephropathy

CON can be caused by a genetic (racial) predisposition, for instance in Australian Aborigines [14]. The latter have a high incidence of CON with enlargement of nephrons that undergo focal segmental glomerulosclerosis, leading to end-stage renal disease. In addition, these particular peoples are prone to diabetes mellitus and diabetic nephropathy. Due to this predisposition and not excluding acquired influences, the incidence of ESRD in Australian Aborigines is about 20 times greater than in non-Aborigine Australians! Most inborn nephron defects, however, are not genetically determined but are sporadic and due to intrauterine events [Table 1]. In a recent study from Tel Aviv, CON was produced by ligation of utero-placental vessels, simulating placental insufficiency [15]. In animals CON is also caused by intrauterine exposure to a variety of drugs that cross the placental barrier [16,17]. The degree of nephron deficit following drug exposure ranges from 20 to 50%. It is unclear whether these, or other, drugs have the same adverse fetal renal effects when administered to the pregnant human female. After many years of painstaking research of renal development in pregnant animals or metanephroi growing in culture, Gilbert and Merlet-Bénichou [18] identified factors of special importance with regard to a congenital nephron deficit: protein deficiency and lack of vitamin A or its metabolites. Even mild vitamin A deficiency during pregnancy causes CON in rats [19]. Hyperglycemia also interferes with nephron formation. Smoking during pregnancy is associated with low maternal vitamin A levels and low birth weight babies.

The number of nephrons in humans is directly correlated to total renal mass. This means that premature babies will be born with a certain deficit of nephrons. This is particularly true in infants not only born prematurely but SGA, due to maternal malnutrition, placental insufficiency or both. Since in western countries approximately 6–7% of all live births are premature (this may reach 15–20% in developing countries), of which 20–25% are SGA infants, this is the most important cause of CON in humans. The degree of reduction in the number of nephrons will obviously depend on the degree of prematurity and/or intrauterine malnutrition.

Table 1. Causes of congenital oligonephropathy in animal experiments and the human condition (For explanation see text)

Animal experiments
Intrauterine exposure to drugs: gentamycin, adriamycin, puromycin, cyclosporin A
Intrauterine protein and vitamin A deficiency
Intrauterine exposure to hyperglycemia
Ischemia of uterine horn
Radiation-induced mutation
Human condition
Solitary kidney(s)
Hypoplastic kidney(s)
Prematurity
Small for gestational age babies

Oligonephropathy and renal insufficiency

During the second half of the twentieth century the study of chronic renal failure in humans took on new dimensions. In addition to finding better treatment modalities for patients with established CRF or ESRD (dialysis, renal transplantation), renal research embarked on preventing, halting or attenuating progression of renal lesions. This was fairly successful regarding the most common cause of ESRD in adulthood, namely diabetic nephropathy which has a relentless progressive course if not recognized and treated early. Almost all the experimental evidence was obtained in animal models with significantly reduced renal mass (5/6th renal ablation), a form of surgical oligonephropathy. In the first stage of the study of uremic mechanisms, Bricker and colleagues [20] described the functional adaptation of the remaining nephrons ("intact nephron hypothesis") in patients with advanced renal disease and in 5/6th nephrectomized animals. In the following decade Brenner et al. [21] concentrated on the adverse renal effect of the hard-working remaining nephrons in rats with 5/6th renal ablation. According to these investigators the functional adaptation of the remaining nephrons is made possible by a rise in intraglomerular blood flow and blood pressure, resulting in increased glomerular filtration ("hyperfiltration theory") [22]. The payoff for this intraglomerular hypertension is progressive nephrosclerosis and accelerated uremia. After another decade the focus of interest changed again because of the well-known – but mostly forgotten – fact that the

CRF = chronic renal failure
ESRD = end-stage renal disease

progression of renal failure correlates better with interstitial renal than with glomerular pathology findings. The "interstitial theory" of Border and Noble [23] and others [24] supposed a primary glomerular lesion with secondary involvement of the interstitium through leakage of noxious substances via an impaired glomerular barrier, for example lipoproteins and a variety of growth factors and cytokines. The development of progressive nephrosclerosis after a primary glomerular injury started to make sense. Finally Remuzzi and co-workers [25] modified this latter theory by placing the burden of evidence for the interstitial damage on the glomerular leakage of protein.

All theories of progressive renal damage represent a certain aspect of what occurs in reality. Each and every theory also had – and still very much has – its therapeutic implications for the treatment of patients with CRF/ESRD. This is particularly true for maintenance of divalent ion metabolism by the Bricker school of thought, and reduction of generalized and glomerular hypertension with calcium-blocking agents and particularly with angiotensin-converting-enzyme inhibition or angiotensin II-receptor antagonists, as well as reduction of urinary protein excretion (the Brenner-Remuzzi "schools").

