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Review Article

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High Risk Assessment of Pregnancy in Rasopathies

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Abstract

Rasopathies are the group of related disorders caused by abnormal functioning of the Ras-mitogen-activated protein kinase (RAS/MapK) pathway., a cohort of common congenital anomaly syndromes, occurring in 1:1,000 to 1:2,500 live births that have unique fetal features, which can be detected on routine prenatal ultrasounds. In the presence of suggestive US (ultrasound) findings, previous studies estimated that pathogenic variants in RASopathy genes could be detected in 6.7–21.7% of cases. Some disease-specific features, such as an increased prevalence of fetal arrhythmias among cases of Costello syndrome. Prenatal-onset HCM (hypertrophic cardiomyopathy) is rare and potentially severe to delineate high-risk genotype and so accurate diagnosis of fetal rasopathies is essential for improved management of affected pregnancies.

Keywords: Rasopathies, Fetal Anomalies, Ultrasound Features, High Risk in Pregnancy, Neonatal Complications, Parental Counselling.

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Introduction

RASopathies are a family of genetic disorders with more than 20 disease-associated genes are identified so far [1,2]. Many genetic syndromes, a part of RASopathy spectrum, including Noonan syndrome (NS), Noonan syndrome with multiple lentigines (previously known as LEOPARD syndrome), Noonan-like syndrome with loose anagen hair, Costello syndrome (CS), cardiofaciocutaneous syndrome (CFCS), and other clinically related disorders are frequently encountered in pre- and postnatal evaluations [3]. Prenatal diagnosis of RASopathies is important as it can improve parental counseling and allow families to make informed decisions with regard to pregnancy management, treatment options, living with a child with a genetic disorder, termination of pregnancy (TOP) and to screen for complications known to occur in pregnancies with RASopathies, like HCM, and prepare the medical team for management of neonatal complications, but challenging, mostly because of their variable expressivity, as well as their nonspecific prenatal presentation due to heterogeneous cohorts with overlapping prenatal phenotypes [4-6].

Etiopathogenesis

Researcher Susan White, a medical geneticist at Royal Children's Hospital. Melbourne, Australia had a clinical and research interest in syndromes of childhood, worked with families for their child's suspected having genetic problems along with VCGS (Victorian Clinical Genetics Services) laboratory team and led the implementation of exome sequencing (a genomic technique for sequencing all of the protein-coding regions of genes in a genome known as the exome) [7].

Prenatal diagnosis with G-banded karyotyping to detect chromosomal abnormalities results in a diagnosis in 9 to 19% of fetal anomalies, and chromosomal microarray analysis provides an additional 6% yield. The cause of the majority of fetal anomalies remains unknown and Exome sequencing has transformed genetic diagnosis after birth and recent studies showed the diagnostic yields of 8.5% and 10% to 29 % in one series with rasopathies, but its usefulness in prenatal diagnosis is still emerging and Trio exome sequencing covers a wide spectrum of genetic change [8, 9]. In utero manifestations of RASopathies are less well characterized since approximately half of RASopathy variants being inherited in postnatal series and the de novo nature of all the RASopathy variants are severe with a wide range of outcomes, from

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relatively mild lymphedema to probable perinatal death, and their clinical management differs greatly [10].

HRAS is a gene that provides instructions for making a protein called H-Ras which is involved primarily in regulating cell division and it is an enzyme in the signaling pathway (MAP kinase signaling cascade) that relays chemical signals from the outside of the cell to the cell's nucleus, telling the cell when to grow and divide and thus acts as a key regulator of MAPK (mitogen-activated protein kinase) pathway mediated by protein kinase Raf which is critical for cell cycle regulation, cellular differentiation and growth [11]. The HRAS gene is in the Ras family of oncogenes, which also includes two other genes, the KRAS and NRAS and the proteins produced from these three genes are GTPases (Guanosine triphosphate hydrolase), which means it converts a molecule called GTP into another molecule called GDP. The H-Ras protein acts like a switch as it is turned on by attaching (binding) to a molecule of GTP and turned off (inactivated) when it converts GTP to GDP [12]. After the protein is bound to GDP, it does not relay signals to the cell's nucleus. When mutated, HRAS can act as an oncogene, causing normal cells to become cancerous and perturbances (dysfunction) of this MAPK pathway during essential cellular functions and development leading to multiple consequences in embryonal and later stages of development [13].

