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Genetic mutations of podocyte proteins as underlying mechanism of glomerular diseases in pediatric and adult patients

Mutacje genów kodujących białka podocyta jako przyczyna uszkodzenia kłębuszków nerkowych u dzieci i chorych dorosłych

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S u m m a r y

Podocyte differentiation and glomerulogenesis in fetal life is controlled by specific genes and any disturbance of this process may lead to further structural defects with clinical consequences. The genetic background of glomerular disease with predominating proteinuria is suspected mainly due to occurrence early in life and/or resistance to specific pharmacotherapy. The younger is the patient, the higher is risk of genetic background. Incidence of genetic background of steroid-resistant nephrotic syndrome was reported as 100% in newborns, 57% in infants, 36% in children, 25% in adolescents and 14% in adult patients. Long-term outcome might be related to specific type of mutation. Some cases do partially respond to long-term cyclosporine A therapy, while on treatment and some are resistant to any therapy. Bilateral nephrectomy and further renal transplantation is the most aggressive management of cases with severe Fin-major mutation of nephrin – related congenital nephrotic syndrome, seen in young children.

Key words: nephrotic syndrome, genetic mutations, podocyte

S t r e s z c z e n i e

Różnicowanie się podocytów i tworzenie kłębuszków jest w życiu płodowym poddawane kontroli swoistych genów. Jakiekolwiek zaburzenie tego procesu może skutkować zaburzeniami budowy i czynności kłębuszków. Wczesne ujawnienie się takich zaburzeń po urodzeniu i/lub oporność na leczenie, skłania do podejrzewania podłoża genetycznego u chorych z białkomoczem. Im młodszy jest pacjent, tym wyższe jest ryzyko obecności tła genetycznego glomerulopatii. Częstość występowania podłoża genetycznego steroido-opornego zespołu nerczycowego wynosi 100% u noworodków, 57% u niemowląt, 36% u dzieci, 25% u młodocianych i 14% u chorych dorosłych. Rodzaj mutacji wpływa na rokowanie. W niektórych przypadkach przy długotrwałym stosowaniu cyklosporyny osiągany jest częściowy efekt terapeutyczny, ale w innych – efektu leczenia nie ma wcale. W najcięższych przypadkach wrodzonego zespołu nerczycowego u dzieci z mutacją typu Fin-major, najbardziej agresywnym sposobem postępowania jest usunięcie obu nerek i docelowo transplantacja nerki.

Słowa kluczowe: zespół nerczycowy, mutacje genetyczne, podocyt

The fetal differentiation and glomerulogenesis is strictly regulated process and many genes are involved in this regulation (1, 2). There is increasing evidence for genetic background of several clinical types of nephrotic syndrome, presented by pediatric, adolescent and adult patients. The major distinctive pattern between specific subgroups of nephrotic syndrome is "syndromic" vs "isolated" type. In "syndromic" pattern renal disease is combined with several extrarenal symptoms, including different types of congenital malformations or malfunctions, present e.g. in Denys-Drash, Frasier's and nail- patella syndromes or Schimke's immunoosseous dystrophy. So-called syndromic nephrosis is mainly presented by infants with other co-morbidities, however it should be stressed, that it may be diagnosed also in adolescent or adult patients, as it is in Charcot-Marie-Tooth disease, where there is a link between INF2 gene mutation, formin protein, podocytes and Schwann-cell function (the last causing severe neuropathy) (3). There are no extrarenal

symptoms in isolated forms of genetic nephrotic syndrome and clinical symptoms are mainly related to severity of proteinuria.

GENOTYPE – FENOTYPE LINK

In some cases there is an evidence for link between type of specific gene mutation and severity of relevant nephrotic syndrome. In congenital nephrotic syndrome of Finnish type, so called Fin-major mutation of NPHS1 causes limitation of number of aminoacids in nephrin molecule from 1241 to 90, while in Fin-minor mutation reduces this number from 1241 to 1108. The clinical expression of those two types is significantly different and in Fin-major related cases the child is delivered being critically ill, with huge general oedema, severe dysproteinemia and renal injury. Those patients do not respond to any antiproteinuric treatment and after short time of vigorous supplementation of protein and albumin – bound vital substances, most of the patients must finally undergo bilateral nephrectomy, to avoid life-threatening complications of massive, untreatable urinary loss of protein. Then the patients are dialyzed until successful renal transplantation, which however may be complicated by "recurrence" of the disease due to anti-nephrin antibodies. Patient with Fin-minor mutation present much more mild clinical course and some of them respond to antiproteinuric treatment with ACEi (captopril) and/or indomethacine. Effect of these drugs is limited to lower proteinuria, while on treatment (4, 5).

Specific mutation may also serve as predictive factor for long-term renal outcome. In the study including 117 patients with early – onset non-Finnish nephrotic syndrome, the presence of podocine mutation was related to significantly better renal survival compared to nephrin mutation. The mean time to end-stage renal disease in patients with podocin mutation was 79 months, compared to 32 months in cases with nephrin mutation ($p = 0.007$)(6). Specific analysis of podocin (NPHS2) has also predictive value in both childhood and adult-onset steroid-resistant nephrotic syndrome. The combined presence of R229Q and A284V allele in adult patients was correlated with lack of response to corticosteroids and immunosuppression, development of focal segmental glomerulosclerosis (FSGS) in biopsy and 8-year progression to end-stage renal disease. On the other hand, it was also correlated with low recurrence rate after renal transplantation (7).

WHO SHOULD BE SCREENED FOR GENETIC BACKGROUND OF NEPHROTIC SYNDROME?

