The Clinical Spectrum of RASopathies

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Introduction

The RASopathies are a specific group of genetic syndromes that occur as a result of germline mutations in genes encoding proteins of the Ras–mitogen-activated protein kinase (RAS–MAPK) pathway (Fig 1). These developmental disorders include Neurofibromatosis type 1 (NF1), the first RASopathy identified, followed by Noonan syndrome (NS), and a host of others including Noonan syndrome with multiple lentigines (NSML), capillary malformation–arteriovenous malformation syndrome (CM-AVM), Costello syndrome (CS), cardio-facio-cutaneous syndrome (CFC) and Legius syndrome. The Ras-MAPK pathway is essential for signal transduction from the cell surface to the nucleus and plays a pivotal role in regulation of cellular proliferation, differentiation and cellular growth. The RAS multigene family includes KRAS, HRAS and NRAS and code for Ras proteins that are guanosine nucleotide bound and cycle between the active GTP-bound form and the inactive GDP-bound form. Activation of RAS occurs as an outcome of binding of the growth factor to the receptor tyrosine kinase (RTK) and SOS1 recruitment, that in turn increases the active GTP-bound Ras form. This further initiates activation of Raf (ARAF, BRAF, CRAF), the first MAPK pathway kinase, which in turn activates MEK1 / MEK2, which then regulate the downstream effector substrates ERK1and ERK2. These further activate downstream nuclear and cytosolic molecules that control cellular proliferation and differentiation (Fig 1) (Tidyman and Rauen, 2009). Understanding the pathophysiology is important to identify possible therapeutic targets for RASopathies, aimed at reduction of activity of RAS signaling (Korf B, et al., 2015; Bezniakow N, et al., 2014).

In the group of malformation syndromes that occur due to the Ras / MAPK pathway dysregulation, germline mutation in any of the genes exhibits numerous overlapping phenotypic features of facial dysmorphism, short stature, congenital heart defects (CHD), skeletal abnormalities, cutaneous abnormalities and variable developmental delay.

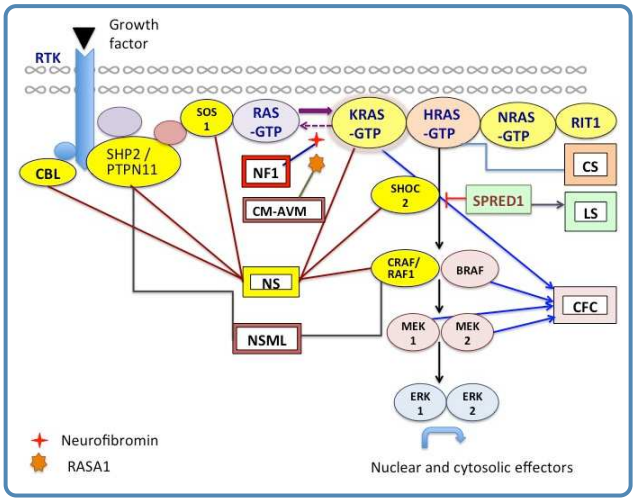

Figure 1 Ras-MAPK signal transduction pathway and molecular basis of RASopathies. NF-1: Neurofibromatosis type 1; NS: Noonan syndrome; CFC: Cardiofaciocutaneous syndrome; CS: Costello syndrome; LS: Legius syndrome; NSML: Noonan syndrome with multiple lentigines; CM-AVM: Capillary malformation-arteriovenous malformation.

These are one of the largest group of malformation syndromes with an estimated incidence of about 1 in 1000 persons. Activating mutations in *PTPN11* are present in 50% patients with Noonan syndrome, other causative genes being *SOS1, RAF1, KRAS, NRAS, SHOC2,* CBL and *MAP2K1 (MEK1)* which are implicated in a subset of patients. Genes associated with the other disorders of this pathway are illustrated in Figure 1. Recently, novel gene

variants, including *RIT1, RRAS, RASA2, A2ML1, SOS2* and *LZTR1*, have in addition been shown to be associated with RASopathies, further expanding the disease spectrum (Aoki Y et al., 2016). Table 1 lists the various genes responsible for causing Noonan and Noonan-like syndromes.

