Congenital nephrotic syndrome

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Abstract

CNS (Congenital nephrotic syndrome) is a disorder characterized by the presence of a nephrotic syndrome in the first three months of life. Different pathologies can cause this syndrome. In general, we can distinguish primary forms (sporadic and hereditary) and secondary forms (acquired and associated with other syndromes). The most common form is the Finnish CNS (CNF, congenital nephrotic syndrome of the Finnish type), a hereditary form whose name derives from the fact that the highest incidence is described in that country (1.2:10,000). The pathogenesis, the clinical picture, the diagnostic criteria, the therapy and the outcome are described in details.

Keywords

Nephrotic syndrome, newborn, proteinuria, hypoalbuminemia, hyperlipidemia, edema, hypercoagulability, hypergammaglobulinemia.

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Definition

Congenital nephrotic syndrome (CNS) is a disorder characterized by the presence of a nephrotic syndrome in the first three months of life with severe proteinuria (> 40 mg/m² or 50 mg/kg/die), hypoalbuminemia (≤ 2.5 mg/dL) and hyperlipidemia (values of serum cholesterol > 200 mg/dL or 6.5 mmol/L) [1-3]. Other characteristic, but not essential symptoms for the diagnosis, are edema [4], a state of hypercoagulability and hypergammaglobulinemia [1, 5].

Etiology

Different pathologies can cause this syndrome [5]. In general, we can distinguish primary forms [4] (sporadic and hereditary) and secondary forms (acquired and associated with other syndromes) [5].

Classification

The most common form is the Finnish CNS (CNF, congenital nephrotic syndrome of the Finnish type), a hereditary form whose name derives from the fact that the highest incidence is described in that country (1:2;10,000) [5, 6], but at present cases with different genetic backgrounds have been identified in other parts of the world [5, 7].

Other less frequent genetic forms include diffuse mesangial sclerosis (DMS), minimal change nephrotic syndrome (MCNS), mesangial proliferative glomerulonephritis (MesPGN) and focal segmental sclerosis (FSGS). These forms include idiopathic variants of CNS [5].

Pathogenesis

Proteinuria is connected to alterations of the slit diaphragm, a structure fundamental in forming a barrier for the passage of plasmatic proteins at the level of the glomerular capillary wall [5].

The etiology differs depending on the type of CNS. In CNF, the pathology is connected to a mutation of the nephrine gene (NPHS1), a protein of transmembrane adhesion with 1,241 residues belonging to the superfamily of the immunoglobulins and synthesized exclusively by glomerule podocytes [1, 8]. The protein is a key component of the fenestrated diaphragm of the podocytes. The gene mutation in question is responsible for most (about 90%) of CNF. The principal mutations implicated are the Fin-major (deletion of 2 pairs of bases in hexone 2) and the Fin-minor mutation (a nonsense mutation in hexone 26) [9-11].

Approximately 100 mutations of the NPHS1 gene have been discovered in the world [12-14].

In 1999, Lenkkeri et al. analyzed the structure of the nephrine gene and studied 35 patients presenting CNF; they found that only 2 patients had the 2 typical mutations. Seven cases presented no mutations of the encoding portion of the NPHS1 gene or of the regions adjacent to the extremity 5', thus suggesting the presence of mutations of the promoter region, of the introns or in a gene that encodes for a protein different from nephrine [15].

Similarly, Kitamura et al. observed the presence of two new mutations of the missense type in two brothers presenting CNF characterized by frequent relapses [16].

DMS may be idiopathic or caused by mutations, including those of WT1 (Wilms Tumor-1), a transcription factor involved in renal and gonadic development. Mutations of the WT1 gene may cause isolated forms of CNS or syndromic forms, such as the Denys-Drash syndrome, the Frasier syndrome and the WAGR (Wilms tumor, Aniridia, Genitourinary malformations, mental retardation syndromes) [17, 18].

In FSGS, more common is the mutation of the podocyte gene (NPHS2), an integral membrane protein found exclusively in the slit diaphragm, whose interaction with nephrine make it responsible, in some cases in which it is altered, for possible changes in the expression of the nephrine itself [19].

cytomegalovirus, hepatitis B and HIV [6], then mercury intoxication and systemic pathologies such as LES and amyloidosis [4].
It is responsible for approximately one half of the cases in European families and has also been found in Japan and other countries [8, 9].

