Cardiology in the Young

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The added value of the electrocardiogram in Noonan syndrome

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Abstract

Noonan syndrome is a genetic disorder characteried by short stature, typical facial features, developmental delay, and CHD. In this single-centre retrospective study, we analysed typical Noonan syndrome-related electrocardiographic features in 95 patients with clinically and molecularly confirmed Noonan syndrome. Typical Noonan syndrome-related electrocardiographic features are left axis deviation, small left precordial R-waves, large right precordial S-waves, abnormal Q-wave, and abnormal wide QRS complex. In this representative cohort, CHD was found in 59 patients (62.1%) and typical Noonan syndrome-related electrographic features in 60 patients (63.2%). The typical Noonan syndrome-related electrographic features were also increased over baseline in patients without CHD (41.7%). Of all 95 patients, left axis deviation was seen in 46.3%, small left precordial R-waves in 30.5%, large right precordial S-waves in 5.3%, and abnormal Q-wave and wide QRS complex in 2.1%. There was no significant difference in the frequency of the individual-specific electrographic features between the group with CHD and the group without CHD. However, there were significantly more patients with a small left precordial R-wave in the subgroup with pulmonary stenosis compared to patients without pulmonary stenosis. *Conclusion*: Specific Noonan syndrome-related electrographic features are frequently present in patients with Noonan syndrome, also in the absence of CHD. These results suggest that there may be a continuum of cardiac anomalies from overt CHD to milder abnormalities that are only seen on electrocardiogram.

Noonan syndrome is a predominantly autosomal dominant disorder with physical, cognitive, and psychosocial features. The estimated incidence rates vary from 1:1000 to 1:2500 live births.[1,2] Noonan syndrome is characterised by short stature, typical facial features, thorax deformities, cardiac abnormalities, renal abnormalities, cryptorchidism, delayed motor development, and bleeding disorders.[2,3] There is a major variation in the severity and nature of these characteristics.[2]

Mutations identified in NS are gain-of-function mutations, which result in increased RAS-mitogen-activated protein kinase signalling.[4,5] The first gene discovered to be responsible for Noonan syndrome was *PTPN11* on chromosome 12q.[6] In recent years, more genes that cause Noonan syndrome has been discovered. Mutations in *PTPN11* (40–67%), *SOS1* (10–26%), and *RAF1* (3–17%) are most common.[4,5,7,8] Other genes involved in Noonan syndrome are *KRAS* (1–5%), *NRAS*, *RIT1* (3–7%), *RRAS*, *CBL*, *SOS2*, *LZTR1*, and *MAP2K1*.[5,8–10] In 18–24% of the patients with Noonan syndrome, no gene mutation is found.[4,10] For this reason, a clinical scoring system has been developed with major and minor features.[11,12] Major cardiac features in this scoring system are pulmonary stenosis, hypertrophic cardiomyopathy, and/or an electrocardiogram typical for NS. Minor cardiac features are "other cardiac defects".

The electrocardiogram in patients with NS often shows typical features (Fig 1). These typical Noonan syndrome-related electrocardiographic features are left axis deviation, small R-waves in the left precordial leads, large S-waves in the right precordial leads, abnormal Q-waves, and/or wide QRS complex.[7,13–15] These typical electrocardiographic abnormalities are present in 50–60% of all patients with Noonan syndrome, and do not seem to be associated with the presence of a (specific) CHD and the presence of a *PTPN11* mutation.[7,13] The reason for these characteristic electrocardiographic features is still unknown.[7,13,15]

More than 60% of NS patients have CHDs. The CHD most commonly seen are pulmonary valve stenosis and hypertrophic cardiomyopathy.[7,16] Other CHD seen in Noonan syndrome are atrial septal defects, ventricular septal defects, patent ductus arteriosus, aortic coarctation, and mitral valve abnormalities.[4,9,13] Recent studies show that PS is more often associated with mutations in *PTPN11* (45–65%), *SOS1* (50–83%), *BRAF* (75%), and *RIT1* (77%), while HCM is associated with mutations in *RAF1* (75 –100%) and *RIT1* (42–56%).[4,5,9,17]