Table 1 Genes responsible for causing RASopathies.

Syndrome	RAS/MAPK pathway gene	Proportion of disease attributed to this gene
Neurofibromatosis 1	*NF1*	>95%
Noonan Syndrome (NS)	*PTPN11*	50%
	SOS1	10%-13%
	RAF1	3%-17%
	KRAS	<5%
	NRAS	4 individuals to date
	BRAF	<2%
	MAP2K1	<2%
	SHOC2	2%
	CBL	
Noonan syndrome with multiple lentigines	*PTPN11*	90%
	RAF1	<5%
	BRAF	2 individuals
	MAP2K1	1 individual
Capillary malformation-arteriovenous malformation	*RASA1*	>70%
Costello syndrome	*HRAS*	80%-90%
Cardio-facio-cutaneous syndrome	*BRAF*	75%
	MAP2K1	25%
	MAP2K2	
	KRAS	<2%-3%
Legius syndrome	*SPRED1*	98%
Novel genes in NS and NS like syndromes (No. of families reported)	*RIT1, RRAS, RASA2, A2ML1, SOS2, LZTR1* (Bezniakow N, et al., 2014; Korf et al., 2015; Aoki et al., 2016; Allanson & Roberts, 2011)	

We discuss here a few of the interesting cases that presented to the genetic clinic at our hospital from 2012 through December 2015, with characteristic features of Noonan and other RASopathies. Neurofibromatosis type 1 is not included in this series except one case of NF1 with developmental delay and craniofacial dysmorphism reminiscent of NS. A total of 20 patients including 13 patients with a provisional diagnosis of Noonan syndrome (NS), 5 patients with a diagnosis of Cardiofaciocutaneous syndrome (CFC), 1 patient with suspected NF - Noonan syndrome and 1 patient of Costello syndrome were seen during this time. The age of presentation varied from 3 months to 22 years and one fetus was evaluated after termination of the pregnancy at 18 weeks gestation. The clinical data of the patients is presented in the Table 2.

Cranio–facial dysmorphism

The most consistently found feature in all patients was the characteristic facial dysmorphism - low set and posteriorly rotated ears, broad nasal bridge, hypertelorism and downslanting palpebral fissures seen in 17/20 (85% of patients). Additionally ptosis was noted in 12/20 (60% of patients) (Fig 2A). In patients with clinical suspicion of cardiofaciocutaneous syndrome (5/20 patients), the face was broader and coarse looking with sparse, thick, curly wooly hair (Fig 2B). In our one patient of Costello syndrome (Table 2-IV) from Nigeria, the facies were much more coarse with thick, fleshy earlobes, full nasal tip and thick lips (Fig 2C; the mother's photo given for comparison). The facial features associated with NS and related disorders vary considerably with age, being most striking in the neonatal period and childhood. Since the presentation can be mild and the typical facies recede with age, the diagnosis may be overlooked. Hence, the facial dysmorphism should be carefully noted at the initial visit as "gestalt" assessment is the commonest diagnostic tool for disorders of the RAS-MAPK pathway.

Cardiac manifestations

Heart disease was present in 17 out of 20 patients (85%) similar to the estimated frequency between 50 - 80% (Allanson & Roberts, 2011). NS and related disorders are one of the most common syndromic cause of heart defects. Several cardiovascular phenotypes are found, with pulmonary valvular stenosis being the most common in our cohort followed by hypertrophic cardiomyopathy and atrial septal defects.

Table 2 Clinical characteristics and mutations of patients with suspected Noonan Syndrome (I.1-I.13), Cardiofaciocutaneous syndrome (II.1-II.5), Neurofibromatosis Noonan syndrome – NFNS (III), Costello syndrome-(IV).