In view of these developments it is quite obvious that COMN was considered an experiment of nature par excellence to test the above theories of progressive renal damage, in particular the "hyperfiltration theory." Congenital hypoplastic kidneys with few, enlarged, hard-working, "hyperfiltrating" human nephrons invariably failed, even with minimal degrees of proteinuria. When acquired, CON also seemed deleterious. Brenner et al. [26] at one point even suggested that in theory two kidneys should be transplanted into patients with ESRD, since the number of nephrons of one kidney would not provide sufficient renal function under all circumstances. The idea was: the more nephrons the better.

In as far as COMN and/or CON is concerned there are two major problems with this rather mechanistic approach. Firstly, the enlargement of *all* parts of the fetal nephrons in COMN has to be explained. Can this be due to a large workload? Probably not. Most excretory and endocrine renal functions of the unborn baby are regulated by bi-directional placental transport. Consequently, the intrauterine nephron enlargement in COMN is probably not due to "hyperfiltration" but to growth factors, though the responsible genes have not yet been delineated. The second point is that CON – in contrast to COMN – does not invariably lead to CRF. A radiation-induced mutation in chromosome 8 of mice resulted in oligosyndactily and an almost 50% reduction in nephrons. All these Os-mice develop renal failure with glomerulosclerosis [27]. However, another heterozygote Os-strain of mice, *with the same 50% reduction in nephron mass*, does not show any evidence of renal interstitial fibrosis and/or glomerulosclerosis. The same holds for the development of diabetic nephropathy in this animal model [28]. With the same reduction in nephron mass, one strain of mice did develop diabetic nephropathy while the other did not. These experiments clearly show that not only does the number of nephrons determine future renal function but that genetics also play an important role in the renal outcome of CON. There is a third point to be considered. The renal pathology endpoint in COMN is primarily glomerular with focal segmental glomerulosclerosis, accompanied by additional interstitial renal damage. This contrasts somewhat with the renal pathology findings in CON, consisting mainly of interstitial extracellular matrix formation with eventually severe glomerulosclerosis, just as in animals with 5/6th reduction in renal mass. In the latter condition, however, glomerulomegaly with focal sclerosis has also been described in the early stages of the progressive lesion [29]. One could therefore argue that COMN and CON represent two rather different renal processes of renal pathology, both leading to progressive renal scarring. If true, this may indicate a different underlying pathophysiology of COMN vs. CON.

Whatever the theories of progression of renal damage and the possible different pathologic endpoints of CON and COMN, there is no doubt that the effect of significant CON and COMN on kidney function in subjects with a genetic predisposition is ultimately deleterious. In this respect CON can be compared to what is seen in humans with diabetic nephropathy.

Low birth weight, CON and its complications in adult life

In 1988 it was postulated – based on observations in humans and certain inbred strains of rats – that a small number of nephrons was associated with (essential) hypertension later in life. This knowledge was later applied to CON [30]. It is interesting to note that already 50 years earlier Hayman and colleagues [31] drew attention to the fact that the number of (functioning) nephrons in humans is related to the state of uremia and that the lower the number of nephrons the higher the systolic blood pressure. *"Plus ça change plus ça reste la même chose."* The pathogenetic mechanism of low nephron number and hypertension was, and still is, unknown but is thought to be a combination of: "interactions between renal hemodynamics, hormonal and hereditary factors, reduced glomerular filtration surface area and probably dietary sodium excess." A few years later Barker and Martyn [32] had a different approach to the same subject. Careful evaluation of epidemiologic data in Britain amassed since 1911 showed a clear correlation between low birth weight and the incidence of cardiovascular disease, hypertension and later also of hyperlipidemia, non-insulin dependent (type 2) diabetes and CRF. These observations have now been substantiated on a worldwide basis in some 200 publications. The correlations are mostly descriptive without providing pathogenic mechanisms [33–35]. In 1991 Seidman et al. [36] published the Israeli experience based on the follow-up of 32,580 individuals born in Jerusalem and examined at age 17 when they were drafted into the army [36]. The correlation between low birth weight and adolescent blood pressure was low and not significant. Most of the worldwide studies, however, yielded different results although the populations studied in the other investigations were generally (much) older than in the study by Seidman et al. All these studies refer to low birth eight as <2,500 g, and often no distinction is made between