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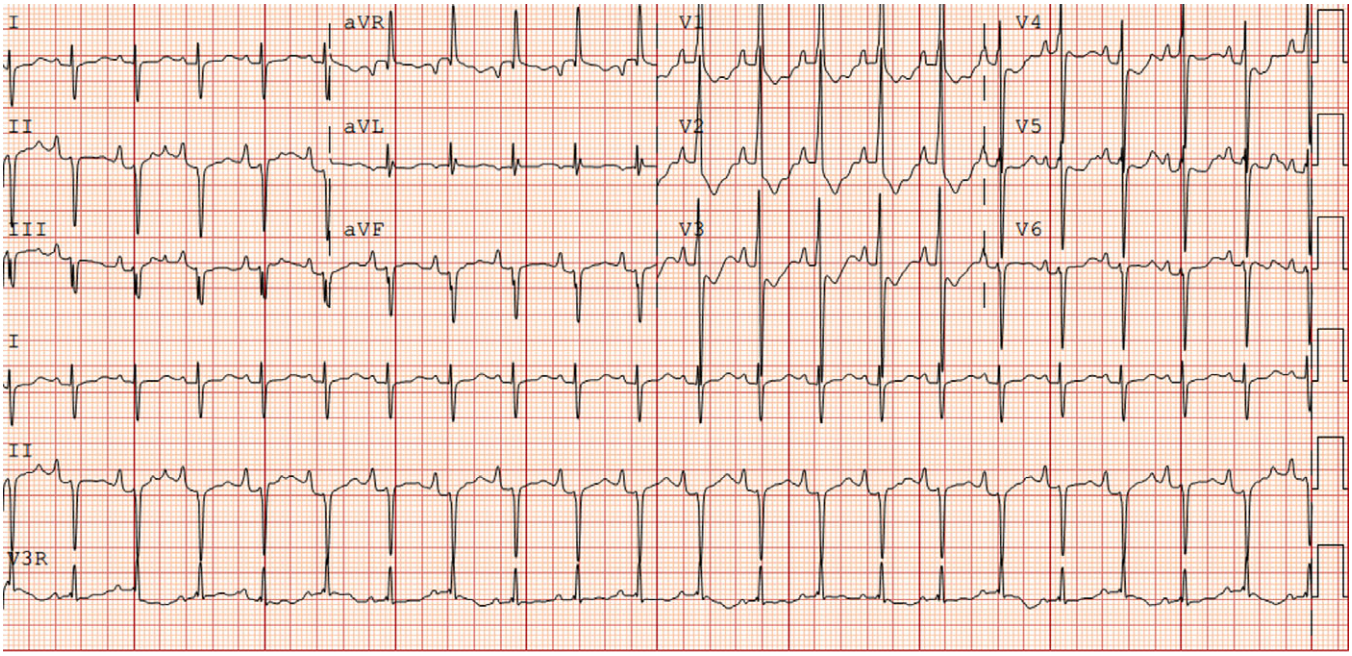

Figure 1. Electrocardiogram (speed 25 mm/sec, voltage 0.1 mV/mm) from a newborn with Noonan syndrome due to PTPN11 mutation with a severe pulmonary valve stenosis.

The purpose of this study is to analyse whether the typical Noonan syndrome-related electrocardiographic characteristics can still be seen as a major feature even with modern echocardiographic possibilities and genetic tests, for example, in patients with clinical Noonan syndrome with a gene variant of unknown significance.

In addition, we investigated whether the typical electrocardiographic features in patients with Noonan syndrome are dependent on the genotype or type of CHD in these patients.

Materials and methods

Patients

In this single-centre retrospective study, we analysed all patients seen in the outpatient department of the Noonan Syndrome Expertise Centre of the Radboud University Medical Center before 2019 with clinically and genetically confirmed Noonan syndrome. The clinical diagnosis of Noonan syndrome was based on the earlier mentioned scoring system of van der Burgt et al and confirmed by DNA analysis.[11,12] Patients without an available electrocardiogram or echocardiogram before the surgical intervention or balloon valvuloplasty were excluded from the study. According to the Medical Ethics Committee of the district Arnhem/Nijmegen, no ethical approval was required for this study (file number 2020-6851).

