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Management of cardiac aspects in children with Noonan syndrome – results from a European clinical practice survey among paediatric cardiologists

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ABSTRACT

Background: The majority of children with Noonan syndrome (NS) or other diseases from the RASopathy spectrum suffer from congenital heart disease. This study aims to survey cardiac care of this patient cohort within Europe.

Methods: A cross-sectional exploratory survey assessing the treatment and management of patients with NS by paediatric endocrinologists, cardiologists and clinical geneticists was developed. This report details responses of 110 participating paediatric cardiologists from multiple countries.

Results: Most paediatric cardiologists responding to the questionnaire were associated with university hospitals, and most treated <10 patients/year with congenital heart disease associated with the NS spectrum. Molecular genetic testing for diagnosis confirmation was initiated by 81%. Half of the respondents reported that patients with NS and congenital heart disease typically present <1y of age, and that a large percentage of affected patients require interventions and pharmacotherapy early in life. A higher proportion of infant presentation and need for pharmacotherapy was reported by respondents from Germany and Sweden than from France and Spain ($p = 0.031$; $p = 0.014$; Fisher's exact test). Older age at first presentation was reported more from general hospitals and independent practices than from university hospitals ($p = 0.031$). The majority of NS patients were followed at specialist centres, but only 37% reported that their institution offered dedicated transition clinic to adult services. Very few NS patients with hypertrophic cardiomyopathy (HCM) were reported to carry implantable cardioverter defibrillators for sudden cardiac death prevention. Uncertainty was evident in regard to growth hormone treatment in patients with NS and co-existing HCM, where 13% considered it not a contraindication, 24% stated they did not know, but 63% considered HCM either a possible (20%) or definite (15%) contraindication, or a cause for frequent monitoring (28%). Regarding adverse reactions for patients with NS on growth hormone therapy, 5/19 paediatric cardiology respondents reported a total of 12 adverse cardiac events.

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Conclusions: Congenital heart disease in patients with NS or other RASopathies is associated with significant morbidity during early life, and specialty centre care is appropriate. More research is needed regarding the use of growth hormone in patients with NS with congenital heart disease, and unmet medical needs have been identified.

1. Introduction

Jacqueline Noonan originally described nine children with similar dysmorphic features and pulmonary valve stenosis (PVS) (Noonan, 1968). Subsequent larger studies have found that Noonan syndrome (NS) can be present without any congenital cardiac anomalies, or can be associated with a number of other cardiac abnormalities (Burch et al., 1993; Hickey et al., 2011; Linglart and Gelb, 2020; Marino et al., 1999). PVS is the most commonly associated lesion that occurs in 40–52% of NS patients. The second most commonly associated condition is hypertrophic cardiomyopathy (HCM), which is found in 22–29% of NS patients (Burch et al., 1993; Linglart and Gelb, 2020). HCM in patients with NS has a significant impact on long-term survival with these patients experiencing decreased survival when compared with children with non-syndromic HCM (Hickey et al., 2011). In NS-associated HCM, overall survival was 71% at three years after diagnosis with a further phase of late-onset mortality starting after 10 years of age (Hickey et al., 2011). The bulk of early mortality was found in children diagnosed before six months of age and presenting with heart failure, where one-year survival was only 31% (Wilkinson et al., 2012). The presence of co-existing cardiac structural abnormality (in 24%) made no significant difference to survival (Wilkinson et al., 2012).

Other cardiac conditions occurring in smaller numbers of NS patients are atrial septal defect (ASD), atrio-ventricular canal defects (usually partial), ventricular septal defect (VSD), mitral valve (MV) abnormalities, coarctation of the aorta, patent ductus arteriosus and tetralogy of Fallot (Linglart and Gelb, 2020). When including other phenotypically similar disorders caused by mutations in genes encoding components of the RAS-MAPK signalling cascade (RASopathies), overall around 80% of children with a RASopathy have associated cardiac abnormalities (Calcagni et al., 2017). There is a lack of international guidelines addressing the management of NS-associated cardiac disease, and this survey attempts to illustrate the contemporary management praxis among European paediatric cardiologists.

2. Methods

2.1. Study design

A clinical practice survey containing 60 questions regarding the diagnosis and clinical management of diseases within the NS phenotypic spectrum was distributed to members of paediatric endocrinology, paediatric cardiology, and human genetics societies throughout Europe between September and October 2020 (García-Miñaúr et al., 2021). The aim was to obtain feedback from relevant patient management centres across the continent, focusing on geneticists, paediatric endocrinologists, and paediatric cardiologists. Further details on the development of the survey architecture and distribution of the survey are published separately (García-Miñaúr et al., 2021). While the survey contained a number of questions that were generally applicable to the three surveyed specialties (questions 1–10, 21–27, 57–60), there were also subsections that contained specialty-specific questions to address more detailed aspects of patient treatment and management, and for paediatric cardiologists those were questions 28–40.

2.2. Statistics

Data are reported descriptively and are depicted as percentages of total respondents to the respective question. For analysis of national response patterns, only the four countries with most responses were compared (Germany, France, Spain and Sweden for cardiology questions). Percentages were calculated from the number of people who answered from each country and not the total number of responders. For statistical comparisons responses were grouped for binary comparisons with "never" and "seldom" (defined as ≤5%) grouped together, and "frequent" (defined as 26–50%) grouped with "most" (defined as >50%). Because of modest numbers of respondents, countries with geographical proximity were pooled (Sweden + Germany n = 40, versus Spain and France n = 54) where comparisons appropriate. If one single country showed an outlier pattern, the results were a posteriori compared against the pooled results of the other three. Differences in proportions were compared by two-tailed Fisher's exact test (GraphPad Prism).