Patient ID	Age at presentation /Sex	Antenatal	Development /Intellect	Stature	Heart disease	Facial features	Skeletal	Others/ Mutation
I.1	18 weeks fetus / M	Bilateral hypoplastic kidneys with oligohydramnios. Echocardiography-Pulmonary stenosis.	-	Crown rump length: 18 cms (18-19 weeks)	Pulmonary stenosis	Telecanthus, broad nose, low set ears, downslanting palpebral fissures	Normal radiographs	-
I.2	3 months / M	NT-5.6 mm, Femur - 5th centile for gestation, Antenatal Karyotype-46,–, Normal	Appropriate	59 cms (50th centile)	not present	Sparse eyebrows, downslanting eyes, triangular chin, low set ears, high arched palate, bulbous tip of nose	Right CTEV, limitation of elbow joint extension, right clinodactyly.	
I.3	5.5 months / M	Antenatal data not available.	Appropriate	55.6 cms (- 4 SD)	Hypertrophic cardiomyopathy	Downslanting eyes, Bulbous nasal tip	Short neck, shield like chest, wide spaced nipples	-
I.4	5.5 months / M	Antenatal period-uneventful	Global development delay	56 cms (-4SD)	Atrioventricular canal defects	No dysmorphic features	-	Juvenile myelomonocytic leukemia, feeding difficulty & vomiting, retrocollis failure to thrive, loose skin, scant hair. Heterozygous mutation (c.218C>T, p.Thr73Ile) in *PTPN11* gene

I.5	10 month / M	Antenatal data not available	Appropriate	63 cms (-3 SD)	ASD with severe valvular pulmonary stenosis	Downslanting eyes	-	Feeding difficulty & vomiting, bilateral undescended testes
I.6	1 year / M	Antenatal data not available	Appropriate	70 cms (-2 SD)	Severe valvular pulmonary stenosis with RVH	Facial asymmetry, left ptosis, hypertelorism, epicanthic folds	Bilateral 2nd-3rd toe syndactyly, left Simian crease	Micropenis
I.7	4 years / M	Antenatal data not available	Mild development delay	90 cms (-2 to -3 SD)	Atrial septal defect	Downslanting eyes, hypertelorism	-	Undescended testes, hypospadias
I.8	4 years / M	Antenatal data not available	Normal	91 cms (-3 to -2 SD) at diagnosis	Atrialseptal defect	Ptosis, broad nasal bridge	-	On Growth hormone therapy
I.9	4.5 years / M	Antenatal data not available	Normal	88 cms (-5 to -4 SD) at diagnosis	Supravalvular tethering of pulmonary valve	Mild ptosis, depressed nasal bridge	Winging of scapula, pectus excavatum, short neck, limitation of elbow extension	On Growth hormone therapy
I.10	7 years / M	Antenatal data not available	Development delay present	100.5 cms (-4 SD)	Soft systolic murmur, recurrent respiratory infections. Echo - Not done.	Downslant palpebral fissures, low set ears, small philtrum, teeth pigmentation	Short neck, small hands and feet	CT head- Hydrocephalus Heterozygous mutation (c.2536G>A, p.Glu346Lys) in exon 16 of *SOS1* gene
I.11	10 years 8 month / F	Antenatal data not available	Mild ID	111 cms (-5 SD)	Echocadiography - Normal	Ptosis	Short neck, pectus carinatum	

I.12	14 years / F	Antenatal data not available	Mild ID	135 cms (-3 SD)	Pulmonic stenosis	Epicanthal folds, hypertelorism, low nasal bridge, downward eye slant, low set ears	-	Lentigines
I.13	22 years / M	Antenatal data not available	Mild ID	158 cms	CHD- Unspecified	Broad nasal bridge, maxillary hypoplasia, small curved eyelashes, preauricular sinus	Bilateral pedal edema, broad laterally deviated toes	-
II.1	1 year / F	Unilateral hydronephrosis	Severe development delay	68 cms (-3 to -2 SD)	Pulmonary stenosis	Depressed nasal root, wide base of nose, bulbous tip	-	Feeding difficulty with GERD
II.2	3 years / F	Polyhydramnios	Mild global development delay	87 cms (3- 50th centile)	Left ventricle hypertrophy, left ventricle dysfunction, mild mitral regurgitation	Coarse facies, downslant palpebral fissures, low set ears, broad forehead, hypertelorism, strabismus	Short broad thumbs, fingers and toes, widely spaced nipples	Generalised dry skin, keratosis pilaris,sparse eyebrows, curly wooly hair
II.3	5 years / M	Antenatal data not available	Moderate ID	95 cms (-3 to -4SD)	Atrial septal defect	Coarse, broad face, downslanting palpebral fissures, bulbous tip of nose.	-	Curly wooly hair