Electrocardiogram

Specific electrocardiographic features included in this study were left axis deviation, large S-waves in the right precordial leads, small R-waves in the left precordial leads, abnormal Q-waves, and/or wide QRS complexes. The features were reviewed on the first ECG available using the following definitions:

- Left axis deviation: QRS axis is less than the lower limit of normal for the patient's age.[18]
- Large S-waves in V2: S-wave is more than the upper limit of normal for the patient's age.[19,20]
- Small R-waves in V5V6: little R deflection over the left precordium with an R/S ratio is lower than the lowest limits of normal and R voltage in V5 and V6 is less than 50% of the mean according to Park and Guntheroth.[20]
- Abnormal Q-wave: Q voltage is greater than the upper limit of normal and wider than 0.04 seconds.
- Wide QRS complex: QRS duration of more than 0.08 seconds under the age of 3 years, above 0.10 seconds between 3 and 12 years, and above the upper limit for QRS duration of 0.12 seconds from 12 years and older.

Echocardiogram

Diagnosis of CHD defect included in this study was established by the first echocardiogram available and this had to be performed before balloon valvuloplasty or surgical intervention. In general, the guidelines and standards for the performance of paediatric echocardiograms were used.[21] Whenever possible, the original recordings were used for diagnosis; otherwise, the recorded diagnosis was used. Pulmonary stenosis was classified as mild (peak gradient <36 mmHg), moderate (peak gradient 36–64 mmHg), and severe (peak gradient >64 mmHg). Hypertrophic cardiomyopathy was diagnosed according to the criteria used by Wilkinson et al.[21]

Statistical analysis

All analyses were carried out using SPSS, version 22.0 (IBM Corp., NY, United States of America). Results are expressed as median with interquartile range, and percentages. Statistical significance was analysed using Fisher's exact test as appropriate with a significance threshold of $p \leq 0.05$.

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Results

Demographics

A cohort of 95 patients was included in this study. Of these patients, 46 (48.4%) were male and 49 (51.6%) were female, and their median (IQR) age at the date of the ECG was 4.9 years (0.9–14.4). Table 1 shows the distribution of the involved genes, the cardiac defects, and typical Noonan syndrome-related electrocardiographic features. Sixty (63.2%) of the patients had a mutation in *PTPN11*, and mutations in *SOS1* and *KRAS* were found in 8 (8.4%) patients.

Congenital heart defects

It was possible to use the initial echocardiographic recordings in 55 of the 95 patients. In 40 patients, the recorded diagnosis was used. Fifty-nine (62.1%) patients had CHD. Pulmonary valve stenosis (mild in 53%, moderate 11%, and severe in 36% of the cases; all severe cases had a therapeutic intervention afterwards) was most frequently seen followed by an atrial septal defect (haemodynamically important in 35%, not important 65%) and hypertrophic cardiomyopathy (of which two needed a surgical intervention afterwards), in, respectively, 44 (46.3%), 13 (13.7%), and 11 (11.6%) patients. Pulmonary valve stenosis was most often seen in patients with a mutation in *PTPN11* (58.3%), *SOS1* (37.5%), *RIT1* (66.7%), and *SOS2* (66.7%). Patients with a *PTPN11* gene mutation had a significantly higher incidence of pulmonary valve stenosis (58.3%) and atrial septal defect (20%) than patients with other gene mutations (respectively, $p = 0.003$ and $p = 0.027$). Hypertrophic cardiomyopathy was more frequently diagnosed in patients with mutations of *RIT1* (66.7%) and *RAF1* (66.7%) genes, which was significantly more frequently than in the other NS genes (respectively, $p = 0.035$ and $p = 0.012$).

Electrographic abnormalities

In 60 patients (63.2%), one or more typical Noonan syndrome-related electrocardiographic features were seen. Most of the patients with CHD did show these typical Noonan syndrome-related electrocardiographic features (45/59, 76.3%). Also, in 15 of the 36 (41.7%) patients with a structurally normal heart on echocardiogram, typical Noonan syndrome electrocardiographic abnormalities were detected (Table 1). There was no significant difference in the incidence of the individual-specific Noonan syndrome-related electrocardiographic features between the group with CHD and the group without CHD, however, specific electrocardiographic features as a group occurred significantly more frequently in patients with CHD ($p = 0.001$).

