Success rate of primary percutaneous balloon angioplasty in children with Pulmonary Stenosis and Noonan syndrome

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Keywords

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Abstract

Background: Noonan syndrome (NS) is associated with different types of congenital heart defects (CHD), the most common of which is supravalvular pulmonary stenosis ((SV)PS). Possible treatment options are percutaneous balloon pulmonary valvuloplasty (BVP) or surgical intervention. The anatomical location of the PS may help predict BVP failure. We aimed to identify factors predicting treatment outcome and reintervention rate of BVP in these patients.

Methods: Medical records of children with a diagnosis of NS and in follow-up at Antwerp- and Ghent University Hospitals from 2000 to 2022 were retrospectively reviewed.

Results: Thirty-two children were identified with a SVPS, either isolated or in combination with other CHD. Sixty-nine percent of the children with PS had SVPS. Isolated SVPS was identified as a risk factor for intervention.

Surgical or percutaneous intervention was necessary in 17/32 patients with PS (53%). All but 2 children with pulmonary valve stenosis had SVPS. Fifteen (13 with SVPS) underwent percutaneous balloon dilatation, of which 10 (67%) needed a second intervention, but all of them ultimately needed surgical repair due to persistent stenosis. The global success rate of percutaneous intervention in children with Noonan and SVPS was (31,1%).

Conclusion: SVPS is a frequently encountered CHD in children with NS. The prevalence of SVPS was similar for all NS associated genes. Isolated SVPS is a risk factor for intervention. The success rate of BVP in patients with NS and SVPS is low. BVP might still be useful in selected cases.

Introduction

Noonan syndrome (NS) is a genetically heterogeneous condition with a high prevalence of heart disease (70-90%) (1). A genetic mutation of the RAS-MAPK signalling pathway can be identified in 75% *(PTPN11, SOS1, KRAS, NRAS, RAF1, RIT1, BRAF, SHOC2 or CBL)* of cases (2). The predominant cardiac lesion is pulmonary stenosis (PS), affecting 50% of patients with NS (3,4). Approximately half of these patients will require treatment (5). First-line treatment of PS consists of a percutaneous balloon valvuloplasty (BVP) (6). This treatment is highly successful in non-syndromic patients with PS, with a re-intervention rate of 5-10% (7). However, the results in syndromic patients (e.g. NS) are suboptimal with a high re-intervention rate (60-65%), and the need for surgery after (repeated) BVP is significant (5,8). The reason why BVP fails to alleviate the stenosis is still not clear. One possible explanation is the associated dysplastic morphology of the pulmonary valve leaflets as the root cause of a suboptimal response (9). Other authors describe the presence of a supravalvular pulmonary stenosis (SVPS) as a predictor of BVP failure (10). Other possible contributing factors that have been studied (age, weight, pre-BVP haemodynamic parameters (e.g. pulmonary valve (PV) pressure gradient), associated cardiac defects) were proven not to be significant predictors of treatment success (5,6). Genotype-phenotypes studies showed higher prevalence of PS and a more severe stenosis in carriers of a pathogenic variant in *PTPN11* compared to other genes (11). Due to the high prevalence of severe PS requiring intervention and the high rate of re-intervention after BVP, identification of risk factors for treatment and re-intervention is warranted. A change in approach to the treatment of PS in NS might be necessary considering that a primary surgical intervention could avoid the need for multiple procedures.

The aims of our study were to examine factors predicting the need for a primary intervention for PS in patients with NS, to evaluate the success rate of BVP as first-line treatment in these patients and to identify possible predictors for re-intervention (treatment failure).

Methods

A retrospective medical record review was performed on all clinically diagnosed NS patients at Antwerp and Ghent University Hospitals between January 2000 and December 2022. Only patients with a PS were included in this study. Patients with a concomitant genetic diagnosis in addition to NS or with an age of more than 18 years of age at the time of diagnosis were excluded from the study.

The subtype of PS was defined according the anatomical location as described by echocardiography and/or catheterisation. Identification of an SVPS by echocardiogram was based on the interpretation of the anatomic location by the operator during catheterisation. PS subtype was determined by the anatomical narrowing of the pulmonary valve as seen during the performance of the angiogram. When a PS was classified differently by angiogram than echocardiogram, the result of the angiogram was deemed superior and therefore decisive as echocardiogram is known to have a significantly lower diagnostic yield (10).

All relevant demographic characteristics such as associated pathogenic gene variant, PV pressure gradient, PS and subtype, other congenital heart

Table 1: Comparison of patients who underwent an intervention for PS with patients who did not.