In some patients presenting CNS, mutations of both the NPHS1 and NPHS2 genes (homozygote mutations in one gene and heterozygote in the other), as a demonstration of the noteworthy heterogeneity and absence of a clear genotype/phenotype correlation of CNS [20-22].

Other genes correlated with CNS are reported below:
- the laminin β2 (LAMB2) gene: laminin β2 is a component of the basal glomerule membrane fundamental in anchoring the membrane to the podocytes. Mutations of LAMB2 have been associated with Pierson’s syndrome [23];
- the gene for phospholipase C epsilon (PLEC1), whose mutation correlates in some cases of CNS with ESRD [24];
- the LMX1B gene, responsible for the nail-patella syndrome [25];
- the LAMB3 gene, associated with mitochondrial myopathies [26] and Herlitz’s junctional epidermolysis bullosa [27].

Instead, the genes responsible for the Galloway-Mowat syndrome, characterized by alterations of the CNS associated with extra-cerebral malformations remain unknown [28].

In the last ten years, two gene loci at the level of chromosome 2p for steroid-responsive FSGS have been mapped; the first was discovered by Ruf’s group in 2004; it showed a transmission modality of the autosomal-recessive type with signs of genetic heterogeneity. Later, Gbadejin et al. discovered a new gene locus on chromosome 2p15 in a group of relatives presenting FSGS characterized by a noteworthy heterogeneity of phenotype and a transmission modality of the autosomal-dominant type [29, 30].

The acquired forms instead show infection as the main cause.

Clinical picture

The clinical picture differs in the various forms. In CNF, children in general show a similar phenotype [1, 10]. They usually are premature [1, 5, 6] (34-36 weeks of gestation) and small for their gestational age [1, 5, 31, 32]. The placenta is usually larger than normal and weighs more than 25% of the child’s weight at birth [5]. Proteinuria begins in the uterus and can be seen already in the first urine sample at birth: it is above 100 g/L and leads to oliguria and edema if not treated [1]. Therefore, the edema may appear in the first weeks of extraterine life [4]. The loss of the proteins in the urine also leads to hypogammaglobulinemia and then to malnutrition, poor growth [1, 6] and a major susceptibility to infections (for IgG values below 2%) [5]. Hematuria is uncommon, but may be present [1]. The babies also show an increased incidence of pyloric stenosis and reflux [4]. Another condition that may present in such babies is hypothyroidism, due to the loss of the globulin binding thyroxin (TBG) in the urine [5, 33]. Babies with CNF also have a characteristic phenotype. The face often appears with a small mouth having a protruding upper lip, a small nose and full cheeks that produce the typical double chin appearance [5], diastasis of the coronal sutures, open bregmatic fontanelles, eyes far apart, low ears and umbilical hernia. The clinical course of such patients is normally characterized by a progressive decline in kidney function, important bacterial infections and early death caused by sepsis and uremia [5].

DMS instead may present both as isolated and in the context of the Denys-Drash syndrome, characterized by the association of gonadic dysgenesis, nephropathy and Wilms’ tumor. This condition presents with proteinuria and evolves towards renal insufficiency within the first year of life [5, 33-36] and death within the third [5, 31, 37]. Subjects affected by DMS, differently from the form described above, are usually born at term, with normal weight at birth and normal size of the placenta [5].

In the forms connected with mutation of the LAMB2 gene, the typical clinical picture is that of Pierson’s syndrome characterized by a nephrotic syndrome and eye anomalies with microcoria. However, cases of mutations of this gene have been reported even without eye anomalies [1, 23].

Some forms of CNS are also present in the Galloway-Mowat syndrome. This syndrome is associated with alterations of the CNS (microcephaly, psychomotor retardation and brain alterations) and is characterized by short stature, hernias, diaphragm anomalies and dysmorphic notes [28].

In the acquired forms, where the picture is more closely connected with the basic pathology, we can distinguish forms linked to congenital syphilis [38], characterized by proteinuria, hematuria and CNS usually not severe, and forms associated with toxoplasmosis, characterized by proteinuria in the first month of life and to which may be associated
eye anomalies and neurological and respiratory alterations [1].

**Diagnosis**

The diagnosis of severe CNS is based on the finding of severe proteinuria (> 20 g/L) associated with severe hypoalbuminemia (< 10 g/L) and anasarca in the neonatal period. The extent of proteinuria varies with the etiology, thus determining different clinical pictures at onset [8].