There were 44 (46.3%) patients with left axis deviation, 29 (30.5%) patients with small R-waves in the left precordial leads, and 5 (5.3%) patients with large right precordial S-waves. An abnormal Q-wave was seen in 2 (2.1%) patients and a wide QRS complex also in 2 (2.1%) patients (Table 2). Typical Noonan syndrome-related electrographic features were not more often seen in patients with a mutation in the *PTPN11* gene than in patients with other gene mutations. Patients with a mutation in the *RAF1* gene had more frequently large S-waves in the right precordial leads ($p = 0.002$), and patients with *SOS1* gene mutation had more frequent wide QRS complexes ($p = 0.006$).

Regarding the 36 patients without a CHD, 15 (41.7%) had specific Noonan syndrome-related electrocardiographic features. These electrocardiographic features were seen in patients with mutations in *PTPN11*, *SOS1*, *KRAS*, *CBL*, *BRAF*, and *A2ML1* genes (Table 3). Left axis deviation was seen in 12 (33.3%) patients, small left precordial R-waves in 7 (19.4%) patients, large right precordial S-waves leads in 2 (5.6%) patients, and wide QRS complex in 1 (2.8%) patient (Table 3). One child with a *SOS1* mutation without CHD had a complete left bundle branch block with left axis deviation with a septal flash on echocardiography (Fig 2a and b).

Patients with pulmonary valve stenosis had more often a small left precordial R-wave than patients without a pulmonary valve stenosis($p = 0.015$). No other significant differences were found (Table 4).

Discussion

In this cohort, CHD was found in 62.1% and typical Noonan syndrome-related electrocardiographic features in 63.2% of Noonan syndrome patients. The typical Noonan syndrome-related electrocardiographic features were also present in 41.7% of patients without CHD. Left axis deviation was seen in 46.3% of patients, small left precordial R-waves in 30.5%, and large right precordial S-waves in 5.3% of the Noonan syndrome patients. There was no significant difference in the frequency of the individual- specific Noonan syndrome-related electrocardiographic features between the group with CHD and the group without CHD.

In this retrospective study, the distribution of mutations in *PTPN11, KRAS*, and *BRAF* is comparable to those reported in the literature, while the distribution of mutations like *SOS1, RAF1*, and *RIT1* is slightly lower than in some earlier studies.[7,9,17,22–28] The reported incidence of the CHD found in this study is comparable with previous studies,[5,7–10,15] also the high incidence of CHD in patients with a mutation in *RIT1* or *RAF1*.[4,5,17] The frequency of pulmonary valve stenosis in patients with *PTPN11* and *RIT1* gene mutations is the same as found in previous studies, in contrast with patients with *SOS1* and *BRAF* gene mutations, who are found to have less often pulmonary valve stenosis in this study than described in the literature.[4,5,7] This may probably be due to the small number of patients with *SOS1* and *BRAF* mutations. Except for the small number of patients with a *SOS1* mutation, this retrospective study can be seen as a representative for patients with NS.

Compared to the 5% incidence in healthy children and adolescents from a large European cohort we find a much higher incidence of specific electrocardiographic abnormalities in patients with Noonan syndrome. These findings are in line with previous studies of Noonan syndrome.[7,13,15,29–31] Although there is no significant difference in the incidence of the individual-specific electrocardiographic features between the group with CHD and the group without CHD, specific electrocardiographic features as a group occur significantly more frequent in patients with CHD ($p = 0.001$). This is in contrast to prior studies, even though the typical Noonan syndrome-related electrocardiographic features are evaluated with the same criteria.[7,13] This may be due to differences in inclusion criteria of CHD. In recent studies on cardiovascular disease in patients with Noonan syndrome, no patients with valvular regurgitations were described.[32,33] In our study, we included also patients with mild valvular regurgitations on echocardiogram, where in earlier studies, maybe due to technical possibilities or definitions, some valvular regurgitations may not have been included.[7,13,33]

A part of the specific Noonan syndrome-related electrocardiographic features may be due to the CHD diagnosed. In patients with pulmonary valve stenosis, the baseline electrocardiogram is often normal in cases of mild pulmonary valve stenosis, and in