	Total cohort	Intervention	No Intervention	p-value
Total number of patients	32 (100%)	17 (53%)	15 (47%)	
Sex	19 female (59%)	9 female (53%)	10 female (67%)	0,491
Age	2,0 months [1,0 – 6,0]	2,0 months [1 – 4,5]	3,0 months [1 – 27]	0,100
Weight	4,1 kg [4,1 – 6,2]	4,9 kg [4,1 – 6,2]	4,9 kg [3,7 – 10,4]	0,807
Associated gene				0,051
PTPN11	17 (53%)	10 (59%)	7 (47%)	
SOS1	6 (19%)	1 (6%)	5 (33%)	
RIT1	4 (13%)	4 (23%)	0 (0%)	
RAF1	1 (3%)	0 (0%)	1 (7%)	
BRAF	1 (3%)	1 (6%)	0 (0%)	
Unknown	3 (9%)	1 (6%)	2 (13%)	
Subtype PS				**0,005**
VPS	10	2 (11,5%)	8 (53%)	
SVPS	9	4 (23,5%)	5 (33%)	
Combined VPS and SVPS	13	11 (65%)	2 (14%)	
PV pressure gradient	40,0 mmHg [25,0 – 70,0]	70,0 mmHg [45,0 – 75,0]	25,0 mmHg [18,0 – 39,0]	**< 0,001**

Abbreviations: VPS = Valvular Pulmonary Stenosis ; SVPS = Supravalvular Pulmonary Stenosis ; PS = Pulmonary Stenosis.

malformations, type of intervention (BVP or surgery) and complications were reviewed. Intervention decision was based on thegradation of PS after multidisciplinary meetings with (interventional) pediatric cardiologists and pediatric cardiac surgeons. Patients were treated whose peak systolic gradient across the pulmonic valve was 60mmHg or greater. Treatment success was defined as not requiring further interventions during the study period.

Statistical analysis was performed using 'IBM SPSS Statistics 26'. All included continuous parameters were assessed for a normal distribution through the use of a Shapiro-Wilk test. None of the included parameters were normally distributed. Continuous data are expressed as median [interquartile range]. Intergroup comparisons were analysed by the Mann-Whitney U-test, Fisher's exact test or Kruskal-Wallis test as appropriate. A p-value of $< 0,05$ was considered as statistically significant.

The study was approved by the medical ethical committee of both the Antwerp- and Ghent University Hospital (EC2022/0141).

Results

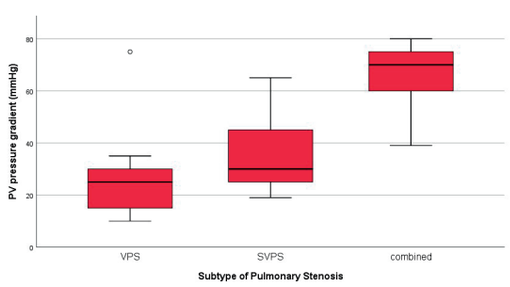
We identified 32 patients with NS that met the inclusion criteria. The median age at diagnosis was 2 months. Of these patients 59% were female. A comparison of patients who underwent an intervention and those who did not is shown in table 1. There were no differences in demographics between the two groups. There were significantly more patients with a combined valvular pulmonary stenosis (VPS) and SVPS who underwent a BVP.

Seventeen patients (53%) had a pathogenic variant in the *PTPN11* gene. Six patients (19%) had a pathogenic SOS1 variant. Four patients (13%) had a pathogenic *RIT1* variant. There was one patient with a pathogenic RAF1 variant and one patient with a pathogenic *BRAF* variant. The other patients did not have a known associated genetic cause. There was no significant difference in the distribution of associated pathogenic gene variants between the two groups.

A total of 22/32 (69%) had an SVPS (either alone or combined with a VPS). The other ten children had an isolated VPS. No subvalvular PS was found in our cohort. A comparison between the three groups is shown in table 2. There were no demographic differences.

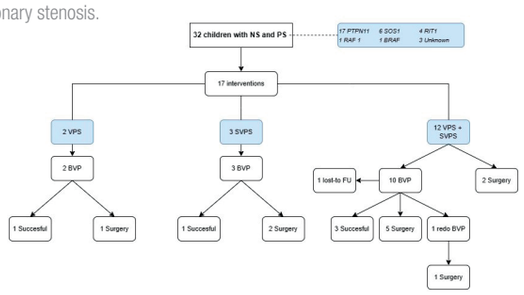
When comparing the existence of isolated VPS with isolated SVPS or a combination of both, there is a significant difference in the PV pressure gradient ($P<0,001$). The PV pressure gradient is highest when a combination of VPS and SVPS is present (figure 1). When comparing the three groups separately, a significantly higher PV pressure gradient

Figure 1: Comparison of the PV pressure gradient by subtype of PS.