A mutation is a change in a DNA sequence. DNA is a chain of many smaller molecules called nucleotides. During protein formation, DNA (or RNA) nucleotide sequences are read three nucleotides at a time in units called codons, and each codon corresponds to a specific amino acid or stop signal (stop codon). Stop codons are also called nonsense codons because they do not code for an amino acid and instead signal the end of protein synthesis [14]. Somatic mutations occur in a single body cell, cannot be inherited and only tissues derived from mutated cell are affected. Germline mutations occur in gametes, can be passed onto offspring and every cell in the entire organism will be affected. In contrast to somatic oncogenic mutations in neoplasia, the Costello syndrome changes are typically introduced in the paternal germline. Missense mutation is a genetic change that results in the substitution of one amino acid in protein for another [15]. A nonsense mutation is a genetic mutation in a DNA sequence that results in a shorter, unfinished protein product. Genetic heterogeneity can be defined as mutations at two or more genetic loci that produce the same or similar phenotypes (either biochemical or clinical) and it is relevant since it can present problems for heterozygote detection [16]. De novo mutation is a genetic alteration that is present for the first time in one family member as a result of a variant (or mutation) in a germ cell (egg or sperm) of one of the parents, or a variant that arises in the fertilized egg itself during early embryogenesis [17]. Codon encoding residues stabilizing the Ras protein in an inhibited conformation and SOS (son of sevenless)1 missence mutations disrupts the autoinhibition of Ras GEF (Guanine nucleotide exchange factor) activity and Ras GEF stimulate the conversion of Ras from inactive GDP bound form to active GTP- bound form. SOSI gain-of-function increases the active form of Ras and thus increase the Ras/MAPK signaling. SOS-RAS activation is operated via FRS2 (Fibroblast growth factor receptor substrate 2) which acts downstream of TRKA (Tyrosine Kinase A) in neurons, and FGFR (Fibroblast growth factor receptor) in embryonic stem cell [18]. HRAS (Harvey-Ras) was the first human proto-oncogene reported and p.Gly12Val in codon 12 is the first oncogenic mutation described and Costello syndrome was the first disorder associated with germline mutations in the RAS family of GTPases [19,20]. A nucleotide change that causes substitution of glycine at codon 12 to serine (p.G12S)) is the most common (80%), c.35G>C nucleotide resulting in p.Gly12Ala was seen in 9% and recently, p.Gly13Cys change was identified as most common amino acid change affecting the glycine in Position 13 [21,22]. Rare phenotypes often lethal in infancy are p.G12D, p.G12C, p.G12E and its manifestations are shown in Table 1 [23,24].

Table 1: Manifestations of Lethal Phenotypes in Infancy

S.no	Severe manifestations
1.	Hypoglycaemia
2.	renal abnormalities
3.	severe early cardiomyopathy
4.	congenital lung and airway abnormalities
5.	pleural and pericardial effusion
6.	chylous ascites
7.	pulmonary lymphangectasia
8.	alveolar capillary dysplasia.

Distinctive phenotypic findings of p.Gly13Cys (mild phenotype) are dolichocilia (extremely long eyelashes), loose anagen hair, fewer have short stature, no malignant risk, papillomata and multifocal atrial tachycardia are not seen [25]. HRAS mutations are associated with 10-15% of cancer risk. Germline HRAS mutations associated with Costello syndrome, which confers a risk for malignant tumors including rhabdomyosarcoma, neuroblastoma in childhood and bladder cancer in adolescence [26].

CBL (casitas B-cell lymphoma), a tumor suppressor gene encodes E3 ubiquitin ligase which negatively regulates Ras/MAPK signaling downstream of RTK (receptor tyrosine kinases) and mediates the association of ubiquitin with activated RTK, necessary for receptor internalization & degradation. Mutation in CBL reduce the turnover of activated RTK leads to increased ERK (Extracellular signal-regulated kinases) activation [27-29]. CBL is a cellular homolog of v-Cbl transforming gene of the Cas NS-1 murine leukemia virus, responsible for intracellular transport and degradation of a large number of proteins and majority of CBL somatic mutations are reported in myelodysplastic/myeloproliferative disorders such as chronic myelomonocytic, juvenile myelomonocytic, atypical chronic myeloid leukemias and germline mutations in CBL are identified in juvenile myelomonocytic leukemia [30]. Introduction of exome sequencing, leads to identification of Novel genes in 10-30% of mutation negative RAS/MAPK syndromes [31,32].

