

Podonet

Consortium for Clinical, Genetic and Experimental Research into Hereditary Disease of the Podocyte Clinical Registry for Steroid Resistant Nephrotic Syndrome and Genetic Exploration of Familial/Syndromal SRNS

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Summary

Steroid-resistant nephrotic syndrome (SRNS) is a rare but important and severe clinical condition. It is observed in approximately 15-20% of children presenting with idiopathic nephrotic syndrome. While in up to 50% of patients intensified immunosuppression can eventually induce disease remission and prevent long-term sequelae, a major subset of cases appears to be caused by genetic abnormalities. The hereditary forms of SRNS typically do not respond to any immunosuppressive medication and progress rapidly to end-stage renal failure. Patients with a genetic cause of SRNS can be spared extended invasive immunosuppressive treatment and show no disease recurrence after renal transplantation. However, the genes identified to date altogether explain less than half of the SRNS cases unresponsive to any immunosuppressive treatment.

The PodoNet project will establish an international SRNS registry. Its objective is to explore the demographics of immunological and known genetic forms of pediatric and adult-onset SRNS and to evaluate genotype-phenotype correlations. Furthermore, we hope to improve clinical management and develop novel therapeutic strategies by analyzing prospectively the outcomes achieved with different treatment protocols. Finally, we will search for new genetic entities of SRNS.

Participation in the PodoNet registry will involve the collection of pseudonymized clinical data every 6 months, of blood and urine samples every 12 months, and of blood for DNA analysis at one point in time.

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1. Background

Idiopathic nephrotic syndrome (INS) is a severe clinical condition predominantly observed in children which is characterized by a loss of glomerular permselectivity and massive urinary protein loss and severe consecutive alterations of protein turnover, lipid metabolism, hemostasis and various endocrine systems. The majority of cases appears to be caused by a dysregulation of the immune system; these patients respond readily to corticosteroid immunosuppression and have an excellent clinical prognosis [1].

In contrast, **steroid-resistant nephrotic syndrome** (SRNS), observed in approximately 15-20% of children presenting with INS, is a much more challenging disease entity. The cumulative prevalence of SRNS in caucasians is approximately 3-4 per 100.000 children. The most common histopathological correlate of SRNS is focal segmental glomerulosclerosis (**FSGS**) [15]. A fraction of SRNS patients (~50%) eventually responds to intensified immunosuppressive treatment [9;10;13]. While the achievement of remission is associated with a favourable long-term prognosis [4], unresponsive patients rapidly progress to chronic and eventually end-stage renal failure [8].

The large subgroup of SRNS remaining unresponsive to any immunosuppressive interventions has been a focus of research in the past decade. In particular, the identification, through positional cloning approaches, of genes involved in rare familial forms of SRNS with Mendelian patterns of either autosomal recessive (AR) [2;3;7;11;12;16] or dominant (AD) inheritance [6;19] allowed the characterization of developmental and structural defects affecting the **podocyte**, an highly specialized visceral epithelial cell lining the glomerular basement membrane, forming interdigitating foot processes and interacting via an unique cell-cell contact, the slit diaphragm, altogether constituting the glomerular filtration barrier.

SRNS is a paradigmatic disorder to illustrate the eminent **clinical relevance** that genetic research can have for affected patients and families. Children with a genetic cause of SRNS can be spared extended invasive immunosuppressive treatment [5;14]. Mutation analysis in the parents can provide a basis for genetic counseling not only with respect to family planning but also to the suitability of relatives as organ donors [11]. Moreover, the risk of recurrence of nephrotic syndrome in a transplant kidney is far lower in patients suffering from structural podocyte defects than in immunological forms of SRNS [17;18]. Finally, from a clinical research point of view, excluding mutation carriers from immunosuppressive protocols will reduce non-responder rates and permit to minimize the numbers of patients required to compare treatment alternatives in clinical trials.

2. Aim of the study

PodoNet is a comprehensive research project dedicated to improving the health of patients suffering from SRNS by a transnational collaborative research strategy involving clinical, genetic and innovative experimental therapeutic approaches. The clinical and genetic projects will benefit present and future SRNS patients and their families by optimizing the treatment and by identifying risk factors for an unfavourable course.

The aims of the clinical and genetic projects of PodoNet are:

1. Collect a critical mass of SRNS patients/families and biological materials for clinical research by establishing an international online registry
2. Study systematically genotype/phenotype correlations including clinical outcomes of SRNS patients with defined genetic abnormalities
3. Provide clinicians with rational clinical practice guidelines to harmonize diagnostic and therapeutic workflows in children with SRNS
4. Establish new nosological entities by identifying abnormalities in new genes causing familial and/or syndromal forms of SRNS

3. Study design

Longitudinal observational study collecting retrospective and prospective information in children with steroid resistant nephrotic syndrome. Data collection will include medical history, laboratory variables and genetic information.

4. Inclusion criteria

- Children (age 0-18 yrs) with steroid resistant nephrotic syndrome in current care at participating centres
- Adults with familial steroid resistant nephrotic syndrome

5. Exclusion criteria

- Steroid sensitive nephrotic syndrome

6. Investigational plan

Retrospective and prospective information regarding clinical disease manifestations, familiarity, associated co-morbidities, pharmacological treatment and the course of disease

will be collected. In the prospective part of the study, data will be recorded every 6 months for at least 3 years. Samples of blood (5 ml) and urine (20 ml) will be collected every 12 months. The study will be continued for at least 3 years. A single blood sample (5-10 ml) will be obtained from the patient, both parents and, if appropriate, other family members for genetic testing.