3. Results

3.1. Description of survey respondents

Including all specialties, the survey was completed by 462 total respondents from 25 countries, for details see companion manuscript (García-Miñaúr et al., 2021). Only the responses from the 110 paediatric cardiologists (García-Miñaúr et al., 2021) were included in this cardiology analysis, with all 110 responding to general questions about patient load and institutions, but approximately one-third skipping the cardiology specialty-specific management questions. The exact number of responding paediatric cardiologists for each question is depicted in the figures representing the data. The specific questions on clinical genetics and endocrinology management are discussed in companion manuscripts (Edouard et al., 2021; García-Miñaúr et al., 2021).

Most of the 110 responding paediatric cardiologists were from Germany (32; 29%), Spain (31; 28%), France (23; 21%), and Sweden (8; 7%). Other countries included Switzerland, United Kingdom, Czech Republic, Austria, Poland, and Romania. Most paediatric cardiologists were associated with a university hospital (74%), with 14% working in a general hospital, 14% in an independent practice, and the remaining in private clinics, specialist centres or other settings, with some working in more than one type of setting. Most paediatric cardiologists from Spain, France, and Sweden (78–100%) answered from university hospitals, whereas only 47% of German paediatric cardiologists were from university hospitals ($p < 0.0001$), with 25% coming from general hospitals and 25% from independent practices.

Seventy percent of paediatric cardiologists encounter ≤10 patients within the NS spectrum per year, and only 5% more than 30 patients/year. Patient care appears to be least centralised in Germany where 84% of paediatric cardiologists encountered ≤10 patients/year, and most centralised in Sweden where 63% encountered ≥11 patients/year. Most respondents (31%) ranked "neonatology" as the most frequent referring specialty, followed by "clinical geneticists" (22%), "other paediatric cardiologists" 20%, "paediatricians" (14%), "paediatric endocrinologists" (8%) and other sub-specialties (6%).

3.2. Diagnosis of Noonan syndrome (clinical diagnosis and genetic testing)

The "most" or "frequent" category combined age at referral is < 1 year for 51% of respondents, 1–3 years for 35%, 4–12 years for 32%, and 13–18 years for 12% of respondents. Presentation in infancy varied between institutions and was significantly more common for

respondents from university hospitals (57%) than for general hospitals and independent practices (40% pooled, p = 0.031).

The leading cause for a clinical diagnosis of NS (rated as 'frequently' or 'most') was congenital heart defects in 86%, characteristic facial features in 65%, short stature in 43%, and rarely others including chest deformities (15%), lymphedema (12%), delay in motor skill development (16%), failure to thrive (14%), undescended testicles (8%), or increased bruising or bleeding (2%). Among paediatric cardiologists, 81% initiated molecular genetic testing for a diagnosis of NS, even if a clinical diagnosis was already made. Genetic testing was ordered by 53% of paediatric cardiologists themselves, and 45% referred to a clinical geneticist for testing. Forty three percent of respondents would offer genetic testing in cases where prenatal features of NS (e.g., increased nuchal translucency, hydramnios, cardiomyopathy) are observed together with a normal karyotype and absence of a family history. According to the answers of 34 paediatric cardiologists, about 30–43% of families would 'frequently' or 'mostly' opt for termination of pregnancy if congenital heart defects, cardiomyopathy, or hydrops were accompanying features present in a foetus with a genetic confirmation of NS.

3.3. Management of patients

The majority of children with NS are being followed at specialist centres (68%). Only 37% of paediatric cardiologists reported that their institution offered a dedicated consultation or transition clinic from child to adult services. According to 95% of the surveyed paediatric cardiologists, the investigation of children with NS should include electrocardiogram (ECG) and cardiac ultrasound at all ages of presentation.

3.4. Quality of life

Most paediatric cardiologists (90%) responded that congenital heart defects affected quality of life in infants (<1 year of age). This reduced gradually with age, with 70% of respondents saying it affected quality of life in toddlers (1–3 years of age), 40% in children (4–12 years of age), and 31% in adolescence (13–18 years of age). Other major factors affecting quality of life according to paediatric cardiologists were lymphedema (43% of respondents answering in the infancy category) and growth retardation in toddlers (38%), children (60%), and adolescents (63%).

4. Cardiology-specific questions

4.1. Need for surgery or interventional catheterization

A need for surgery or interventional catheterization in NS patients with cardiac disease was most commonly reported for PVS ('frequently' or 'most': 53%), which is significantly more than in obstructive HCM (10%; p < 0.0001), MV-anomalies (6%; p < 0.0001), and ASD/VSD (31%; p = 0.014). Obstructive HCM and MV-anomalies were also reported to have a lesser need for intervention than ASD/VSD (p = 0.0038 and p = 0.0003, respectively) (Fig. 1).

With regards to the timing of cardiac surgery or interventional cardiac catheterization, 39% of respondents report interventions 'frequently or mostly' below one year of age, with a non-significant trend (P = 0.097) for higher proportions in Germany and Sweden than in France and Spain. The 'frequently or most' category then fell with increasing age: 26% of respondents in toddlerhood (1–3 years of age), 18% of respondents in childhood (4–12 years of age), and 8% of respondents in adolescence (13–18 years of age) (Fig. 2).