The cardiac hypertrophic response implicates signal transduction pathways initiated by ligand-stimulated membrane-bound receptors (RTKs, GPCRs (G protein-coupled receptors)) and biomechanical stress sensors (integrins). GPCR receptors, also known as seven-transmembrane receptors (7-TM receptors), are a large and diverse family of cell surface receptors found in eukaryotes and play a crucial role in cell signaling [33]. It acts

through EPAC (Exchange Protein Directly Activated by cAMP) and ERK, activate RAS proteins and induce the release of internal Ca2+ stores through calcineurin/NFAT (Nuclear Factor of Activated T-cells) proteins to elicit pathological hypertrophy. All these pathways converge on the modulation of transcriptional factors (MEF2 (Myocyte Enhancer Factor 2), JUN and GATA4), which induce the expression of genes of the hypertrophic program. Some "red flags" such as facial dysmorphism, lentigines, sensorineural deafness, PVS (Pulmonary Valvular Stenosis) and biventricular hypertrophy which is reflected by an extreme right axis deviation (a "superior" QRS axis) on the electrocardiogram and represents a specific disease marker [34-37]. Germline mutations in RAF1 are found in 3–5% of NS subjects and show normal valvuloseptal growth, but exhibit eccentric cardiac hypertrophy, probably due to enhanced MEK-ERK signaling [38]. In contrast to non-syndromic primary HCM, HCM in RASopathies confers a high risk of mortality in infancy, which could be attributed to earlier age at presentation and occurrence of heart failure [39]. Among the neurodevelopmental anomalies, the most common is chiari malformation and other findings include delayed myelination, ventriculomegaly, nonspecific white matter abnormalities and corpus callosum hypoplasia [40].

Prenatal Diagnosis of Rasopathies

Prenatal testing should be done when any US finding suggestive of lymphatic dysplasia, CH (cystic hygroma), increased NT (nuchal thickness or translucency) or NF ((Nuchal fold- an ultrasound finding during the second trimester of pregnancy, indicating a thickened area at the back of the fetal neck (≥ 6mm) and it is a soft marker for Down syndrome (Trisomy 21) and other chromosomal abnormalities, though the baby may not have a genetic condition)), hydrops fetalis (HF) or effusions, congenital heart disease (CHD), such as valvular dysplasia or hypertrophic cardiomyopathy (HCM); polyhydramnios (excess amniotic fluid, often >90%), renal anomalies and skeletal abnormalities like short long bones (humerus and femur) and ulnar deviation of wrist [41].

NT (nuchal thickness or translucency) is the amount of fluid behind the fetus's neck in the first trimester of pregnancy detected by ultrasound. A small amount of fluid is normal, and measuring the amount of fluid can help to find the chances of the fetus has a chromosomal or genetic variant. An anechoic space is visible and measurable sonographically in all fetuses between the 11th and the 14th week of the pregnancy as in Figure 1. For most pregnancies, NT above 3 millimeters prompts a discussion of genetic counseling and additional testing. The diagnostic yield of increased NT was significantly higher as 20% when it was greater than 6 mm and 10 % when it was lower than 6 mm and much lower as 1% when this finding was seen as isolated.

The association between the increased NT and the chromosomal abnormalities has been well documented (Figure 2). It helps us to identify the high-risk fetuses for trisomy 21 and other chromosomal abnormalities [42]. The rate of chromosomal aberration and pathogenic CNVs (copy number variations) on chromosomal microarray is high among fetuses with NT between 3.0 and 3.4 mm [43].

Underlying pathophysiological mechanisms for nuchal fluid collection under the skin include cardiac dysfunction, venous congestion in the head and neck, altered composition of the extracellular matrix, failure of lymphatic drainage, fetal anemia or hypoproteinemia and congenital infection [45]. The abnormal accumulation of nuchal fluid decreases after the 14th week.