Affected subjects often present hematuria and leukocyturia at the urine analysis, arterial hypotension (connected with hypoalbuminemia) or arterial hypertension in the case of evolution of the pathology towards advanced stages of chronic kidney disease. Serum creatinine and azotemia are often normal at the time of diagnosis. Sometimes we observe increased weight of the placenta (> 25% of weight at birth) [10] and associated extra-renal malformations, which in most cases lead to syndromic forms of CNS; among these, we can mention genital anomalies (in forms caused by mutations of the \( \text{WT1} \) gene), eye defects (\( \text{LAMB2} \) gene) and neurological alterations (Mowat Galloway) [8].

Kidney biopsies may not be diagnostic of CNS since the lesions are often focal [8].

The prenatal diagnosis of CNS in families at risk by means of a genetic investigation is of great importance. In the case of high values of \( \alpha \)-fetoprotein in the prenatal period it is recommended to repeat the dosage of this parameter prior to the 20th week of pregnancy, since it is highly indicative of mutations of the \( \text{NPHS1} \) gene [8].

Despite growing knowledge of mutations causing steroid-responsive nephrotic syndrome, there are still cases of families with early onset in which it has not been possible to recognize the mutation at the origin of the disease. Therefore, in the last few years more and more studies based on next generation sequencing applied to the diagnosis of CNS have been performed [39]. In 2013, Bull et al. used methods of whole-genome sequencing to isolate a mutation of the \( \text{LAMB2} \) (3p21) gene in a murine strain with nephrotic phenotype associated with the development of Pierson’s syndrome [40].

Lovric et al. have described a new method for mutation analysis through the use of a PCR based on the microfluid technology, which makes possible the rapid and simultaneous analysis (in less than 3 weeks) of the presence of single mutations of 21 genes that cause the steroid-responsive nephrotic syndrome. This method is low-cost (< 1/29th) compared to traditional methods and revealed the presence of mutations in about 33% of the 48 subjects examined presenting steroid-responsive nephrotic syndrome with infantile onset [41].

**Therapy**

Classically, the CNSs caused by mutations of the \( \text{NPHS1} \) and \( \text{NPHS2} \) genes are often resistant to therapy with corticosteroids and immunosuppressive drugs since they are correlated with a non-immunitary pathogenesis [11]. On the contrary, immunosuppressive therapy may increase the risk of sepsis in these patients [42].

Therefore, CNS therapy consists of three fundamental steps: correction of the edema, prevention of complications such as infection and thrombosis, and proper nutrition. In the case of failure, the ultimate therapeutic choice is kidney transplantation [8].

Correction of the edema is based on the parenteral infusion of albumin at 20% (5-20 mg/kg/die) in 6 hours associated with a bolus with furosemide by means of central venous catheter (0.5-1 mg/kg), which is administered with half the dose during and the other half at the end of the albumin infusion. Thiazidic diuretics and antagonists of aldosterone may be associated for better control of the edema [8].

Sreedharan et al. described a case of CNS of unknown etiology that responded with success to the sole ACE-inhibitor therapy; at the end of the therapy the patient showed a reappearance of proteinuria, with a new, complete remission when the therapy began again, a demonstration of the effects of angiotensin II on the integrity of the podocytes [45].

Reynolds et al. described a case of CNS of unknown etiology that responded with success to the sole ACE-inhibitor therapy; at the end of the therapy the patient showed a reappearance of proteinuria, with a new, complete remission when the therapy began again, a demonstration of the effects of angiotensin II on the integrity of the podocytes [45].

The administration of intravenous albumin is recommended for almost all patients presenting CNS in its initial stage. Reynolds et al. described 5 cases of CNS treated at home with albumin by the central line, which was found safe, well tolerated and with a lower rate of complications compared to other parenteral therapies; the authors also demonstrated that such home therapy potentially delays the times of hospitalization and
Congenital nephrotic syndrome and calcium (500-1,000 mg/die) [8]. With supplementation of magnesium (50 mg/die), E and hydrosoluble vitamins associated administration of vitamins of the A, D group (400 µg/kg/die) content is recommended [8, 48]. Basically, also recommended is the administration of vitamins of the A, D group (400 UI/die), E and hydrosoluble vitamins associated with supplementation of magnesium (50 mg/die) and calcium (500-1,000 mg/die) [8].