Abbreviations: PA = Pulmonary Artery ; VPS = Valvular Pulmonary Stenosis ; SVPS = Supravalvular Pulmonary Stenosis.

Figure 2: Flowchart of treatment outcome of children with Noonan and (supra)valvular pulmonary stenosis.



Abbreviations: PS = Pulmonary Stenosis ; NS = Noonan Syndrome ; BVP = Balloon Valvuloplasty; SVPS: Supravalvular pulmonary stenosis ; VPS = Valvular Pulmonary Stenosis ; FU = Follow-up.

Table 2: Comparison between groups according to the anatomical location of the PS.

	Total cohort	VPS	Isolated SVPS	Combined	p-value
Number of patients	32 (100%)	10 (31%)	9 (28%)	13 (41%)	
Sex	19 female (59%)	5 female (50%)	6 female (67%)	8 female (61%)	0,815
Age	2,0 months [1,0 – 6,0]	4,5 [0,8 – 88,8]	1,0 months [1,0 – 2,0]	4,0 months [2,0 – 4,5]	0,051
Weight	4,1 kg [4,1 – 6,2]	5,1 kg [3,1 – 11,4]	4,8 kg [4,3 – 5,2]	5,0 kg [4,1 – 6,7]	0,726
Associated gene					0,876
PTPN11	17 (53%)	5 (50%)	5 (56%)	7 (54%)	
SOS1	6 (19%)	2 (20%)	1 (9%)	3 (23%)	
RIT1	4 (13%)	1 (10%)	1 (9%)	2 (15%)	
RAF1	1 (3%)	0 (0%)	1 (9%)	0 (0%)	
BRAF	1 (3%)	0 (0%)	1 (9%)	0 (0%)	
Unknown	3 (9%)	2 (20%)	0 (0%)	1 (8%)	
PV annulus	7,0 mm [7,0 – 8,5] (n=20)	7,5 mm [5,5 – 9,5] (n=4)	7,0 mm [6,5 – 8,5] (n=7)	8,0 mm [7,0 – 8,8] (n=9)	0,709
PV pressure gradient	40,0 mmHg [25,0 – 70,0]	25 mmHg [12,5 – 32,5]	30,0 mmHg [22,5 – 46,0]	70,0 mmHg [55,0 – 75,0]	**<0,001**
Intervention performed	17 (53%)	2 (20%)	4 (44%)	11 (85%)	**0,005**

Abbreviations: VPS = Valvular Pulmonary Stenosis ; SVPS = Supravalvular Pulmonary Stenosis ; PV = Pulmonary Valve.

is found in a combined PS in comparison to an isolated VPS (respectively 70,0 mmHg [55,0 – 75,0] vs. 25,0 mmHg [12,5 – 32,5] ; p = 0,001) and in comparison to an isolated SVPS (respectively 70,0 mmHg [55,0 – 75,0] vs. 30,0 mmHg [22,5 – 46,0] ; p = 0,001). No statistical difference was found between an isolated VPS and isolated SVPS (respectively 25,0 mmHg [12,5 – 32,5 vs. 30,0 mmHg [22,5 – 46,0] ; p = 0,286).

The need for intervention is significantly higher in the combined group (11/13 (85%)) compared to isolated SVPS (4/9 (56%)) or VPS (2/10 (20%)) (p = 0,005).

Seventeen patients (53%) needed treatment for PS. In five (33%) patients PS subtype was classified differently due to the results of the angiogram. A flowchart of the treatment outcome can be found in figure 2.

Fifteen patients (2 VPS and 13 SVPS) underwent BVP as first-line treatment. Of these patients, ten (67%) required re-intervention due to treatment failure. The success group was compared with the re-intervention group in table 3. There were no differences in demographics. Carrying a pathogenic variant in the *PTPN11* gene was significantly associated with a successful treatment (p = 0,010). Of the patients who needed a second intervention, one underwent a repeat BVP. All other patients underwent a surgical correction (commissurotomy (with shaving) and autologous patching of the main pulmonary artery) either as a second or third re-intervention. All BVP's were done with a Tyshak II balloon. Median time to re-intervention was 1 month [1 – 3,5]. Eight (89%) re-interventions were performed within three months. One re-intervention was performed after approximately 3 years. One patient requiring a re-intervention was transferred to another centre. One patient died after surgical intervention due to cardiac failure. Median time to follow-up in the success group was 134 months [67 – 144]. Two patients had primary surgical treatment to correct multiple cardiac defects during one intervention.