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Table 1. Cardiac heart defects and ECG abnormalities in patients with Noonan syndrome

		PTPN11	SOS1	KRAS	RIT1	SHOC2	CBL	SOS2	RAF1	BRAF	A2ML1	MAP2K2	LZTR
	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)
N	95	60 (63.2)	8 (8.4)	8 (8.4)	3 (3.2)	3 (3.2)	3 (3.2)	3 (3.2)	2 (2.1)	2 (2.1)	1 (1.1)	1 (1.1)	1 (1.1)
CHD													
PS	44 (46.3)	35 (58.3)	3 (37.5)	0	2 (66.7)	0	0	2 (66.7)	0	0	0	1 (100.0)	1 (100.0)
HCM	11 (11.6)	4 (6.7)	1 (12.5)	0	2 (66.7)	1 (33.3)	0	0	2 (100.0)	0	0	0	1 (100.0)
ASD	13 (13.7)	12 (20)	0	0	0	0	0	1 (33.3)	0	0	0	0	0
VSD	1 (1.1)	1 (1.7)	0	0	0	0	0	0	0	0	0	0	0
AVSD	1 (1.1)	1 (1.7)	0	0	0	0	0	0	0	0	0	0	0
CoA	1 (1.1)	1 (1.7)	0	0	0	0	0	0	0	0	0	0	0
AI	4 (4.2)	2 (3.3)	1	1 (12.5)	0	0	0	0	0	0	0	0	0
MI	3 (3.2)	1 (1.7)	0	0	0	1 (33.3)	0	0	1 (50.0)	0	0	0	0
TI	2 (2.1)	1 (1.7)	1 (12.5)	0	0	0	0	0	0	0	0	0	0
AS	3 (3.2)	1 (1.7)	0	1 (12.5)	1 (33.3)	0	0	0	0	0	0	0	0
PA dilatation	3 (3.2)	2 (3.3)	0	0	1 (33.3)	0	0	0	0	0	0	0	0
BAV	1 (1.1)	1 (1.7)	0	0	0	0	0	0	0	0	0	0	0
DCRV	1 (1.1)	0	1 (12.5)	0	0	0	0	0	0	0	0	0	0
MAPCA	1 (1.1)	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0
AV canal	1 (1.1)	1	0	0	0	0	0	0	0	0	0	0	0
Total	59 (62.1)	43 (71.7)	4 (50.0)	1 (12.5)	3 (100.0)	2 (66.7)	0	2 (66.7)	2 (100.0)	0	0	1 (100.0)	1 (100.0)
ECG abnormalities													
Left axis deviation	44 (46.3)	29 (48.3)	3 (37.5)	2 (25.0)	3 (100.0)	1 (33.3)	1 (33.3)	0	2 (100.0)	1 (50.0)	1 (100.0)	0	1 (100.0)
Large S in V2	5 (5.3)	1 (1.7)	1 (12.5)	0	0	0	0	0	2 (100.0)	0	0	1 (100.0)	0
Small R in V5/V6	29 (30.5)	21 (35.0)	3 (37.5)	0	1 (33.3)	0	0	1 (50.0)	1 (50.0)	0	1 (100.0)	0	1 (100.0)
Abnormal Q wave	2 (2.1)	1 (1.7)	0	0	0	0	0	1 (50.0)	0	0	0	0	0
Wide QRS complex	2 (2.1)	0	2 (25.0)	0	0	0	0	0	0	0	0	0	0
Total	60 (63.2)	39 (65.0)	6 (75.0)	2 (25.0)	3 (100.0)	1 (33.3)	1 (33.3)	2 (100.0)	2 (100.0)	1 (50.0)	1 (100.0)	1 (100.0)	1 (100.0)

AI = aortic insufficiency; AS = aortic stenosis; ASD = atrial septal defect; AV = atrioventricular; AVSD = atrial ventricular septal defect; BAV = bicuspid aortic valve; CHD = congenital heart defect; CoA = coarctatio aortae; DCRV = double-chambered right ventricle; ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; MAPCA = major aortopulmonary collateral artery; MI = mitral insufficiency; PA = pulmonary artery; PS = pulmonary stenosis; TI = tricuspid insufficiency; VSD = ventricular septal defect.