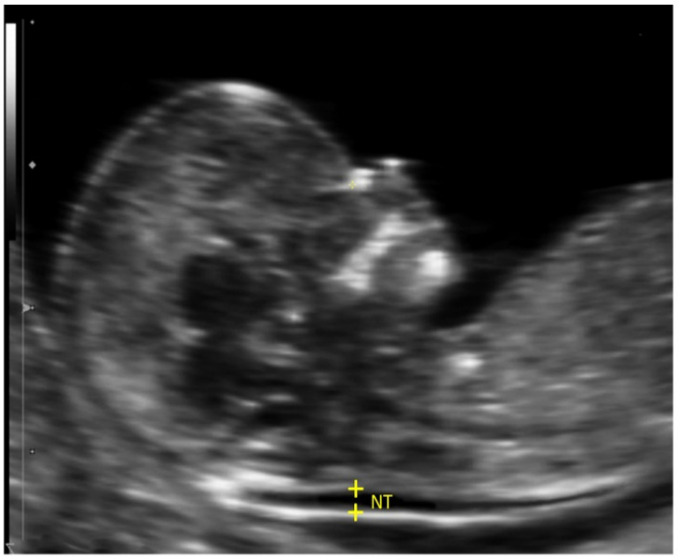

Figure 1: Normal Nuchal Translucency Thickness (NT)

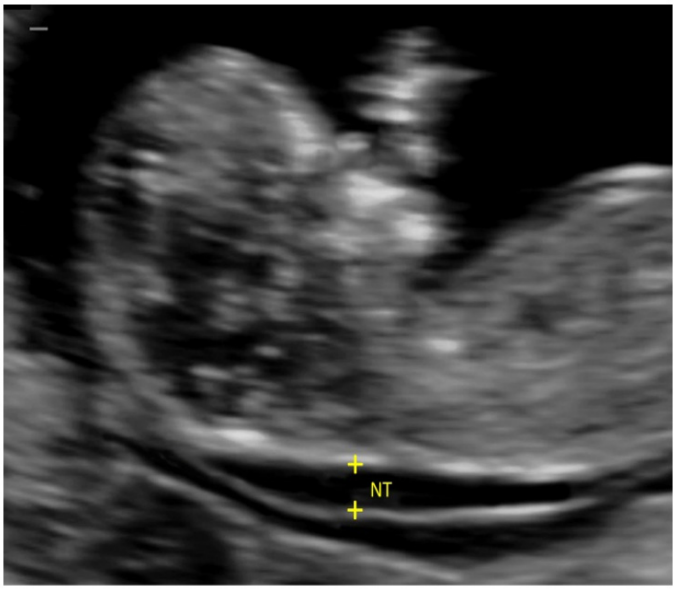

Figure 2: Increased Nuchal Translucency Thickness (NT) [44].

Hydrops fetalis as shown in Figure 3 is characterized by abnormal fluid accumulation in fetuses, presents a significant risk of stillbirth and neonatal mortality, categorized into immune hydrops due to blood type (RhD)-incompatible pregnancy and NIHF (Non-immune hydrops fetalis) and recent studies have highlighted genetic factors as crucial determinants. Whole-exome sequencing (WES) reported an overall diagnostic rate of 29% to 37% and the predominant disease category observed was RASopathies in NIHF cases affects approximately one in 1700–3000 pregnancies. Functional analysis of the mutant channels revealed a loss-of-function defect in the voltage-dependent sodium channels (Nav), with one channel exhibiting no conduction and the other showing a reduced channel opening due to missense variants of the SCN4A gene encoding these channels [46-49].

