NOONAN SYNDROME AND RASOPATHIES—INTERESTING AND IMPORTANT

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Back in 1962 the characteristic for any pediatric specialty innate curiosity lead Dr. Jacquelene Noonan to the discovery of a new syndrome later named after her—the Noonan syndrome (OMIM#63950, ORPHA:648) (1). Being a pediatric cardiologist, at a scientific meeting she described 9 patients (6 boys and 3 girls) with pulmonary stenosis and characteristic face and body signs that made their appearance similar. She was bold enough to publish the series in 1963 in the Journal of Pediatrics together with Ehmke, and refer to these patients as a "new syndrome", based on the fact that she diagnosed both boys and girls while before this presentation, only a few boys were presented in the literature, all referred to as "male Turner" patients due to the resemblance in the extracardiac features. Six years later, in 1968, she published her second paper adding 8 more patients (5 males and 3 females), 2 of whom did not have valvular pulmonary stenosis but patient ductus arteriosus (1). The paper was not only convincing but a real breakthrough that inspired better recognition of the syndrome, and naturally led to its naming after her.

After years of oblivion or just episodic interest, Noonan syndrome (NS) has been of great interest to physicians and basic scientists in the last 20 years, and especially nowadays not only because for a rare disease it is actually quite common (1 in 2000 newborns, on the borderline of rare conditions definition which is 1 in 2000 affected individuals). In 2001 the first discovered genetic change was reported—mutations in the so-called PTPN11 gene (2), nowadays identified in around 50% of all studied patients (3). The overall quantity of known genetic background increased to changes in more than 20 genes, and about a total of 85% of patients can currently be genetically confirmed. The fast step of genetic discoveries of different genes made it clear that they belong to the RAS/mitogen-activated protein kinase (RAS-MAPK) cellular cascade. This explains why so many different genes from different chromosomes affect individuals clinically in a similar way. The RAS-MAPK pathway proteins are expressed in many cells and are responsible for cellular proliferation, migration and differentiation during intrauterine development (3).

In the recent years, new genotype-phenotype correlations have become evident, such as short stature connected to PTPN11 mutations or more frequent pulmonary stenosis connected to SOS1 mutations, etc. This newly acquired knowledge made the formulated by van der Burgt in 2007 clinical diagnostic criteria quite outdated, and the scientific community eagerly awaits the new diagnostic criteria to be published, most probably later on this year or early in 2023.

All patients should be diagnosed as children since the most prevalent feature is impaired growth and short stature due to mild growth hormone and/or IGF-1 insensitivity accompanied also by delayed puberty—the earlier the diagnosis, the better the treatment outcome. Recombinant human growth hormone (rhGH) treatment was officially approved in several countries, incl. USA, in 2007, and is applied widely nowadays with excellent results and fewer safety issue compared to the initially expected (4). Moreover, the increased access to genetic diagnosis and the high diagnostic yield of the contemporary methods makes it possible to start formulating phenotype-genotype correlations also in the view of safety of rhGH treatment. Thus, many scientific groups in the world look at their patient populations again in an attempt to critically assess the level of care and improve it. Moreover, it became clear that the cardiac anomaly, even the hypertrophic cardiomyopathy, is not an rhGH treatment contraindication. In the view of all these positive developments it is strange why RASopathies are not yet easily diagnosed and their treatment and follow-up is not fully structured. Yet, more boys than girls are diagnosed worldwide, representing severe cultural discrimination of females based most probably on societal stature conceptions. All published case series or even registries' data are based on much smaller patient numbers compared to, e.g., growth hormone deficiency.

Being a rare disease, RASopathies require a proactive approach by both medical community and patient advocacy representatives in order to get the attention they deserve. Although RASopathies have so many different aspects (cardiac, hematological, ophthalmological, neurocognitive), the pediatric endocrinologist (PE) is the core specialist in the multidisciplinary team. The original paper "Noonan Syndrome Patients with Short Stature at a Single Paediatric Endocrinology Centre" in this issue of Scripta Scientifica Medica by a group of PEs led by Dr. Yana Deyanova presents data from a single Bulgarian Expert Centre of Rare Endocrine Diseases. Being part of the European Reference Network of Rare Endocrine Diseases (5) and specifically of the Main Thematic Group 5 "Growth and Genetic Obesity Syndromes" (MTG5), the authors are executing one of their partnership obligations—to study, report, and provide better care for patients affected with rare diseases (6). On the top of being not timely and widely diagnosed in our country although the van der Burg original paper was translated and presented to the Bulgarian public 2 years after the original publication by Dr. Robeva in "Nauka Endocrinologia", the prevalence of more boys, the relatively late start of rhGH treatment and the lack of reimbursement of the rhGH treatment are impeding the progress in the field. In this aspect, the paper is important addition to the field although the series of patients is relatively small. The study's most useful aspects are the evidence that these patients follow the general rules in rhGH treatment if they have confirmed GH deficiency or are treated under the indication "small for gestational age children," both indications per se a very small share of all NS patients. In order to increase access to treatment and improve outcomes, the NS indication should be applied especially with available baseline genetic workup. This will allow using the recommended higher doses of rhGH and achieve better final height results. Families will feel better supported, and children not being short at the end of their growth will benefit more than if not diagnosed and not treated.

Last but not least, the paper draws attention to the still lacking national referral of patients to expert centers of rare diseases. This is currently an established practice in Europe, the USA, and other countries, because all analyses show that this is the way to improve diagnosis, outcome, and costs of care of patients with rare diseases. Although Bulgaria supports the concept of rare disease care and has declared readiness to introduce a system of national referrals, nothing has been done so far in this aspect. The already existing centers are not supported financially or even politically by the state or the national insurance. The patient advocacy groups exert not well focused, fragmented, and episodic pressure for improvement. Thus contemporary care is not yet accessible to Bulgarian patients with rare diseases, nor is there established or innovative treatment. We believe the paper of Deyanova et al. could prompt efforts in this direction.

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