4.2. Management of pulmonary valve abnormalities

The first-line treatment of a neonatal critical pulmonary stenosis

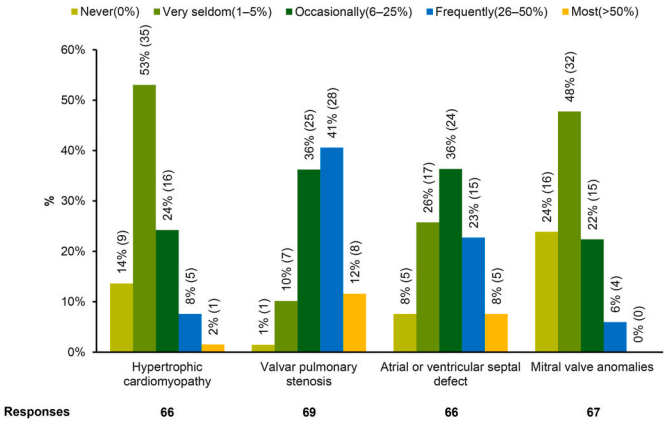

Fig. 1. *How frequently do your patients with both Noonan syndrome and a cardiac diagnosis require any type of cardiac surgery or interventional cardiac catheterization?*
Of the 110 paediatric cardiologists included in this analysis, 69 (63%) answered this question. Physicians could provide answers for one or more cardiac diagnosis. The number of respondents who answered for each is depicted below the chart.

with a dysplastic valve chosen by 76% of respondents was attempt at balloon dilatation, followed by surgical valvotomy (chosen by 17%), and only 3% would use stenting of the right ventricular outflow-tract (Fig. 3).

4.3. Management of HCM

4.3.1. Heart failure in infants and pharmacotherapy

There were geographic differences in the perceived frequency of encountering infants with heart failure. For obstructive HCM, 30–33% of respondents from Germany and Sweden reported that it occurs 'frequently or mostly' (i.e., >26% of cases), whereas only 6% and 7% of respondents from Spain and France reported an occurrence of >26% of cases, respectively (p = 0.032 v. Germany + Sweden, Fig. 4, panel A). There was a similar pattern for non-obstructive HCM (Fig. 4, panel B).

Similar differences were noted when respondents were asked how frequently their patients with NS require pharmacological therapy for their cardiac diagnosis. Thirty-seven percent and 33% of respondents in Germany and Sweden, respectively, reported the need for pharmacological therapy 'frequently or mostly' (i.e., ≥26% of cases), which was in contrast to only 13% and 20% of respondents in Spain and France, respectively (Germany + Sweden versus Spain + France: p = 0.014).

4.3.2. Pharmacotherapy

In all countries, beta-blockers were the most commonly used drugs for HCM patients, followed by diuretics and calcium-channel blockers (Fig. 5). Regarding beta-blocker use, Spain was an outlier with 26% of Spanish respondents using it 'frequently or mostly' versus 55%–100% in the other countries (p = 0.0026). A high proportion of respondents who skipped this question also came from Spain (Fig. 5). There were national differences also in the use of calcium-channel blockers with no respondents using them at all in Sweden, and only 29% of respondents using them in ≤5% of patients in Spain. In France, 17% of respondents used them occasionally, and in Germany, 6% of respondents used them frequently and 31% occasionally. When combining 'occasionally, frequently and most' for this question, Germany uses calcium-channel blockers significantly more frequently than the other three countries pooled (p = 0.0063). Disopyramide was added to beta-blockers most frequently in Sweden with 33% of respondents using it 'frequently', and least commonly in France, where 17% of respondents added it 'very seldom', i.e. in 1–5% of patients (Fig. 5). It was also possible for respondents to list other medical therapies given to patients with NS and