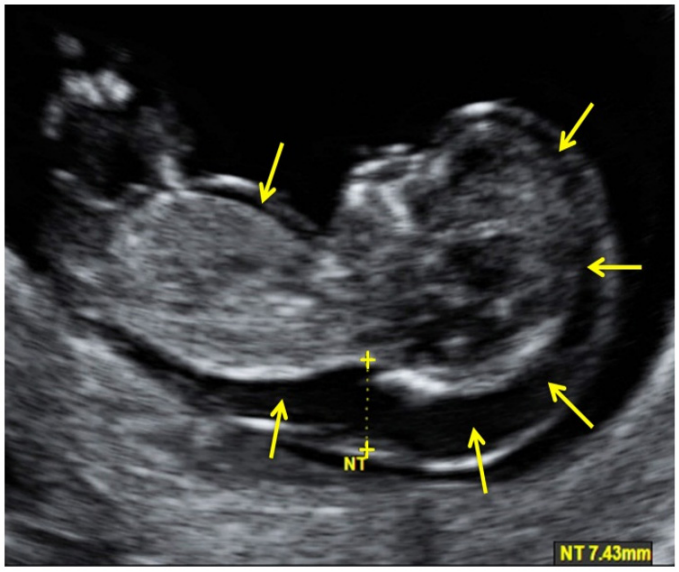

Figure 3: Hydrops Fetalis

The most frequent isolated finding in RASopathy patients is CH (cystic hygroma- 4%), a benign congenital malformation of the lymphatic system due to lack of development of communication between the lymphatic and venous systems and its incidence is approximately 1/6000 live births [50,51]. At the end of the fifth week of gestation, the lymphatic system starts to develop and fluid accumulation within and along the lymphatic vessel tracts and enlargement of the jugular lymphatic sacs are due to this connection failure and may resolve if an alternate route of drainage develops. 70–80% of cystic hygromas occur in the neck, usually in the posterior cervical triangle and 20–30% occurs in the axilla, superior mediastinum, chest wall, mesentery, retro-peritoneal region, pelvis and lower limbs [52,53]. Lymphangiomas may be divided histologically into two major groups based on the depth and the size of abnormal lymph vessels. The superficial ones are called lymphangioma circumscriptum. The more deep seated ones are cavernous lymphangioma or cystic hygroma in areas of areola or loose connective tissues [54]. They are multilocular cysts filled with clear or yellow lymph fluid and brilliantly transilluminant [55]. The mass increases in size and may compresses the neurovascular and respiratory structures as shown in Figure 4 to cause fetal bradycardia and airway obstruction. Noonan syndrome is one of the RASopathies and this group of disorders is often associated with cystic hygroma. Prenatal diagnosis by ultrasound is based on the demonstration of a septated or non-septated, bilateral cystical lesion in the fetal occipitocervical region in both a sagittal and axial plane. Implementation of assessment of the fetal nuchal translucency (NT) in first-trimester screening programs for aneuploidy, the rate of detection has been increased and fetuses with a nuchal translucency thickness more than 10 mm and hydropic fetuses had a worse outcome [56].

Prenatal detection of hypertrophic cardiomyopathy (HCM) through advanced echocardiographic imaging is crucial for early diagnosis [58] and its key features include interventricular septal hypertrophy as shown in Figure 5, which serves as a primary diagnostic marker [59].

Figure 4: Cystic Hygroma in the Neck of a Full-Term Infant [57].

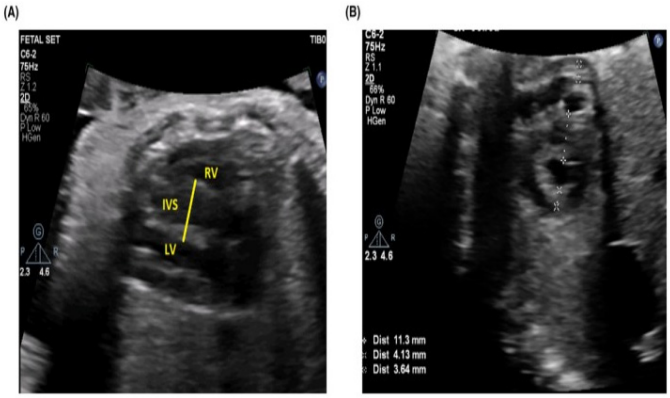

Figure 5: (A) Axial view of the fetal heart demonstrates significant hypertrophy of the interventricular septum (IVS) and cardiomegaly, with clear visualization of the right ventricle (RV) and left ventricle (LV). (B) Short-axis view of both ventricles reveals marked asymmetric hypertrophy of the interventricular septum [60].

