Management of endocrine aspects of Noonan syndrome across Europe: A sub-analysis of a European clinical practice survey

Thomas Edouard1, Martin Zenker1, Ingegerd Östman-Smith1, Eduardo Ortega Casteló2, Cordula M Wolff1, Emma Burkitt-Wright1, Alain Verloes1, Sixto García-Miráñiz3, Marco Tartaglia1, Guftar Shakh1*1, Jan Lebl1*1

1Endocrine, Bone Diseases, and Genetics Unit, Children’s Hospital, Tulln University Hospital, RESTORE INSERM UMR1301, Toulouse, France. 2Institute of Human Genetics, University Hospital Magdeburg, Magdeburg, Germany. 3Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden. 4Department of Statistics and Data Science, Faculty of Clinical Studies, Complutense University of Madrid, Madrid, Spain. 5Department of Congenital Heart Defects and Pediatric Cardiology, German Heart Center Munich, Technical University of Munich, Munich, Germany. 6DNHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany. 7Manchester Centre for Genomic Medicine, Manchester University NHS Foundation Trust and University of Manchester, Manchester, UK. 8Department of Genetics, Hospital Robert Debré, Assistance Publique des Hôpitaux de Paris (AP-HP), Paris, France. 9Institute of Medical and Molecular Genetics (INGEMM), Hospital Universitario La Paz Research Institute (IdiPAZ), Hospital Universitario La Paz, Madrid, Spain. 10Genetics and Rare Diseases Research Division, Ospedale Maggiore Policlinico, IRCCS, Rome, Italy. 11Department of Paediatric Endocrinology, Royal Hospital for Children, Glasgow, United Kingdom. 12Department of Pediatrics, 2nd Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic. 13G.S. and J.L. contributed equally to this work.

Background

• Noonan syndrome (NS) is characterised by the presence of distinctive facial features, congenital heart disease, short stature, skeletal abnormalities, mild developmental delay, and predisposition to myeloproliferative disorders.1

• The European Medical Education Initiative on NS developed a clinical practice survey to assess the diagnosis and management of diseases within the NS phenotypic spectrum across Europe.

• Here, we present a sub-analysis of the overall survey results focussing on the endocrine aspects of NS.

Methods

• A 60-question survey was distributed to clinical geneticists, paediatric endocrinologists, and paediatric cardiologists by several European and national specialist societies.

• In this sub-analysis, the responses of paediatric endocrinologists were mainly reported, analysed according to their country of origin, and compared with those of clinical geneticists and paediatric cardiologists where appropriate.

• Differences between specialties and countries were assessed using contingency tables and the Chi-Squared test for independence. The Friedman’s test was used for related samples.

Results

• Answers from 364 respondents were included in the final analysis set:
  • 146 (40%) Paediatric Endocrinologists
  • 110 (30%) Paediatric Cardiologists
  • 108 (30%) Clinical Geneticists

Figure 1 – Responses to survey question “Which growth charts do you use for the follow-up of patients with Noonan syndrome?”

Figure 2 – Responses to survey question “In your experience, which is the optimal age at which to begin growth hormone treatment for patients with Noonan syndrome and short stature?”

Figure 3 – Responses to survey question “Are you concerned about any of the following regarding growth hormone treatment in children with Noonan syndrome?”

Figure 4 – Responses to survey question “Do you consider hypotrophic cardiomyopathy a contraindication to the use of growth hormone therapy?”

Screening and investigation of short stature

• Paediatric endocrinologists mostly refer to national growth charts for the general population when monitoring growth (p < 0.0001), whereas geneticists mostly refer to NS-specific growth charts (p < 0.005) (Figure 1).

Concerns about GH treatment

• There are three main concerns regarding GH treatment for patients with NS (Figure 3):
  • Hypertrophic cardiomyopathy (HCM): Geneticists were less concerned about HCM compared with paediatric endocrinologists and cardiologists (p = 0.041).
  • Increased risk of malignancy: Paediatric cardiologists were less concerned about the increased risk of malignancy compared with paediatric endocrinologists (p < 0.0001).
  • Limited efficacy: 33% of geneticists and 35% endocrinologists were concerned about limited efficacy.

Conclusions

• International guidelines regarding the screening and management of the endocrine aspects of NS are needed.

• A knowledge gap regarding GH therapy in the presence of HCM has been identified.

• Possible genotype-phenotype correlations in terms of efficacy and safety of GH need to be studied.

References


Acknowledgements: We would like to acknowledge the national and European specialist societies for their valuable assistance with distribution of the survey. The authors are also extremely grateful to the physicians who completed the survey. We would like to thank Novo Nordisk EUC-A/S for funding. We are also very grateful to Nick Fischer, Christèe Kroumova and Monika Schmirt, from Amedis MedCommes GmbH (Mannheim, Germany) for their assistance with survey development and implementation, analysis of survey results, and poster development.

Funding: The initiative was supported by an unrestricted grant from Novo Nordisk Europe A/S, with Steering Committee members receiving honoraria for survey development. Novo Nordisk has had no influence on the scientific content or materials generated as part of this project.