The clinical data will be submitted to a web-based registry in a pseudonymized fashion (by locally defined letter or number code), allowing only the local investigator to assign data to an individual patient. Also, the blood, DNA and urine samples will be coded in a manner that will enable no investigator other than the local physician in charge of the patient to relate results of the research to an identified patient.

7. Withdrawal from the study

A patient will be withdrawn from the study upon request of patients or his/her parents, or if the patient is not able to comply with the diagnostic procedures of the study.

8. Statistics

The study is designed as an explorative, epidemiological, longitudinal data collection. Formal calculation of minimal cohort size requirements is not possible for this kind of study design since the frequencies of genotypes and expression of phenotypes are not known a priori.

Endpoints to be tested statistically with respect to effects of individual genotypes, a general effect of the presence of an underlying genetic disorder or an effect of parental consanguinity will include age at first disease manifestation, rate of renal failure progression, actuarial renal survival rate and time to end-stage renal disease, and the risk of disease relapse following kidney transplantation.

Tests of differences in proportions (Chi², Maentel-Haenszel, Fisher), ANOVA with Newman-Keuls testing for multiple comparisons, logistic regression analysis, and Kaplan-Meier life table analysis with Cox proportional hazard modeling will be used as appropriate to address the individual questions under study.

9. Ethical aspects

This application is related to the clinical and genetical part of the PodoNet Project involving human subjects. The studies will conform to all ethical rules, laws and regulations set by the European Union and the countries where the research will be carried out. The Consortium is aware of and will respect the contents of the Declaration of Helsinki, the Council of Europe Convention for the Protection of Human Rights and Biomedicine, the Universal Declaration

on Bioethics and Human Rights and the CIOMS/WHO International Ethical Guidelines for Biomedical Research Involving Human Subjects and the EU Directive on Data Protection ([95/46/EC](#)). Moreover, the consortium will follow the codes of the Additional Protocol on the Prohibition of Cloning Human Beings and the Universal Declaration on the human genome and human rights.

Approval will be obtained from all local Ethical Committees / Institutional Review Boards in charge of the institutions participating in the registry. Care will be taken to fulfill any particular national or local ethical requirements in individual institutions.

The project will involve children, whose competence to understand the goals, contents and risks of the research varies with age. Whenever possible, information will be presented in an age-adjusted, comprehensible manner both verbally and in written form, and informed consent will be obtained both from the patients and their parents. In children typically younger than 9-10 years of age and in mentally retarded adolescents and adults, their legal guardians will be asked to give surrogate informed consent.

Both the children and adult family members will be informed about the possibility to refuse to enter the study or to retract at any time without any consequences. No inducements will be given to influence the willingness to participate in the research. Whenever possible approval will be obtained in the presence of a witnessing community representative.

Prior to enrolment in the clinical registry and trial, the patients and their families will receive detailed information about the goals and procedures of the PodoNet project (see attached patient information and consent forms). They will learn that participation in the study may or may not have a benefit for their own disease course or turn out helpful to them or their relatives' future family planning. They will learn that the research results may have a global impact on our understanding of genetic kidney disease and the improvement of health on the society level and may well become helpful to patients at risk of or born with SRNS in the future by the development of better strategies of prevention, diagnosis and treatment.

They will also be informed that the burden of participating in these studies is very small and does not expose them to any additional health risks. In view of the minimal risks involved in these observational studies, a patient insurance will not be required.

The laboratories carrying out the human genetic and biochemical studies will receive coded DNA or serum samples which indicate the center and patient code and permit to track the familial relationships between donors of samples, but not the donors' identities.

The investigators may incidentally find abnormalities of immediate clinical relevance to the patient and/or other family members. In these cases the participating laboratories will be obliged to report the study results to the local physician who will have the responsibility to transmit the information to the families, which only he or she will be authorized to identify.

Families will be informed about clinical relevant genetic findings. Families will also be provided with the information that the samples will not be used for any other purpose than identifying genes related to SRNS without their explicit approval.

10. Data protection issues

Attention will be given to apply the highest ethical standards with respect to data protection. In particular, the EU Directive 95/46/EC for the protection of individuals with regard to the processing of personal data will be respected.

Optimal confidentiality, accuracy, security and lawful management of data will be secured by the following measures:

- All clinical information and biological samples and tissues obtained will be transmitted to the central office and laboratories in a pseudonymized fashion. Only the physician in charge will be able and entitled to re-allocate examination results to an identified subject. In this way, all processing of data and materials outside the clinical center will be completely 'de-personalized' and full identity protection guaranteed.
- Clinical data will be entered to a secure website, observing the state-of-the-art encryption technology. While retrospective data will be taken from the patient files, prospective data collection will be carried out directly online.
- The use of a uniform case report form menu will ensure that only adequate and relevant information will be recorded.
- Data will be processed only for the purposes outlined in this proposal. Use for other purposes will require explicit patient approval. Also, data will not be transferred to any laboratories or places outside the Consortium without patient consent.
- Data and materials will only be stored for the terms dictated by national laws and regulations.

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