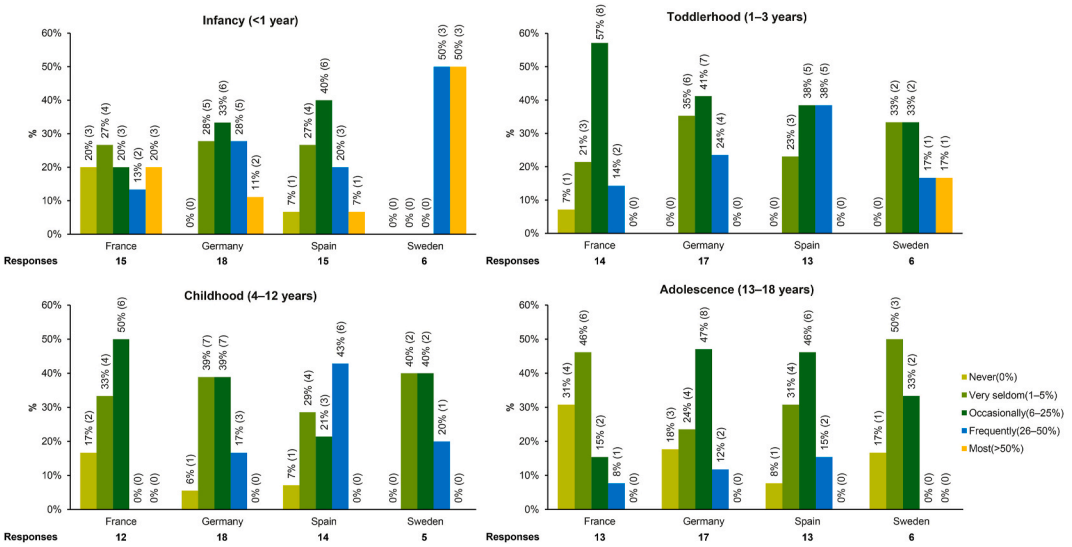

Fig. 2. *At what age do your patients with both Noonan syndrome and a cardiac diagnosis require any type of cardiac surgery or interventional cardiac catheterization?* Of the 94 paediatric cardiologists from France, Germany, Spain, and Sweden included in this analysis, 56 (60%) answered this question. Physicians could provide answers for one or more age groups.

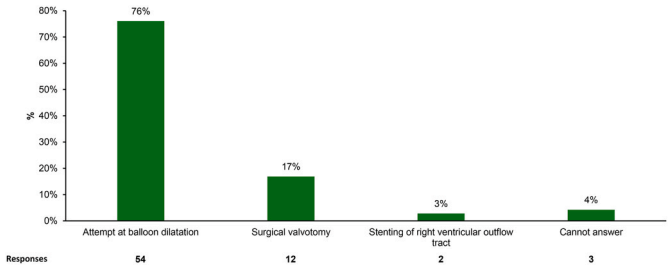

Fig. 3. *What is your first-line treatment for neonatal critical valvar pulmonary stenosis with a dysplastic valve in a patient with Noonan syndrome?* Of all 110 paediatric cardiologists included in this analysis, 71 (65%) answered this question. The number of responses is shown below each first-line treatment.

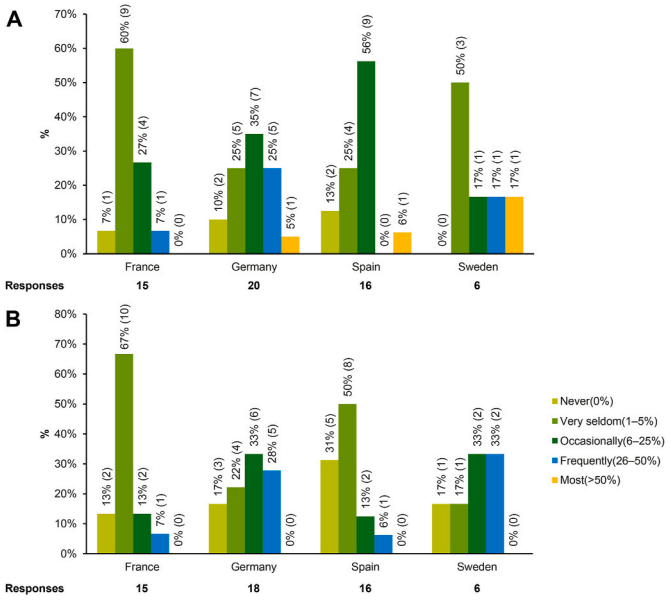

Fig. 4. *Have you seen severe heart failure in infants with Noonan syndrome?* Of the 94 paediatric cardiologists from France, Germany, Spain, and Sweden included in this analysis, 57 (61%) answered the question. For this question, physicians could answer within two categories: Heart failure with hypertrophic cardiomyopathy and right and/or left ventricular outflow obstruction (panel A); and Heart failure with hypertrophic cardiomyopathy and no obstruction (panel B). The number of respondents answering for each category is depicted under the country.

HCM in an open comment field. Other medications added individually by one respondent each included Amiodarone for post-operative arrhythmias, Sildenafil and Bosentan. With regard to new therapies, one respondent added "Everolimus" and three respondents commented on mitogen-activated protein kinase inhibitors MEKi ("Trametinib" and "2 patients on Trametinib therapy" and "in neonates/infants very surprising results with TKI (Mekinist)". No further details were provided by the respondents.

4.3.3. *Surgery or intervention for HCM*

Surgical myectomy is the most commonly used interventional therapy for outflow obstruction in HCM in all surveyed countries, with short-atrioventricular delay pacing a distant second, and percutaneous septal alcohol ablation being very rarely undertaken (Fig. 6, panel A).

4.3.4. *Primary prevention of sudden cardiac death*

Respondents answered that most patients with NS and cardiomyopathy 'never' or 'very seldom' carried an implantable cardioverter defibrillator (ICD) (Fig. 6, panel B). It appears that those patients with NS who receive an ICD most commonly have it implanted for secondary prevention after a malignant arrhythmia event, with 59% of respondents never having encountered any patients with primary prevention ICDs, and only 2% reporting it as 'frequent', the latter two respondents coming from France. In general, ICD-implantation appears an infrequent occurrence; even for secondary prevention ICDs, 77% of respondents reported having encountered it either not at all, or 'very seldom' (Fig. 6, panel B).