In the study including 125 adult and pediatric patients with primarily steroid-resistant nephrotic syndrome, overall 37 (34%) demonstrated relevant podocine mutation. The incidence of mutation was conversely related to the age and was 100% in symptomatic newborns, 57% in infants, 36% in children, 25% in adolescents and 14% in patients with adult-onset nephrotic syndrome (8). Basing on this observation the relevant algorithm of genetic screening in steroid-resistant nephrotic syndrome was released. The authors suggest that regarding the age of disease onset, the first step of screening should be testing for NPHS1 (nephrin) in newborns, NPHS2 (podocin) in infants and children, and specific R229Q polymorphism of podocin in adolescents and adults. Negative result of the first-step screening suggests looking for other mutations, including WT1, TRPC6, ACTN4 and PLCE1 (8).

DOES GENETICALLY DETERMINED NEPHROTIC SYNDROME RESPOND TO ANY TREATMENT?

In cases of the most severe congenital nephrotic syndrome (and nephrin mutations) the symptomatic treatment is based on aggressive supplementation of protein and albumin-bound hormones and vitamins lost into urine. There is no effect of steroid therapy or immunosuppression. Attempts to reduce heavy proteinuria include use of captopril and indomethacin, and uni- or bilateral nephrectomy, preceding temporary dialysis and further renal transplantation is reported option (9). Steroid-resistance is seen in patients with mutations of podocin. There are specific mutations, which determine the age of disease onset, such as R229Q heterozygotic variant, associated with adult-onset steroid-resistant nephrotic syndrome (10, 11). Patients with steroid-resistance are put on long-term cyclosporine therapy, which does not cure the disease, however may at least partially control the severity of proteinuria (12).

There is increasing evidence, that in genetically determined, steroid-resistant nephrotic syndrome, some other mechanisms of cyclosporine (beyond the effect on interleukin-2 and T-cells) are associated with it's therapeutic effect. One of them is related to protection of podocyte synaptopodin from cathepsin L – mediated degradation, achieved by diminished dephosphorylation – associated with calcineurine inhibition (by cyclosporine). This stabilizes actin, the important protein of podocyte cytoskeleton and in consequence reduces proteinuria (13, 14). This phenomenon justifies the opinion, that podocyte is a direct target of specific immunosuppressive drugs (15). This also may explain the partial remission achieved with cyclosporine in patients with nephrotic syndrome and WT1 mutation (16). One of the clinical subtypes of genetically determined nephrotic syndrome, which respond to calcineurine inhibition is TRPC6 channel mutation. Defect of this functional channel, present in the podocyte causes steroid-resistant nephrotic syndrome and segmental sclerosis (FSGS) (17). The inhibition of calcineurine by specific drug (cyclosporine) interacts with the TRPC6 channel molecules and improves it's dysregulation (18, 19).

Despite some effect of cyclosporine on reduction of proteinuria, overall efficacy of this drug in steroid-resistant genetic nephrotic syndromes is limited and in comparison to steroid-resistant non-genetic forms. One multicenter report showed that response to therapy was 68% vs 17% ($p = 0.005$), in favor to non-genetic cases (20).

Angiotensin receptor-1 (AT1R) blockers may be useful in reducing proteinuria, as they directly prevent a reduction in the expression of the slit diaphragm functional molecules, however thay may serve only as additional supplementary management (21).

SUMMARY

Genetic background of nephrotic syndrome should be suspected in young-age – onset disease and primary steroid-resistance (fig. 1).

The incidence of genetic background is reversely correlated with age at onset of the disease.

Majority of cases of genetic nephrotic syndromes do not respond to steroids nor immunosuppression in terms of achieving complete remission; in minority of cases partial remission (defined as reduction of proteinuria) may be achieved and maintained with cyclosporine in long-term therapy.

Genetic background determines renal outcome and mutation of nephrin is associated with worse renal survival compared to mutation of podocin.

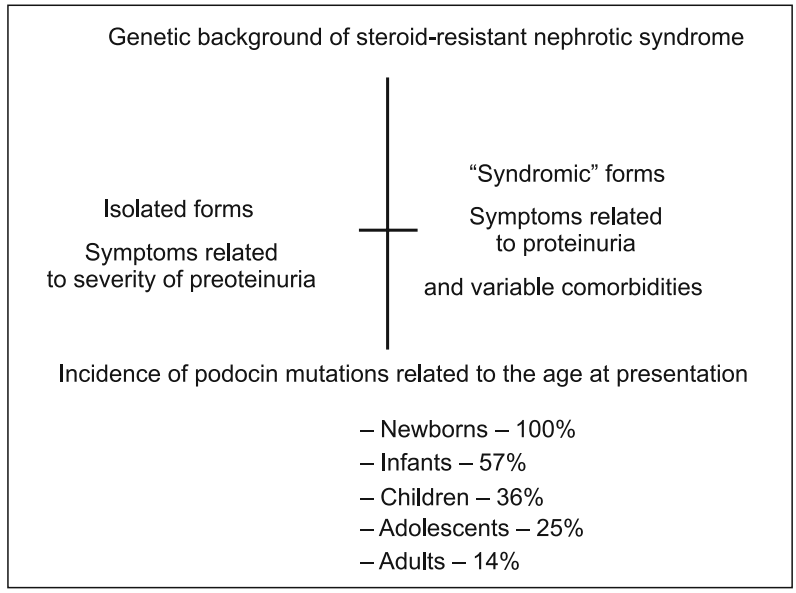

Fig. 1. Major types and incidence of genetically determined steroid-resistant nephrotic syndrome.

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