II.4	8 years / M	Antenatal data not available	Moderate ID	115 cms (-2 to -3SD)	Hypertrophic cardiomyopathy	Coarse, broad face. downslanting palpebral fissures, bulbous tip of nose. ptosis	-	Curly hair
II.5	18 months / M	Polyhydramnios	Mild development delay	73 cms (-3 SD)	Atrial septal defect	Coarse, broad face. downslanting palpebral fissures, bulbous tip of nose.	-	Curly, scant hair
III	15 months / M	Antenatal data not available	Mild development delay	71 cms (-3 SD)	-	Downslanting palpebral fissures, bulbous tip of nose	-	Multiple café au lait spots, plexiform neurofibroma Heterozygous mutation (c.2033dupC) in exon 18 of *NF1* gene
IV	6 year / F	Antenatal data not available	Delayed psychomotor development	107 cms (5^{th} to 25^{th} centile)	Hypertrophic cardiomyopathy	Coarse facies, broad forehead, depressed nasal bridge, epicanthic folds, hypertelorism, thick, fleshy earlobes, full nasal tip, thick lips		Sparse, fine scalp hair, skin - small papilloma at the root of the nasal tip was noticed, hyperkeratosis of palms & soles

NT: nuchal translucency; CTEV: congenital Talipes equinovarus, ID: intellectual disability; M: male; F: female; RVH: right ventricular hypertrophy; GER: gastro-esophageal reflux.

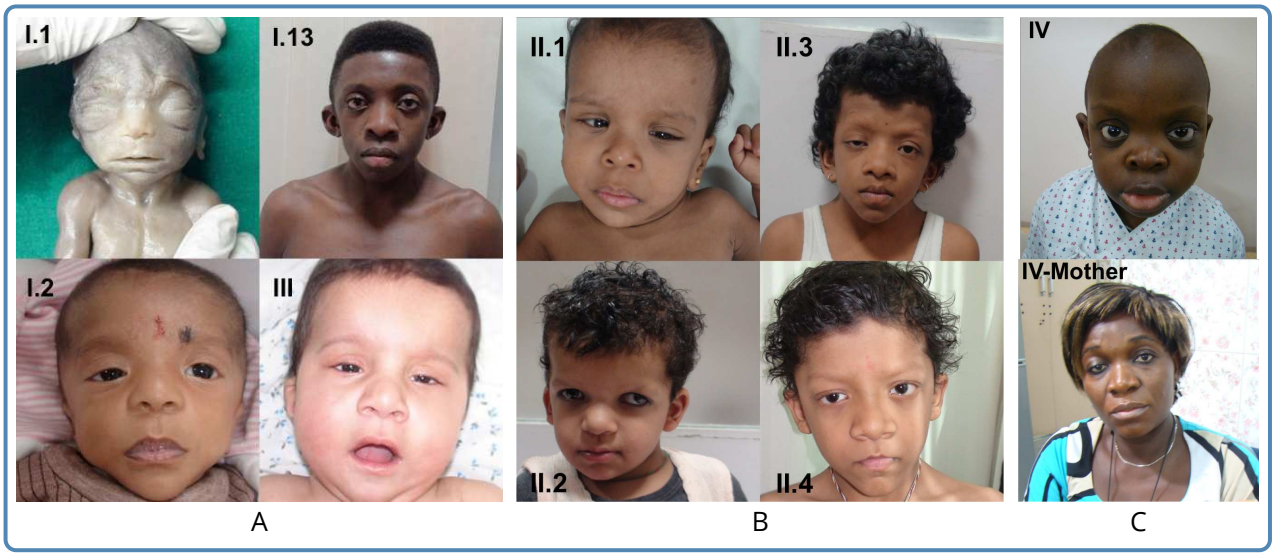

Figure 2 Facial features of patients with suspected Noonan syndrome (A), Cardio-facio-cutaneous syndrome (B) and Costello syndrome (C).