Table 2. Specific ECG features in patients with Noonan syndrome with and without CHD

	Total (%)	CHD (n = 59) Total (%)	No CHD (n = 36) Total (%)	Fisher p-value
ECG abnormalities				
Left axis deviation	44 (46.3)	32 (54.2)	12 (33.3)	0.058
Large S in V2	5 (5.3)	3 (5.1)	2 (5.6)	1.000
Small R in V5/V6	29 (30.5)	22 (37.2)	7 (19.4)	0.107
Abnormal Q wave	2 (2.1)	2 (3.4)	0	0.524
Wide QRS complex	2 (2.1)	1 (1.7)	1 (2.8)	1.000
Total	60 (63.2)	45 (76.3)	15 (41.7)	0.001

Table 3. Specific ECG features in patients with different gene mutations without CHDs

	Total (%)	PTPN11 Total (%)	SOS1 Total (%)	KRAS Total (%)	SHOC2 Total (%)	CBL Total (%)	SOS2 Total (%)	BRAF Total (%)	A2ML1 Total (%)
No CHD	36	17(47.2)	4 (11.1)	7 (19.4)	1 (2.7)	3 (8.3)	1 (2.7)	2 (5.5)	1 (2.7)
ECG abnormalities									
Left axis deviation	12 (33.3)	5 (29.4)	3 (75)	1 (14.3)	0	1 (33.3)	0	1 (50)	1 (100)
Large S in V2	2 (5.6)	1 (5.8)	1 (25)	0	0	0	0	0	0
Small R in V5/V6	7 (19.4)	5 (29.4)	1 (25)	0	0	0	0	0	1 (100)
Abnormal Q wave	0	0	0	0	0	0	0	0	0
Wide QRS complex	1 (2.8)	0	1 (25)	0	0	0	0	0	0
Total	15 (41.7)	8 (47.1)	3 (75)	1 (14.3)	0	1 (33.3)	0	1 (50)	1 (100)

Table 4. Specific ECG features in patients with Noonan syndrome with and without pulmonary stenosis and with and without hypertrophic cardiomyopathy

	PS (n = 44) Total (%)	No PS (n = 51) Total (%)	Fisher p-value	HCM (n = 11) Total (%)	No HCM (n = 84) Total (%)	Fisher p-value
ECG abnormalities						
Left axis deviation	21 (47.7)	23 (45.1)	0.839	8 (72.7)	36 (42.9)	0.105
Large S in V2	1 (2.3)	4 (7.8)	0.369	2 (18.2)	3 (3.6)	0.101
Small R in V5/V6	19 (43.2)	10 (19.6)	0.015	5 (45.5)	24 (28.6)	0.302
Abnormal Q wave	2 (4.5)	0	0.212	0	2 (2.4)	1.000
Wide QRS complex	0	2 (3.9)	0.497	1 (9.1)	1 (1.2)	0.219
Total	33 (75)	27 (52.9)	0.034	9 (81.8)	51 (60.7)	0.205

cases with more severe pulmonary valve stenosis, there may be a slight right axis deviation or signs of right ventricular hypertrophy. However, there was no difference between patients with and without pulmonary valve stenosis regarding the specific Noonan syndrome-related electrocardiographic abnormalities (including left axis), except that patients with pulmonary valve stenosis had more often a small R-wave left precordial, which cannot be explained electrophysiologically by the pulmonary valve stenosis. An abnormal electrocardiogram is common in patients with hypertrophic cardiomyopathy. In literature, most often, abnormal repolarization and Q-waves are reported, and/or left axis deviation.[34,35] However, in our study, left axis deviation or abnormal Q-waves occurred not more often in patients with hypertrophic cardiomyopathy than in patients without hypertrophic cardiomyopathy. We have the experience that the characteristic features (left axis, small R-wave left precordial), do not change in life or after intervention (surgical intervention, trametinib), however, may be somewhat less accentuated (data are not shown).