Reduces recourse to nephrectomy and substitutive renal therapy [46]. In some cases the loss of urinary proteins leads to an altered equilibrium of the coagulation factors, thus predisposing the subject to the development of thrombotic episodes that require the use of piastrinic antiaggregants such as aspirin and dipyridamole, infusions of antithrombin III and warfarin, the latter used with success in patients affected by CNF associated with mutations of the NPHS1 gene [8].

The risk of infection in subjects with CNS relates to the urinary loss of gamma globulin and complementary proteins. There is no scientific demonstration of the efficacy of an antibiotic prophylaxis in affected patients. An early antibiotic therapy is recommended in the case of suspected sepsis, in some cases associated with the infusion of immunoglobulin [8].

The progression of the pathology also leads to a progressive loss of the globulin that binds thyroxin, with a consequent increase in TSH, which requires the substitutive hormonal therapy with thyroxin (at the initial dose of 6.25-12.5 µg/kg) [8].

Dagan et al. reported on five cases of babies presenting the steroid-resistant congenital nephrotic syndrome diagnosed at an age between 3 and 11 years; in the course of the subsequent 5 to 42 months of follow-up there developed a picture of non-autoimmune hypothyroidism. The subjects studied showed a progressive deterioration of renal functions within 1.5 to 14.5 years from the diagnosis, with subsequent normalization of the levels of the thyroid hormones on reaching a picture of end stage renal disease (ESRD) and the beginning of hemodialysis. Three cases affected by FSGS with subsequent kidney transplantation did not develop hypothyroidism in association with the recurrence of the nephrotic syndrome. The authors agree that hypothyroidism should be actively searched for as a potential complication of steroid-resistant congenital nephrotic syndrome, especially in the case of progressive deterioration of kidney function [47].

In patients affected by CNS a diet with a high caloric (about 130 kcal/kg/die) and protein (3-2 g/kg/die) content is recommended [8, 48].

Kidney transplantation represents the only definitive therapy in cases of CNS that do not respond to medical treatment. It requires a body weight of > 9 kg and the possibility of positioning the transplanted organ outside the peritoneum [8]. Some centers practice early unilateral nephrectomy for the purpose of reducing the frequency of albumin infusions and thus delaying the transplant. The approach followed by the group of Jalanko et al. is that of performing a bilateral nephrectomy when the child weighs 7 kg and beginning peritoneal dialysis to avoid the complications of the nephrotic stage. When the patient has reached a weight above 9 kg and extra-peritoneal positioning of the transplant is possible, transplantation is performed. Another possibility is that of performing an early transplant with intraperitoneal positioning of the organ [8]. Following the transplant, an immunosuppressive therapy is required to prevent rejection and proper hydration (3,000 mls/m²/die) to ensure good renal aortic perfusion to reduce the risk of thrombosis and the subsequent loss of the new organ [50].

In the case of a post-transplant recurrence of CNS, plasmapheresis and the administration of cyclophosphamide is indicated [51]. Post-transplant survival at 5 years is above 90% [52, 53].

Holmberg et al. found an increased risk of post-operative proteinuria in a subgroup of patients with CNF. Most of the subjects presented a nonsense homozygotic mutation (Fin-major mutation) of the nephron gene (NPHS1), which resulted in complete absence of the protein. Following kidney transplantation, these patients developed anti-nephron antibodies with subsequent proteinuria, which was treated successfully with plasmapheresis associated with cyclophosphamide and anti-CD20 antibodies. Mutations of the gene that encodes for podocin (NPHS2) have also been associated in some cases with forms of recurrent post-transplant nephrotic syndrome. Differently from the Fin-major mutation, anti-podocin antibodies have not been found and the pathophysiology and best therapy for this condition are still little-known [54].

Opinions are divided as concerns vaccination of patients with CNS; in the light of their poor immunitary response, some authors do not support the use of such a methodology, even though it is part of the regular protocols prior to transplantation. In disagreement with this opinion, Nguyen et al. reported on a case of CNS which had regular kidney pre-transplant vaccinations with a suitable response [55].
Prognosis

The prognosis in patients affected by CNS is severe, with death ensuing in the first months of life or at approximately 5 years [56]. In some cases it is possible to obtain good control of the pathology with early and aggressive treatment, also including a kidney transplant [57, 58].

Declaration of interest

The Authors declare that there is no conflict of interest.

References