Growth

Neonates with NS usually have normal birth weight and body length. Infants, however have feeding difficulties that result in failure to thrive, most evident in the first year of life. Severe feeding difficulty and gastroesophageal reflux disease were present in three of our patients (Table 2- I.4, I.5, II.1), requiring prolonged gastrostomy in one of them.

In childhood, short stature is almost a universal finding and height usually follows the third centile with an attenuated pubertal spurt. A study reported that 30% of individuals with Noonan syndrome have a height in the normal adult range while 40 – 50% individuals have an adult height below the third centile (Noonan et al., 2003). This may be due to growth hormone deficiency because of neurosecretory dysfunction or growth hormone resistance. The US Food and Drug Administration in 2007 approved Growth Hormone (GH) replacement therapy with recombinant human growth hormone for Noonan Syndrome. Several long and short term studies on the use of GH in different parts of the world reveal significant improvement in the height velocity in children with NS (Tamburrino et al., 2015; Romano et al., 2009; Noordam et al., 2008; Osio et al., 2005; Ogawa et al., 2004).

In our study cohort, sparing an adult and a fetus, short stature was recorded in all the patients. Two patients have been receiving growth hormone therapy for a few years. One of the boys (Table 2- I.9) had height at -5 to - 4 SD at 4.5 years of age, delayed bone age, low IGF-1 levels and inadequate response to clonidine in growth hormone stimulation test. On receiving an average 0.15 units/ kg /day of GH subcutaneously, he showed significant increase in height velocity initially and gained 7.5 cm in the first year of therapy. At 14 years of age, his height is at -2SD from the mean (comparable to the mid parental height centile). For the second boy (Table 2- I.8) who received growth hormone treatment, GH was initiated at 0.15 units/kg/day from 4 years of age. The height increased from -3 SD to -2 SD within 3 years of initiation of therapy. However, it has not increased beyond -2 SD from the mean demonstrating a short-term increase in growth. There were no complications of hypertrophic cardiomyopathy or hematologic disturbances in these patients.

Occasionally NS is referred to as 'Pseudo-Turner or Male Turner syndrome', due to similar findings of short stature, webbed neck and lymphedema. Interestingly, we had one girl (Table 2- I.10) who was evaluated for short stature. The karyotype revealed 45,X [3] / 46, XX [47] confirming the diagnosis of mosaic Turner syndrome. However, she also had some characteristic NS-like craniofacial dysmorphism and systemic malformations - epicanthic folds, hypertelorism, low nasal bridge, downward eye slant, low set ears, pulmonary stenosis and lentigines. Molecular panel testing for

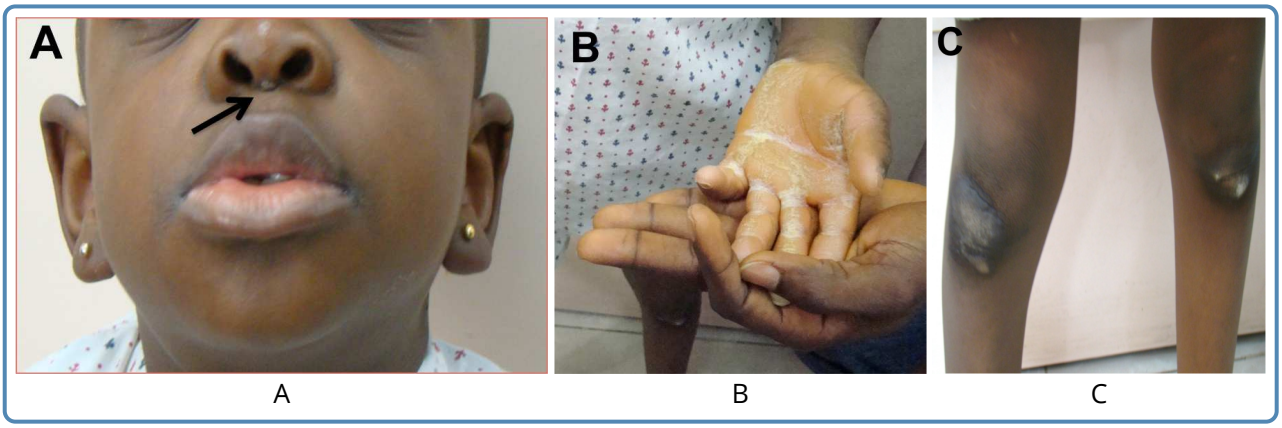

Figure 3 Patient IV- Costello syndrome. (A) Skin papilloma (B) Deep skin creases (C) Hyperkeratosis.