Within the subgroup of patients with SVPS fifteen patients (4 with isolated SVPS) underwent treatment of which 2 surgical treatment and 13 BVP. Six patients (4 in the BVP group) were successfully treated and did not need a re-intervention. Nine were unsuccessful (of which one lost to follow-up). There was no statistical difference between the two groups (p = 1,0). Due to the low number of patients it was not possible to perform a survival analysis.

Discussion

The main goals of this study are to identify factors predicting treatment for PS in children with NS, to evaluate the success-rate of BVP as first-line treatment and to identify factors predicting treatment failure with BVP.

The main results are listed below. These results will be discussed one by one.

1. In children with NS and PS there is a high prevalence of SVPS.
2. SVPS is associated with a significantly higher PV gradient in comparison to other subtypes of PS, leading to more interventions.
3. Children carrying a pathogenic variant in *PTPN11* were less likely to need a re-intervention.
4. The re-intervention rate after failed BVP for PS in patients with NS is high.
5. Higher immediate drop in PV gradient after BVP was associated with treatment success.
6. SVPS is associated with high re-intervention rates but could still benefit from BVP.

Our study showed that 70% of patients with NS and PS actually had SVPS (either isolated or in combination with VPS). It has been widely described that the most common congenital heart defect in children with NS is a PS. The prevalence of SVPS as a subtype of PS however has not been clearly stated in other cohorts (3,7). Only two studies treated SVPS as a separate entity and reported a prevalence of 35-50% (5,10), which is markedly lower than in our study. However, both studies excluded patients with a mild stenosis (defined as a PV pressure gradient < 40mmHg) which could explain the differences between their findings and ours.

Valve dysplasia has been regularly discussed as a possible reason for treatment failure. Patients with NS are recognised to have dysplastic pulmonary valve leaflets that may inherently be more refractive to relief of obstruction by BVP resulted in a high re-intervention rate after BVP (7).This was in agreement with McCrindle et al. who described that the associated dysplastic morphology of the pulmonary valve leaflets in NS patients was thought to be the root cause of a suboptimal response (9). In our cohort the main reason of re-intervention or intervention failure seems to be the existence of an SVPS.

Table 3: Comparison between success group and re-intervention group after BVP.

	Total cohort	Success group	Re-intervention group	p-value
Total number of patients	15 (100%)	5 (33%)	10 (67%)	
Sex	8 female (53%)	1 female (20%)	7 female (70%)	0,119
Age	4,0 months [2,0 – 7,0]	6,0 months [3,0 – 41,5]	3,0 months [2 – 6,3]	0,201
Weight	6,3kg [4,7 – 6,5]	6,0 kg [5,6-15,0]	5,0 kg [4,1 – 6,4]	0,061
Associated gene				0,093
PTPN11	8 (53%)	5 (100%)	3 (30%)	
SOS1	1 (7%)	0 (0%)	1 (10%)	
RIT1	4 (27)	0 (0%)	4 (40%)	
BRAF	1 (7%)	0 (0%)	1 (10%)	
Unknown	1 (7%)	0 (0%)	1 (10%)	
Type of PS				0,660
SVPS	3 (20%)	1 (20%)	2 (20%)	
SVPS + VPS	10 (67%)	3 (60%)	7 (70%)	
VPS	2 (13%)	1 (20%)	1 (10%)	
PV annulus	7,0 mm [6,25 – 8,75] (n=13)	7,5 mm [6,25 – 9,5] (n=4)	7,0 mm [5,0 – 9,0] (n=7)	0,600
PV pressure gradient pre-intervention	74,0 mmHg [62,5 – 75,0]	67,5 mmHg [60,0 – 75,0]	75,0 mmHg [70,0 – 80,0]	0,232
PV pressure gradient post-intervention	55,0 [36,0 – 69,0]	40,0 mmHg [28,0 – 42,0]	66,5 mmHg [58,8 – 72,5]	**0,006**
BVP balloon dm to PS annulus ratio	1,29 [1,17 – 1,40]	1,2 [1,18 – 1,43] (n = 3)	1,33 [1,14 – 1,4] (n = 7)	0,967

Abbreviations: PS = pulmonary stenosis; SVPS = supravalvular pulmonary stenosis; VPS = valvular pulmonary stenosis; PV = pulmonary valve; PA = Pulmonary Artery; BVP = balloon valvuloplasty; dm = diameter.