Os = oligosyndactily

prematurity (gestation <37 weeks, birth weight <2,500 g) and SGA babies who have a birth weight not corresponding to the length of gestation. SGA indicates intrauterine fetal malnutrition due to maternal malnourishment, placental insufficiency, or both. It is thought that primarily the SGA infants, not those born prematurely with a "normal for fetal-age birth weight," are prone to have CON. Adult, type 2 diabetes mellitus in SGA babies is probably due to abnormalities in the pituitary-adrenal axis from childhood [37], combined with impaired peripheral glucose utilization [38]. Barker and Martyn [32] suggest that intrauterine malnutrition will cause a reduced number of cells in many fetal organs, including the kidneys, the initiating event. When postnatally these cells are charged with a relatively large workload, they may ultimately fail. This is seen as the amplification factor. In favor of this course of events is the clinical observation that especially the SGA subjects that grow fast after birth and are rather tall or obese in later life will have a tendency towards cardiovascular disease, hypertension and CRF. But this hypothesis has never been definitely proven. In fact only two studies, both from European (pediatric) centers, tested the association of low birth weight, renal function, CON and hypertension, Vásárhelyi et al. [39] evaluated 20–22 year old Caucasian males in Budapest, 49 with a birth weight <2,500 g (low birth weight) and 16 born with a weight >2,500 g (controls). None had proteinuria. The young adult Hungarians with a low birth weight had a mean systolic/diastolic blood pressure that was 5/3 mm higher than in the control subjects. Glomerular and tubular functions in the low birth weight group were normal. The low birth weight males had a higher mean urinary sodium excretion than the controls, whereas their mean red blood cell Na-K-ATPse content was lower. In this 'pediatric' study, unfortunately no distinction was made between prematurity and SGA infants. It was done in the report by Kistner and colleagues from Stockholm [40]. In 50 women aged 26 $\pm$ 1.9, either born preterm (n=15) or at term but SGA (n=18), and 17 control subjects, casual blood pressures as well as ambulatory 24 hour blood pressure was measured, as were glomerular filtration rate, renal plasma flow and urinary albumin excretion. The 24 hour ambulatory blood pressure measurements were not different in the three groups, but the casual blood pressure measurements were elevated in the preterm-born females, not in those born SGA at term. Renal glomerular and tubular functions were normal. More important than the actual results of these studies is that they were done at all. Similar, much larger follow-up studies of renal function in low birth weight adults, born prematurely or SGA, are urgently needed.

Conclusions

The incidence of prematurity (low birth weight) and fetal malnutrition (SGA babies) is considerable, particularly in less well-developed and economically deprived societies. Epidemiologic studies clearly show that low birth weight babies will have a tendency to develop hypertension later in life. What percentage will follow this course is unknown as yet. Probably only a relatively small number of infants will be born with *significant* CON, which in genetically prone individuals will progress to CRF and possibly ESRD. Even when that percentage is indeed low – and that is still a moot point – it is not negligible. The worldwide accumulated experience indicates that the recognition of a pathogenic link between low birth weight (SGA), CON and its adult complications poses a public health problem that can no longer be ignored.

The present knowledge on CON clearly calls for further study of its pathogenic mechanisms, prevention of intrauterine malnutrition, more reliable methods for glomerular counting in renal tissue specimens, and early recognition of individuals at risk to develop hypertension, hyperlipidemia, diabetes, CRF and heart disease. The public health attitude should be balanced. It should provide information on the risks of low birth weight babies for possible future disease on the one hand, while preventing unwarranted concern or panic, especially at a young age, on the other. Today, the minimum that is required is: a) that all those involved in the prenatal care of mother and fetus be aware of the accumulated evidence on the link between low birth weight, CON and the adult complications; b) to stress the importance of a good maternal nutritional state; c) to consider administering vitamin A to pregnant women, preventively; d) that physicians who treat adults should incorporate questions on gestation and birth weight in their medical history-taking, in particular when dealing with hypertensive patients; and e) to measure blood pressure, infrequently but regularly from late adolescence onwards, in subjects who were low birth weight infants and particularly SGA babies – a non-invasive and low cost intervention that in the long run may well pay off.

Finally, the author, a (retired) pediatrician and pediatric nephrologist, cannot resist adding two general observations. The first obviously is that the study of rare pediatric illnesses using modern techniques is more rewarding today than ever before. This is evidenced by medical conferences devoted solely to adult outcome of (renal) disease in early childhood. Secondly, pediatrics has traditionally been concerned, more than any other of the main subspecialties, with preventive medicine. The emphasis has changed from preventing infectious diseases to protecting the growing individual from the dangers of a variety of 'metabolic disorders'. When protection is unattainable, the effect of a specific disease entity can often be attenuated. The preventive pediatric attitude has not changed with the emergence of molecular biology and new understandings of genetic mechanisms including mapping of the human genome. On the contrary, the new developments offer hope for new treatment modalities for hereditary disease, unheard of in the recent past. With regard to COMN and CON, the challenge now is to provide better healthcare far beyond childhood. Basic genetic and molecular as well as epidemiologic research showed the way, but the end result will only be achieved by time-honored clinical evaluation and care – not a minor task.

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Addendum. Since the submission of this paper, Fattal-Valevski et al. reported their findings in the last November issue of *IMAJ* (2001;3:805–8). They measured (manually) blood pressure in 58 children aged 4–6 years, born SGA at term in a Tel Aviv Hospital and 58 age-matched controls with a term birth weight appropriate for gestational age. The SGA group had a mean systolic/diastolic blood pressure that was 6.1/5.2 mmHg higher ($P<0.05$) than in the control children. The mean arterial pressure of preterm SGA babies (n=21) at 4–6 years was 10.4 mmHg higher ($P<0.0001$) than in the preterm controls (n=20). These data indicate that even in early childhood the low birth weight and SGA babies tend to have relatively high blood pressures, fully justifying careful follow-up.

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