Noonan-related genes identified a heterozygous mutation (c.2536G>A) in the *SOS1* gene that has been implicated in Noonan syndrome.

Psychomotor development

In most affected individuals of NS, intelligence is within the normal range, with the intelligence quotient ranging from 70-120. Mild to severe learning disability is reported in 25% and 10% of the patients respectively. Furthermore, in literature it has been noted that the verbal performance is significantly lower than the non-verbal performance. In contrast, neurologic abnormalities have been reported to be universally present in CFC and range from mild to severe (Yoon et al., 2007). In our cohort of NS patients, development / intellect was appropriate for age in 54% (7/13) of patients. The children with a clinical diagnosis of CFC syndrome and Costello syndrome in the cohort had global development delay that was of mild to moderate severity.

Dermatological manifestations

Among the RASopathies, the dermatologic findings are the most common in cardiofaciocutaneous syndrome (CFC). These include xerosis, hyperkeratosis, ichthyosis, keratosis pilaris, ulerythema ophryogenes, eczema, pigmented moles, hemangiomas, and palmoplantar hyperkeratosis. The hair is typically sparse, curly, fine or thick, wooly or brittle; eyelashes and eyebrows may be absent or sparse. Nails may be dystrophic or fast growing. Apart from these similar features, Costello syndrome is characterised by papillomas of face and perianal region, as also found in our patient IV (Fig 3).

Patients with NF1 have café au lait spots, axillary freckling and neurofibromas in skin. NS may also have skin manifestations, particularly follicular keratosis over extensor surfaces, lentigines and café-au-lait spots. One child in the current cohort (Table 2-III) presented with clinical features characteristic of both neurofibromatosis type 1 and Noonan syndrome (NFNS syndrome- OMIM 601321). The NF1 features at presentation were > 6 café-au-lait spots. Follow up MRI identified cervical plexiform neurofibroma (Fig 4A, 4B). In addition the child had short stature, hypertelorism, ptosis, nystagmus, low-set ears, webbed neck and pectus deformity suggestive of NS. Mutation analysis revealed a heterozygous truncation mutation in *NF1*:c.2033dupC, thereby confirming the diagnosis of NFNS. The parents were normal on clinical examination. Recently, a similar report of a family with multiple café au lait spots and NS-like facial features in a child (fulfilling criteria of NF1) and mother (not fulfilling criteria for NF1) revealed mutation in MAP2K2 gene (Takenouchi et al., 2014). This gene has been originally implicated in CFC syndrome which further illustrates the phenotypic and genetic overlap in RASopathies.

Leukemias and other malignancies

Individuals with Noonan syndrome have upto three fold increased risk of malignancies which include juvenile myelomonocytic leukemia, acute lymphoblastic leukemia, acute myeloid leukemia