5. Disease course

5.1. *Re-intervention later in life*

A need for re-intervention was reported most frequently for PVS, where the aggregate figures suggested 20% of respondents saw it 'frequently' and 'mostly'. German and Swedish respondents reported

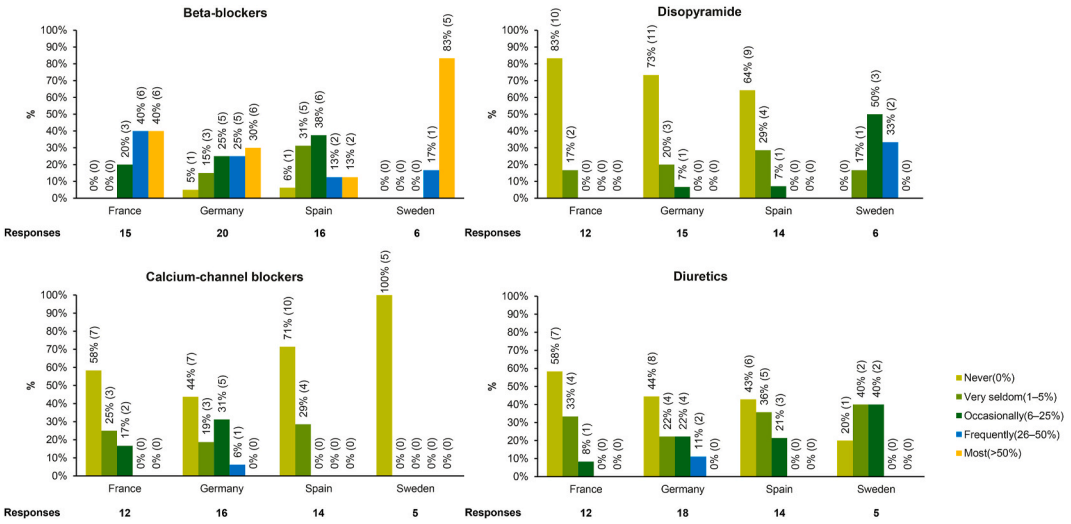

Fig. 5. *What type of medical therapies have you given to patients with Noonan syndrome and hypertrophic cardiomyopathy?*
Of the 94 paediatric cardiologists from France, Germany, Spain, and Sweden included in this analysis, 57 (61%) answered this question. Physicians could provide answers for one or more medical therapy. The number of respondents is depicted under each country.

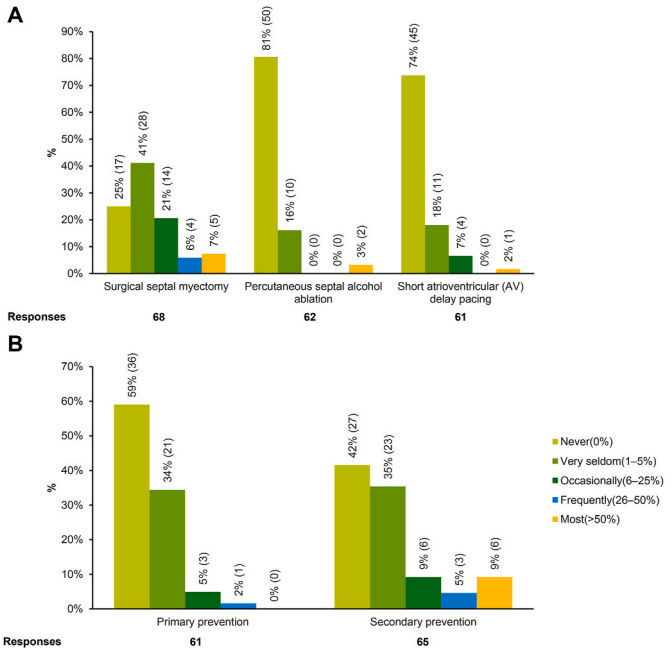

Fig. 6. *For which of the following surgical or interventional treatments for hypertrophic cardiomyopathy would your patients with Noonan syndrome be referred? (panel A) and How often do your patients with Noonan syndrome and cardiomyopathy carry an implantable cardioverter defibrillator (ICD) as for primary/secondary prevention of sudden cardiac death?* (panel B).
Of the 110 paediatric cardiologists included in this analysis, 68 (62%) answered for panel A, and 67 (61%) answered for panel B. Not all responders provided answers for each option. The number of respondents answering is depicted under each chart.

aggregates of those categories of 35% and 33%, respectively, but Spanish and French respondents both reported 13%. Re-intervention needs classed as 'frequently' or 'most' were reported less commonly for HCM (3%; p = 0.0011), ASD (2%; p = 0.0011) and MV anomalies (0%; p = 0.0001) (Fig. 7).

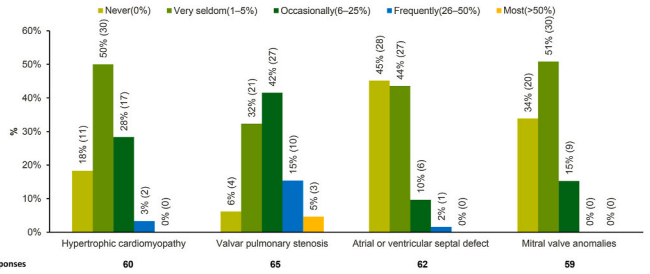

Fig. 7. *How often do your Noonan patients with the following heart conditions require re-intervention (surgery or interventional catheterization) later in childhood?*
Of the 110 paediatric cardiologists included in this analysis, 66 (60%) answered this question. Physicians could provide answers for one or more condition. The number of respondents answering is depicted below the chart.