Embryonal RMS (Rhabdomyosarcomas) is characterized by a loss of heterozygosity at 11p15.5 and whole or partial gains of chromosomes 2, 8, 12, 13, and/or 20.2 Mutations in the FGFR4/RAS/AKT pathway and increased PTEN (Phosphatase and TENsin homolog) hypermethylation has also been detected in this subtype. Embryonal Rhabdomyosarcoma of the Bladder in a male toddler is shown in Figure 6. The incidence of RMS in patients with CS is 8.7% due to HRAS mutation All individuals with malignancy had a codon 12 mutation (especially G12A) and the rare G12V mutation is associated with a more severe, early lethal phenotype; some patients die from respiratory distress, hypertrophic cardiomyopathy, or malignant tachycardia prior to being diagnosed with CS [61,62].

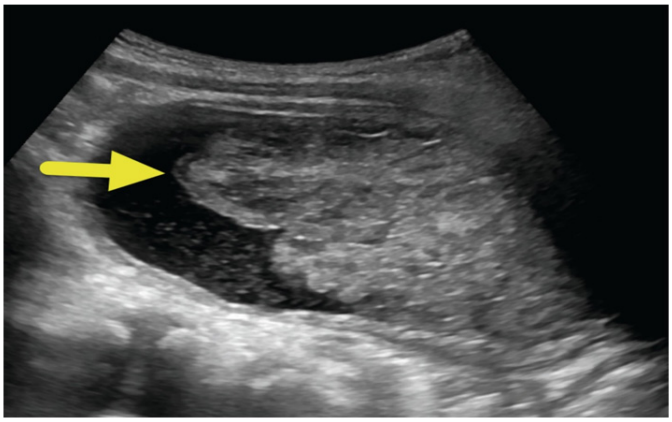

Figure 6: Longitudinal Ultrasound of the Bladder Showing a Lobulated Mass [63].

Operative image indicating the presence of tumor originating in the left medial UL (umbilical ligament) as shown in Figure 7 in a 4.4-year-old female on preterm delivery at 34 weeks and right medial umbilical ligament as shown in Figure 8 in 5.4-year-old female with pregnancy complicated by polyhydramnios.

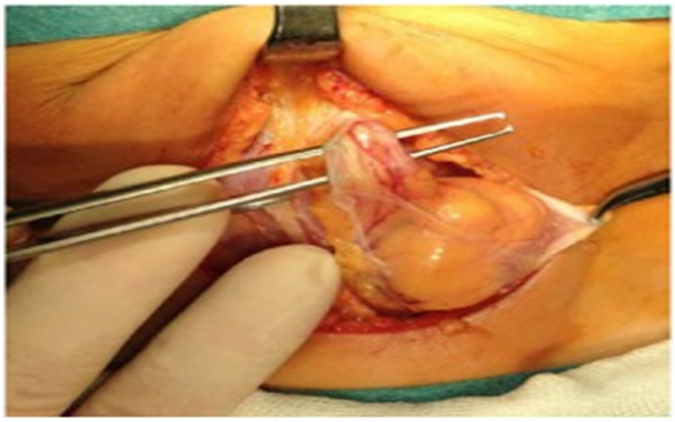

Figure 7: Showing the Rhabdomyosarcoma of Left Medial Umbilical Ligament

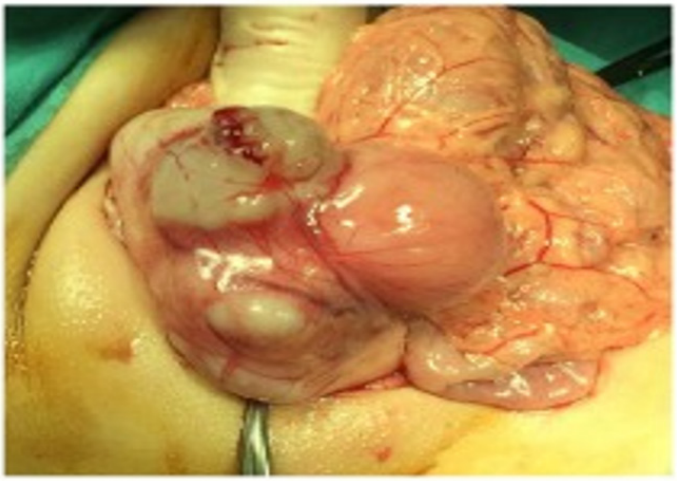

Figure 8: Showing the Rhabdomyosarcoma of Right Medial Umbilical Ligament [64].