Previous studies have demonstrated electrocardiographic abnormalities in patients with Noonan syndrome with multiple lentigines (formerly LEOPARD syndrome), mostly reflecting left ventricular hypertrophy.[35] More strikingly, a recent study found that non-re-entrant atrial tachycardias, multifocal atrial tachycardia, and ectopic atrial tachycardia can arise from the gain-of-function mutations in multiple genes giving rise to

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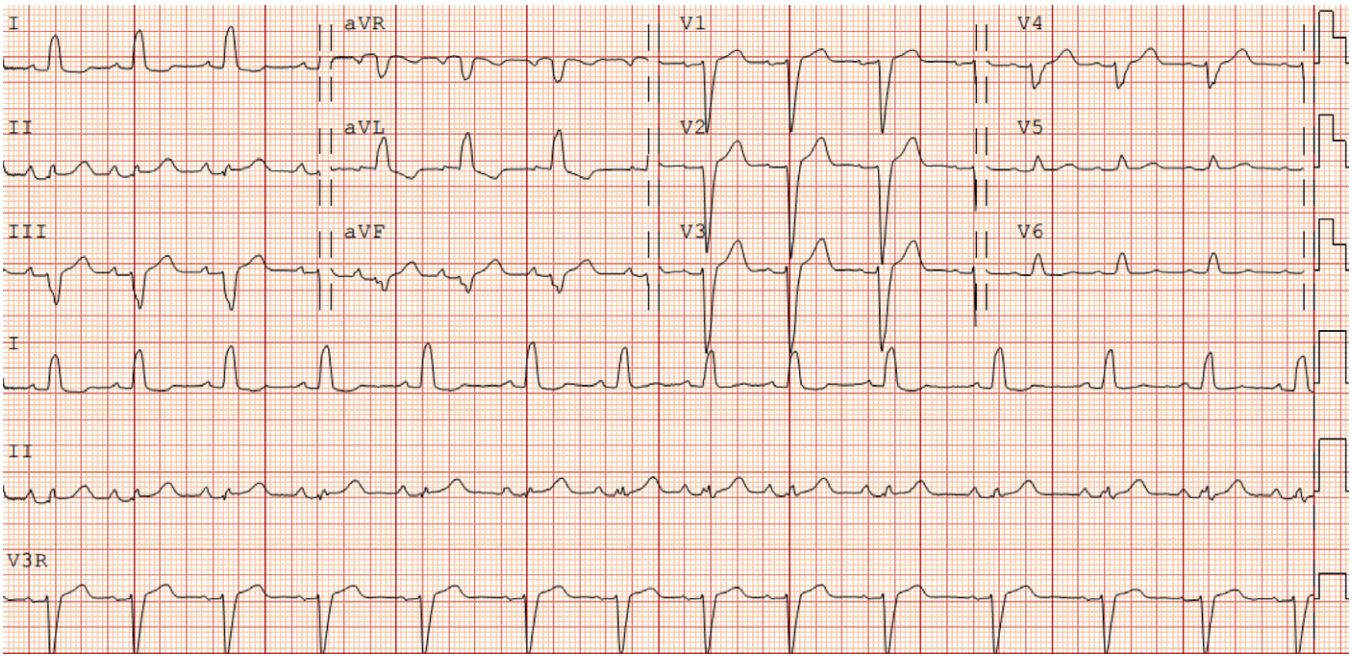
(*a*)