5.2. Regression of heart disease

With regards to natural history, spontaneous regression of PVS or right outflow-gradient had been seen 'frequently' (>26–50% of cases) by 19% of respondents, and 'occasionally' (6–25% of cases) by 36% of respondents. Regarding HCM, 39% of respondents had at least occasionally encountered a spontaneous regression of severity, whereas regression of severity associated with pharmacological therapy varied roughly corresponding to how often pharmacotherapy had been used. In fact, 100% of Swedish respondents reported at least occasionally, or more frequently, having seen regression associated with pharmacotherapy, followed by 53% of German respondents, 36% of French respondents and 25% of Spanish respondents.

6. Management of growth hormone (GH) treatment in NS patients from a cardiology stand-point

When asked if the presence of HCM constituted a contraindication to GH treatment (Fig. 8, Panel A), 39/110 (35%) of paediatric cardiologists skipped the question, and of those who answered, 24% replied that they could not answer the question. Thirteen percent of respondents (24% from Spain) considered it not a contraindication at all. Fifteen percent of respondents (33% in Sweden) considered it a clear contraindication, 20% that it sometimes could be a contraindication, and around one third of respondents in Germany, Sweden, France and Spain considered it not

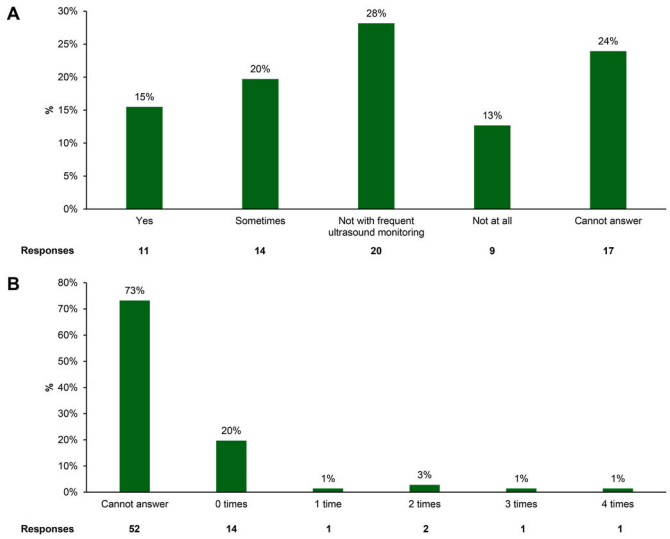

Fig. 8. *Do you consider hypertrophic cardiomyopathy a contraindication to the use of growth hormone therapy? (panel A) and How many times have you encountered an adverse cardiac response to growth hormone treatment? (panel B).*
Of the 110 paediatric cardiologists included in this analysis, 71 (65%) answered both questions. The number of respondents for each option is depicted below both charts.

a contraindication if carried out with frequent ultra-sound monitoring. The same proportion of respondents (35%) also skipped answering the question whether they had encountered an adverse cardiac response to GH treatment, with a notable 73% of those who actually answered stating that they were unable to answer the question. Concerning adverse reactions to GH therapy (Fig. 8, Panel B), there were only 19/71 respondents who felt they were in a position to reply. Of these 19 respondents, 14 had not encountered any adverse reactions, and five respondents (26% of those who could reply) had encountered 12 adverse reactions (type was not asked for in questionnaire, but one respondent volunteered "pulmonary hypertension").

7. Discussion

7.1. Cardiological screening for patients with Noonan syndrome

In line with the fact that around 80% of children with NS or a related syndrome have associated cardiac abnormalities (Calcagni et al., 2017), 95% of paediatric cardiology respondents consider that ECG and cardiac ultrasound should be carried out at all ages of presentation of an individual with NS. While patients with PVS readily announce the presence of a cardiac anomaly with systolic murmurs, neither HCM, ASD nor MV anomalies necessarily have clear pathological cardiac murmurs, and those conditions might be missed unless a routine cardiac assessment is carried out after the diagnosis of NS and associated syndromes. This is particularly important for those patients who may be considered for later GH therapy. Since 43% of patients presented with short stature, it is a little surprising that only 8% of respondents ranked paediatric endocrinologists as the most common referring specialty. This may be related to the fact that heart defects usually present earlier than short stature in NS and that patients are already under cardiological care when they are first seen by endocrinologists. Recent reviews unequivocally recommend a full cardiac assessment with both ECG and cardiac ultrasound at diagnosis, and depending on initial findings, even subsequent cardiac surveillance (Carcavilla et al., 2020; Linglart and Gelb, 2020). Care should be taken to evaluate for early cardiomyopathic changes such as increased cardiac wall thickness z-scores, abnormal wall-to-cavity ratios (Östman-Smith and Devlin, 2001), hyperdynamic systolic function, or evidence of early diastolic dysfunction as this has been described in patients with NS and related disorders (McMahon et al., 2004; Nagueh et al., 2003). This survey did not contain a question about the performance of cardiac surveillance later in life in asymptomatic NS patients.

7.2. Differences in organisation of care

As illustrated by the small annual caseloads, with the majority of respondents reporting <10 cases/year, it is obvious that the cardiac problems associated with NS are a small part of the workload of paediatric cardiologists everywhere, but in particular for those working outside university hospitals. What is noted is that countries where a large proportion of patients are handled in university hospitals report larger annual caseloads than countries such as Germany, where 25% were followed in a general hospital and 25% in independent practices. The latter pattern has the advantage that care is more accessible locally, but close exchange with university hospitals will be required in a subset of patients with complex cardiac problems.