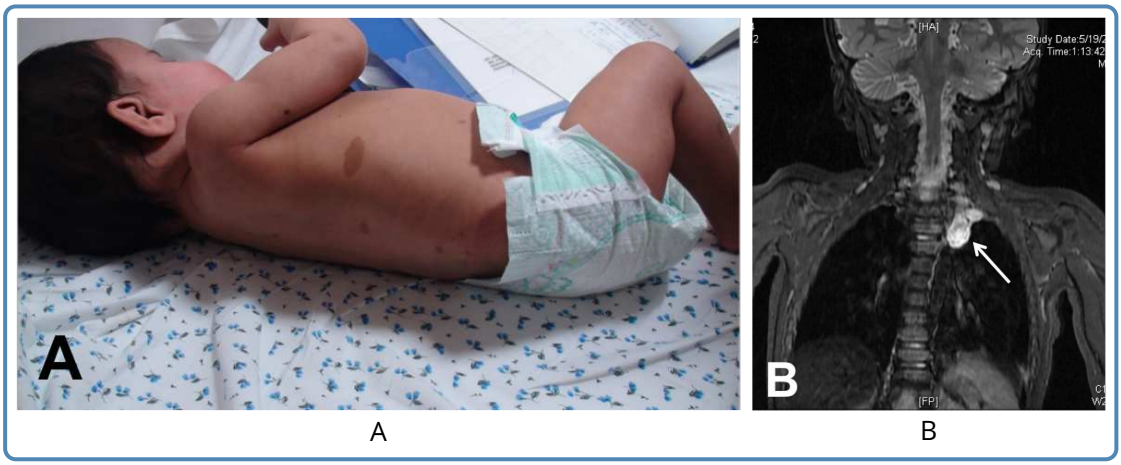

Figure 4 Patient III (A) Café au lait spots (B) Plexiform Neurofibroma.

and solid tumours such as rhabdomyosarcoma and neuroblastoma (Jongmans et al., 2011; Strullu et al., 2014).

In particular, individuals with germline mutations in the *PTPN11* gene have a predisposition to Juvenile myelomonocytic leukemia (JMML) (Strullu et al., 2014). In our cohort, patient I.4 was diagnosed with JMML at 3 months of age. He also had atrioventricular canal defect, feeding difficulties and severe failure to thrive. In view of these, he was clinically suspected and found to be carrying a heterozygous mutation in the *PTPN11* gene (c.218C>T, p.T73I), confirming the diagnosis of Noonan syndrome. This mutation has been previously identified in multiple Noonan patients with JMML, with a milder clinical course (Aoki et al., 2008).

Prenatal Diagnosis

For prenatal diagnosis, the ultrasonographic markers for NS are non specific. In the absence of family history NS is not routinely suspected and prenatal testing is not typically offered. In our cohort, the antenatal data of five patients was available and showed abnormalities. One patient (Table 2-I.2) had increased nuchal fold thickness (NFT) of 5.6 mm with femur length at 5th centile and polyhydramnios in the 2nd trimester scan. Fetal chromosomes were tested and were normal. The neonate came to medical attention at 3 months of age for dysmorphism and joint movement restriction.

One fetus (Table 2-I.1) which was terminated in view of increased NFT (5.68 mm), bilateral hypoplastic kidneys and severe pulmonary stenosis on antenatal ultrasound at 18 weeks gestation was clinically diagnosed with Noonan syndrome in view of the facial phenotype.

The other three patients (Table 2-II.1, II.2, II.5) who had antenatal polyhydramnios and unilateral hydronephrosis came to medical attention after birth for developmental delay, facial dysmorphism and congenital heart disease.

The prenatal features described for NS are increased nuchal translucency (NT), distended jugular lymphatic sacs (JLS), cystic hygroma, hydrops fetalis, pleural effusion, polyhydramnios, congenital heart disease and renal abnormalities (Myers et al., 2014).

Out of these, increased NT has the strongest association with Noonan syndrome. However, there is considerable debate as to when to offer prenatal molecular testing for Noonan syndrome, either following a first trimester increased NT or if there are associated anomalies in the 2nd trimester scan with normal fetal chromosomes.

In recent studies in fetuses with an increased NT and a normal karyotype, mutations have been reported in 9–18% of cases. Lee et al. (2009) identified *PTPN11* mutations in 2% of fetuses with increased NT and 16% of fetuses with increased NT and cystic hygroma. In another study, in fetuses with increased NT and normal karyotype, *PTPN11* and *KRAS* mutations were found in 15.8%. This group strongly advocated genetic counseling and testing for Noonan syndrome in case of increased NT and normal karyotype, even in the absence

of additional associated abnormalities (Houweling et al., 2010). On the other hand, Croonen et al. (2013), based on their mutation detection rate of 17.3% in fetuses with ultrasound findings of increased NT, distended jugular lymphatic sacs (JLS), hydrothorax, renal anomalies, polyhydramnios, cystic hygroma, cardiac anomalies, hydrops fetalis and ascites, recommended prenatal testing of *PTPN11*, *KRAS* and *RAF1* in pregnancies with an increased NT and at least one of the additional ultrasonologic features.