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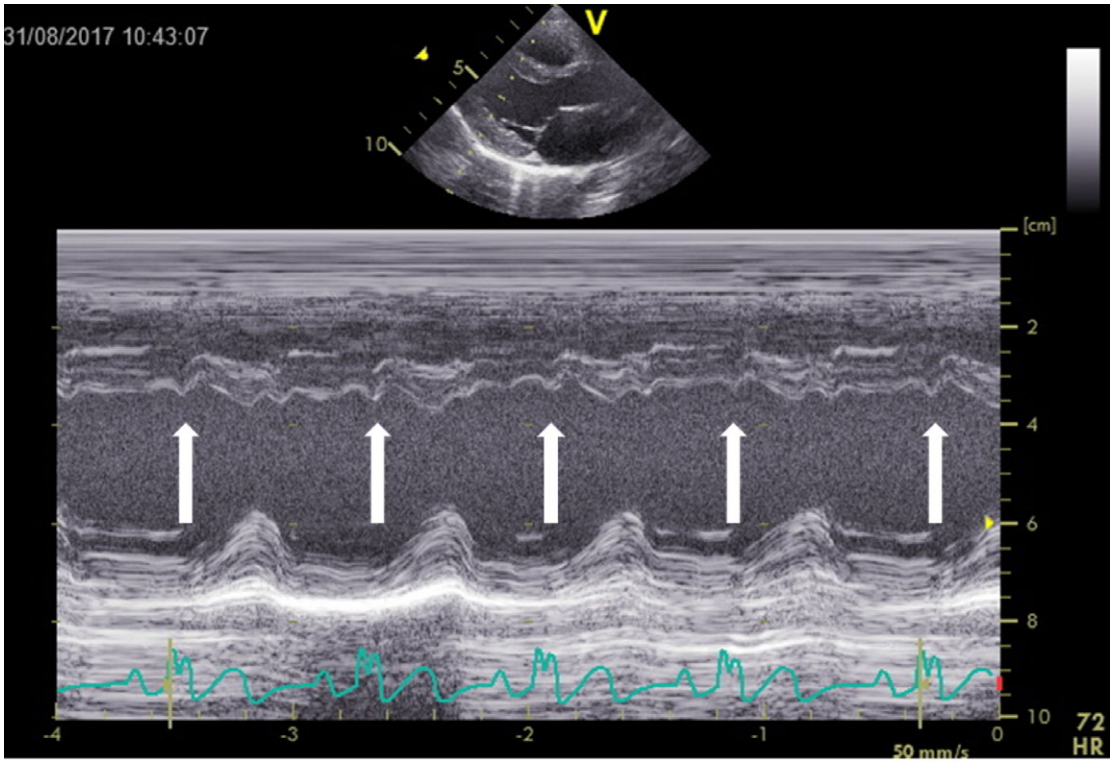

Figure 2. (*a*) Electrocardiogram (speed 25 mm/sec, voltage 0.1 mV/mm) from an 8-year-old girl with a SOS1 mutation with complete left bundle branch block (LBBB). In addition to an duration increase in QRS, please note the distinctive mid-QRS notching in leads I and aVL, along with mid-QRS-slurring in leads V5 and V6. (*b*) Echocardiographic assessment of the septal movement in the long-axis in this patient revealed a septal flash (white arrows), which is a marker of left ventricular electromechanical desynchrony in the presence 'of LBBB.

RAS-MAPK pathway dysregulation.[36] These cardiac arrhythmias occurred in patients with Noonan and Costello syndrome both in the presence or absence of hypertrophic cardiomyopathy, suggesting that the atrial arrhythmias seen in these patients are not simply caused by the pressure load in these patients.[37] In our study, no serious arrhythmias were seen.

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A limitation of this retrospective study is that the echocardiograms were made in a clinical setting, and it was only possible to study 55 of the 95 original recordings. However, all echocardiograms were made according to standard guidelines.

In conclusion, this study seems to be a representative of patients with a genetically proven Noonan syndrome. Specific Noonan syndrome-related electrocardiographic features seen were mainly left axis deviation and small R-waves in the left precordial leads, in patients with or without CHD. Even though some CHD and specific Noonan syndrome-related electrocardiographic abnormalities are significantly more frequent in some gene mutations, the presence is widespread over all mutations. Our results suggest that typical Noonan syndrome-related electrocardiographic features are the one end of the cardiac spectrum and overt CHD the other end.

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Author contribution. Eefke Vos: conceptualisation and design of the study, data analysis and interpretation, drafting of the manuscript, approval of the final manuscript. Erika Leenders: conceptualisation and design of the study, critical review of the manuscript, approval of the final manuscript. Sterre R. Werkman: conceptualisation and design of the study, drafting of the manuscript, approval of the final manuscript. Floris E. A. Udink ten Cate: conceptualisation and design of the study, drafting of the manuscript, approval of the final manuscript. Jos M.T. Draaisma: conceptualisation and design of the study, data analysis and interpretation, critical review of the manuscript, approval of the final manuscript.

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Conflicts of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (please name) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Medical Ethics Committee (CMO) of the district Arnhem/Nijmegen (file number 2020-6851).

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