7.3. Management of patients with Noonan syndrome and congenital heart defects

There was consistency with respondents regarding the management and outcome of infants within the NS spectrum presenting with PVS due to dysplastic valves. The responses found in the survey mirror the reports in the literature on a high need for repeat intervention or surgery after initial balloon angioplasty for critical neonatal PVS and dysplastic valves (Holzmann et al., 2018; McCrindle, 1994; Prendiville et al., 2014) with usually good early and long-term results from surgery (Hemmati et al., 2019). Presumably, the high need for intervention or surgery contributed to the fact that many paediatric cardiologists responding considered the presence of heart defects as the most important factor to impact quality of life, particularly in the infant group.

A difference in the responses to questions regarding infant presentation of HCM in patients with NS was noted between different countries. Respondents from Northern Europe (Sweden, Germany) reported a significantly higher frequency of infants presenting with heart failure compared with respondents from South-western Europe (France, Spain), $p = 0.032$. Given a mortality as high as 71% in those infants, and even 100% in the absence of intense pharmacological treatment (Hickey et al., 2011; Östman-Smith et al., 2005; Wilkinson et al., 2012), these infants might not reach paediatric cardiologists in those countries where cardiologists report few infant presentations. Different rates of termination of pregnancy due to prenatal diagnosis of NS with cardiac anomalies might potentially also play a role, as illustrated in the companion article, which shows Spain to have a significantly higher termination rate for NS foetuses with co-existing congenital heart defects or cardiomyopathy than the other countries studied (García-Miñaúr et al., 2021). Apart from a difference in the organisation of prenatal and neonatal care, the observed difference in infant presentation might also be secondary to the distinct genetic background of the populations. A different spectrum of causative genes and/or their pathogenic variations might influence severity of the disease course; however, no data are available yet to support such a concept.

Some geographical differences were also noted concerning pharmacotherapy of NS patients with HCM between countries. Probably related to the higher proportion of infants presenting with heart failure, paediatric cardiologists in Germany and Sweden reported using pharmacotherapy in significantly higher proportions of patients compared with Spain and France. The majority of patients with NS-related HCM reported to receive pharmacotherapy were treated with beta-blocker therapy, which is appropriate according to guidelines, and which, if given in doses >4.5 mg/kg/day, is associated with a reduced cardiac mortality in both NS-associated HCM and non-syndrome associated HCM (Östman-Smith et al., 1999, 2005, 2017; Skinner et al., 1997). Calcium-blocker therapy in HCM was first introduced in Germany, and it is noteworthy that it is used significantly more commonly in Germany

than in the other countries. However, it should be used with caution as it can aggravate heart failure in HCM. Unlike beta-blocker therapy, calcium-blocker therapy is not associated with a reduction in cardiac mortality in NS-associated HCM (Östman-Smith et al., 2005), and in adult obstructive HCM, calcium-blocker therapy has been shown to be associated with increased cardiac mortality (Javidgonbadi et al., 2019). Heart failure in infancy with HCM is often due to diastolic dysfunction and is often associated with outflow-tract obstruction (Östman-Smith et al., 2005). To control this, beta-blockers may need to be titrated to high doses in infants, and if not sufficient on their own, the addition of disopyramide might help to both improve diastolic function and to reduce outflow obstruction (Östman-Smith, 2010; Sherrid et al., 2013). For patients where causative mutations are known, there are newly emerging treatment options such as MEK-inhibitors, which have shown promise with some mutations (Andelfinger et al., 2019), (Hahn et al., 2015). When respondents were asked if there were other medications used for HCM in patients with NS apart from beta-blockers, disopyramide, calcium-channel blockers, or diuretics, the MEK-inhibitor trametinib was mentioned by three respondents, and the use of the mTOR-inhibitor Everolimus was mentioned by one respondent. Surgical myectomy is the first-line option when pharmacotherapy fails, but short AV-delay pacing can also be useful (Elliott et al., 2014; Hickey et al., 2011, 2012; Honda et al., 2005; Javidgonbadi et al., 2018; Rishi et al., 1997).

7.4. Risk stratification for sudden cardiac death

One early study of cardiac involvement in NS reported absence of sudden cardiac deaths (SCD) (Shaw et al., 2007), but subsequent studies with larger groups of NS-associated HCM have reported significant numbers of SCD, a few occurring during the first year of life, but the majority after a late hazard period starting at 10 years of age (Calcagni et al., 2017; Hickey et al., 2011; Östman-Smith et al., 1999). The annual hazard has been calculated to between 1.5% and 2.3% during the 8–18 year age-span in small-sized geographical cohorts (Östman et al., 1999, 2021). Unfortunately, all existing guidelines for SCD risk-stratification exclude syndromic HCM from their risk assessment algorithms (Miron et al., 2020; Norrish et al., 2019; O'Mahony et al., 2014). This might explain the observation of the current survey in which respondents stated that few NS patients in general carry ICDs, and that those few reported had received their ICDs as secondary prophylaxis following a malignant arrhythmia event. Very few had referred patients for a primary prevention ICD. Very little has been published on specific risk factors for NS, but severe hypertrophy (>190% of upper limit of normal for age) and very large ECG voltages in the six limb leads (>10 mV) seemed to increase risk significantly (Östman et al., 2005, 2021). Additionally, patients carrying *PTNP11* mutation-associated NS with multiple lentigines (formerly LEOPARD syndrome) also appear to be at increased risk (Calcagni et al., 2017). Since HCM associated with NS comprises about 22–27% of childhood HCM, it is desirable to initiate international collaborations to obtain more information on risk factors for sudden death.