In conclusion, Noonan syndrome and the other RASopathies have multisystem morbidities. The clinical features are overlapping and there is extensive genetic heterogeneity. In case of antenatal or postnatal clinical suspicion, with availability of next generation panel testing, the genes in the Ras/MAPK pathway implicated with the phenotypes of RASopathies can be tested for confirmation of diagnosis. Furthermore, in view of multisystemic involvement, multidisciplinary management and follow up of diagnosed patients is essential.

References

1. Allanson JE, Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2011 Aug 4]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1124
2. Aoki Y, et al. The RAS/MAPK Syndromes: Novel Roles of the RAS Pathway in Human Genetic Disorders. Hum Mutat 2008; 29: 992-1006.
3. Aoki Y, et al. Recent advances in RASopathies. J Hum Genet 2016; 61: 33-9. doi: 10.1038/jhg.2015.114.
4. Bezniakow N, et al. The RASopathies as an example of pathway disturbances- Clinical Presentation and Molecular Pathogenesis of selected syndromes. Dev Period Med 2014; 18: 285-296.
5. Croonen EA, et al. Prenatal diagnostic testing of the Noonan syndrome genes in fetuses with abnormal ultrasound findings. Eur J Hum Genet 2013; 21: 936-942.
6. Houweling AC, et al. Prenatal detection of Noonan syndrome by mutation analysis of the PTPN11 and the KRAS genes. Prenat Diagn 2010; 30: 284–286.
7. Jongmans MC, et al. Cancer risk in patients with Noonan syndrome carrying a PTPN11 mutation. Eur J Hum Genet 2011; 19: 870-874.
8. Korf B, et al. The Third International Meeting on Genetic Disorders in the RAS/MAPK Pathway: Toward a Therapeutic Approach. Am J Med Genet A 2015; 167: 1741–1746.
9. Lee KA, et al. PTPN11 analysis for the prenatal diagnosis of Noonan syndrome in fetuses with abnormal ultrasound findings. Clin Genet 2009; 75:190–194.
10. Myers A, et al. Perinatal features of the RASopathies: Noonan syndrome, Cardiofaciocutaneous syndrome and Costello syndrome. Am J Med Genet Part A 2014; 164A: 2814–2821.
11. Noordam C, et al. Long-term GH treatment improves adult height in children with Noonan syndrome with and without mutations in protein tyrosine phosphatase, non-receptor-type 11. Eur J Endocrinol 2008; 159: 203–208.
12. Ogawa M, et al. Clinical evaluation of recombinant human growth hormone in Noonan syndrome. Endocr J 2004; 51: 61–68.
13. Osio D, et al. Improved final height with long-term growth hormone treatment in Noonan syndrome. Acta Paediatr 2005; 94: 1232–1237.
14. Romano AA, et al. Growth response, near-adult height, and patterns of growth and puberty in patients with Noonan syndrome treated with growth hormone. J Clin Endocrinol Metab 2009; 94: 2338–2344.
15. Strullu M, et al. Juvenile myelomonocytic leukaemia and Noonan syndrome. J Med Genet 2014; 51: 689-697.
16. Takenouchi T, et al. Multiple café au lait spots in familial patients with MAP2K2 mutation. Am J Med Genet A.2014; 164A: 392-396.
17. Tamburrino F, et al. Response to long-term growth hormone therapy in patients affected by RAsopathies and growth hormone deficiency: Patterns of growth, puberty and final height data. Am J Med Genet A 2015:167: 2786-294.
18. Tidyman WE, Rauen KA. The RASopathies: Developmental syndromes of Ras/MAPK pathway dysregulation. Curr Opin Genet Dev 2009; 19: 230–236.
19. Noonan JA, et al. Adult height in Noonan syndrome. Am J Med Genet A. 2003; 123A: 68–71.
20. Yoon G, et al. Neurological complications of cardio-facio-cutaneous syndrome. Dev Med Child Neurol 2007; 49: 894–899.