Among all NS patients screened, pathogenic variants in the *PTPN11* gene were most frequently reported (56%). This is similar to previous literature reports (11). Although carrying a *PTPN11* gene variant has been associated with more severe PS, needing treatment in approximately 50% of cases, we were unable to confirm this association (11). We found that there was a significantly higher proportion of patients carrying a variant in the *PTPN11* gene that had a successful treatment in comparison to patients carrying a variant in a different involved gene or to patients in whom the molecular cause was not found. It was not possible to evaluate other genes as a separate group due to the low number of patients. RAF1 for example is known to be associated with the risk of a more severe PS (12). However in our study only one patient had a RAF1 mutation and did not require any treatment.

The re-intervention rate of BVP after primary treatment was 67%. Of the nine patients needing a re-intervention and in whom follow-up data was available, only one underwent a second BVP. This treatment was unsuccessful. The other nine patients underwent a successful surgical repair. Although in non-syndromic patients re-intervention rates were reported to be as low as 15% (8), the re-intervention rate in NS has been shown to be much higher, ranging from 41% to 65% (5,7,12). These results are similar to those found in our study.

In our study there is a significantly lower post-procedural PV pressure gradient in the success group. This is consistent with McCrindle et al. who found that a higher post-BVP residual gradient is associated with a suboptimal outcome in non-syndromic patients (9). Holzmann et al. however found no difference in the residual gradient in patients with NS. Notably, the results in the study of Holzmann et al. showed a lower PV pressure gradient in the success group, although it did not reach statistical significance (5).

In our study, there was no significant difference in the need for re-intervention in patients with VPS versus patients with an SVPS. This result is consistent with the work by Holzmann et al. who reported similar results (5). However, a recent study by Abumehdi et al. reported that SVPS is significantly associated with the need for a re-intervention after BVP (12). A major difference is that our cohort size is smaller than the cohort size of Abumehdi et al. (n = 15 vs. n = 52), which is the largest reported series of performed BVP's in children with NS until present. In our study there were only 2/15 (13%) patients with a VPS that needed treatment in comparison to 22/54 (41%) in the study by Abumehdi et al. It is possible that a larger cohort could lead to a different result. In these studies, there are no children reported with an isolated SVPS. It would be beneficial in future studies to include this as a separate entity.

None of the patients in the success group needed a second intervention. However, follow-up is short so far. It should be noted that the time to re-intervention was around 1-3 months. The success group has a median follow-up of 134 months, making the need for re-intervention unlikely.

Limitations

This study is performed retrospectively over more than 20 years. Therefore the information gathered from older patients is subjected to unavailability and therefore leads to missing data.

Secondly, the small number of patients in this cohort means results should be interpreted with caution. For example, the genotype-phenotype correlation between carriers of pathogenic variants in *PTPN11* and success rate could be a random finding due to the low number of included patients.

The decision to perform a re-intervention was done in a multidisciplinary setting with cardiologist and cardiac surgeons. However, in about 20 years the treating clinicians have changed. It can't be excluded that this has resulted in a different threshold to perform a(n) (re)intervention.

The definition of supravalvular stenosis is not clearly defined in the literature which could lead to interpretation bias. It would be relevant for future studies to address the lack of definition to reduce heterogeneity and facilitate comparisons.

Conclusion

SVPS is a frequent manifestation of PS in patients with NS and leads to a more severe PS when combined with a VPS, frequently mandating early treatment. Isolated SVPS was found in approximately 1/3 of all pulmonary stenoses and seems to be less severe. No other factors could be found predicting treatment necessity.

The re-intervention rate after BVP of a PS in children with NS is higher than in non-syndromic patients. SVPS may be a risk factor predicting failure, though could not be withheld in this study. Next to that, the underlying pathogenesis of an isolated SVPS is most likely different from that of combined VPS and SVPS. One of the problems identified in this study is that the echo prediction of SPVS is unreliable as catheterization laboratory findings frequently differed (33%). Therefore, BVP might still be useful as the intervention is significantly less invasive compared to surgery and has a success rate of 31,1%. These findings need to be discussed with the parents in order to make a joint decision on the best primary treatment option on an individual basis. A greater post-procedural drop in PV pressure gradient seems to be predictive of successful treatment, also in children with NS but obviously this is known only after having performed the procedure. A pathogenic *PTPN11* gene variant in association with NS with PS might be associated with a higher success rate of BVP. Larger studies are needed to hopefully identify which patients will benefit most from primary BPS and in whom it should not even be attempted.

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Conflicts of interest

The authors declare that they have no conflicts of interest to report regarding the present study.

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