7.5. GH therapy in HCM associated with Noonan syndrome and other RASopathies

To the question whether HCM was a contraindication for the use of GH therapy, 35% of the responding paediatric cardiologists did not answer, and 24% stated that they did not know. The reason for the uncertainty regarding this question might be the lack of controlled trials of cardiac effects where GH therapy was initiated in the presence of co-existing HCM, and theoretical concerns. The GH/IGF1-axis has important effects on the heart. GH stimulates hypertrophy in myocytes in cell-culture, and pathological hypersecretion of GH from pituitary tumours causes HCM (Twickler et al., 2004). In biopsies from patients with HCM, there is myocardial overexpression of IGF1 compared to myocardium hypertrophied due to other conditions (Li et al., 1997). Furthermore, IGF1 receptor numbers in the HCM myocardium are increased (Li et al., 1998; Toyozaki et al., 1993) and studies suggest a strong stimulating GH effect on myocardial tissue (Decker et al., 2012). A large study showed that GH therapy in short non-syndromic children with normal hearts resulted in a rapid increase in left ventricular mass indexed to body surface area (i.e., greater increase than body growth) already after three months, with a slow sustained increase throughout two years of therapy, whereas cardiac function remained normal (Nygren et al., 2012). Because of the growth stimulating effect on myocardial tissue, an HCM-diagnosis was a contraindication for inclusion in the early trials on GH therapy in NS (Brown et al., 2002; Cotterill et al., 1996). Thus, most clinical studies on GH treatment have not included NS patients with pre-existing HCM in their analysis (Brown et al., 2002; Cotterill et al., 1996; Jeong et al., 2016). The results of other studies, mostly reporting small cohorts or poorly defining cardiac parameters, are conflicting (Romano et al., 2009; Noordam et al., 2001; Horikawa et al., 2020; Kobayashi et al., 2010). The largest report on GH therapy in NS is from the KIGS-database and is not specific about exclusion criteria but among 429 NS-patients commenced on GH therapy seven adverse cardiac reactions were reported: cardiac arrhythmias, angina pectoris, new left ventricular hypertrophy and one cardiac transplantation for cardiomyopathy after 10.7 years of GH therapy (Otten and Noordam, 2007). The pre-existing cardiac situation before treatment in those patients with adverse reactions was not specified in the KIGS study, thus it is unknown if they consisted of *de novo* cardiac disease or aggravation of existing disease.

When paediatric cardiologists in the present survey were asked whether they had encountered an adverse cardiac response to GH treatment the majority selected "cannot answer". The fact that only 19 did express an opinion attests to the paucity of clinical experience with GH therapy and co-existing HCM. A total of 12 adverse reactions were reported by the 19 respondents who answered the question. It has to be noted that emergence or progression of HCM in the age range when GH treatment is usually given, may also occur in the natural course of NS and that results of this survey do not allow further specification of underlying cardiac pathology of the patients reported on. In HCM, the risk for fatal complications is strongly linked to ECG- and ultrasound measures of cardiac hypertrophy also in HCM related to NS (Östman et al., 2005, 2021). This might explain why 63% of the cardiology respondents considered HCM a definite or possible contra-indication to GH therapy, or that therapy could only take place with close monitoring. Recent reviews also stress the need for continued cardiac surveillance for appearance of HCM, even when initial cardiac examination is normal (Carcavilla et al., 2020; Linglart and Gelb, 2020).

Taken together, despite the concerns coming from experimental data, an obvious knowledge gap has been identified with lack of empirical evidence regarding the impact of GH therapy on the incidence and progression of HCM in NS. Clearly, there is a need for further research on this topic, and a post-marketing surveillance registry of NS patients receiving GH therapy containing detailed cardiac information would help answering certain questions.

7.6. Limitations of study

The survey was distributed by national professional societies, and by the Association of European Paediatric and Congenital Cardiology, but respondents selected themselves by showing an interest in the topic. Thus the aim was a snapshot of the care given by practitioners regularly caring for patients with Noonan syndrome in different countries. As the results are not based on exact numbers of patients and procedures, but rather approximate classifications and estimations, we have analyzed data based on grouping of the results into defined categories (never - seldom - frequent - most). Unfortunately, the United Kingdom and Italy were under-represented among cardiology respondents, so could not be included in national comparisons, although responses from those

countries and other countries with few responders were included in all merged data.

8. Conclusions

The care of patients with NS or other RASopathies and congenital heart disease seems to be largely centred in specialty care university hospitals. Most respondents report a high need for interventional and pharmacological management of affected children, specifically during the first year of life. There seem to be differences in subspecialty teams taking care of critically sick infants presenting with heart failure between countries. More research is needed regarding the use of growth hormone in patients with NS and co-existing congenital heart disease, and unmet medical needs have been identified.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2021.104372.

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Author contributions

SGM, EBW, AV, GS, JL, IÖS, CW, MT, MZ and TE contributed to development of the survey questions, and analysis of the results. IÖS performed statistical analysis, and C.W, IÖS and MZ drafted the manuscript, with input from all other authors. All authors have read and approved the final version of the manuscript for submission.

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