Historically, NF1 (neurofibromatosis type 1) was the first described RASopathy, diagnosed through clinical analysis and characteristic phenotypical features such as café-au-lait spots, intertriginous freckling, neurofibromas, and skeletal dysplasia [65]. Genomic DNA analysis of the RASopathy genes to find the pathogenic genetic variants by Sanger sequencing as well as whole-genome sequencing (WGS) and in the case of NS, where approximately 10–20% tested were negative [66]. The second most common type of biomarker used in RASopathies is at the RNA level, involving qualitative and quantitative analysis of mRNA and non-coding RNA (ncRNA), such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs)[67]. Elevated anti-thyroid peroxidase (anti-TPO) antibody levels (> 500 units/ml) are indeed associated with both Noonan syndrome (NS) and cardiofaciocutaneous syndrome (CFCS), which are RASopathies, found in 59% of patients with thyroiditis but in none of the controls or the patients with non-thyroidal illness [68,69].

The most common cutaneous malignant tumor to have a mutation in the RAS/MAPK pathway is malignant melanoma. A recent study done by Scott et al, used parallel or Sanger sequencing for identifying various mutated genes in prenatal diagnosis. Next-generation sequencing (NGS) has found a few other genes that were altered in patients of RASopathies, but functionally they have been not validated yet. KAT6B, RREB1, and CDC42 alterations have been found to be associated with NS-like features, while a mutation in YWHAZ has been associated with cardio-facio-cutaneous syndrome (CFCS) [70].

Genetic testing in cases of unexplained aborted or sudden cardiac deaths, even in previously healthy children, can be valuable in establishing a diagnosis, determining the prognosis, and assessing risk to family members. A previously healthy infant who suffered aborted sudden cardiac death was found to have a de novo genetic mutation in the SOS1 gene, typical of Noonan syndrome. Ventricular fibrillation arrest associated with a RASopathy in the absence of the typical structural cardiac phenotypes of hypertrophic cardiomyopathy or pulmonary stenosis [71,72]. Genetic mutations that disrupt ion channel function, which are associated with inherited cardiac arrhythmias. Dysfunctional HCN4 (hyperpolarisation-activated cyclic nucleotide-gated) channels might directly cause rhythm disorders related to mutation of SCN5A (9) gene [73].

Therapeutic Options

MEK Inhibitors

The efficacy of small molecule inhibitors for the treatment of HCM associated with the RASopathies, employed knockin strategies and prenatal or postnatal treatment of the MEK inhibitor, PD0325901, successfully rescued embryonic lethality, growth, and cardiac defects in NS-associated Sos1E846K mice [74]. Interestingly, although prenatal treatment of the NS-associated KrasV14I mutant mice with PD0325901 rescued HCM, when administered postnatally, HCM was not rescued [75]. NS-associated mutant might engage distinct pathways postnatally for the progression of HCM and so treating pregnant mothers with MEK inhibitors, the failure of PD0325901 to reverse HCM postnatally is disappointing. Postnatal treatment of the NS-associated Raf1L613V mutant mice with the MEK inhibitor completely rescued HCM with accompanying improvement in cardiac functionality [76].

Trametinib, a highly selective reversible allosteric inhibitor of MEK1/2 activity, was found to reverse progressive HCM in an NS infant harboring either RITS35T or RITF82L mutation. Upon

trametinib treatment, an amelioration of the increased ventricular mass was observed, accompanied by reduced outflow tract obstruction and improved parameters of heart failure [77]. NS can be associated with severe cardiovascular and lymphatic anomalies, potentially lethal during infancy, neonatal and fetal periods and trametinib is a promising drug in these critically ill children [78].

Certain RASopathy mutants will not be responsive to MEK inhibition. The phosphatidylinositol 3′-kinase (PI3K)-AKT pathway positively regulates cardiac tissue mass and AKT activation through the mammalian target of rapamycin (mTOR) increases protein synthesis and prevents muscle atrophy and apoptosis, resulting in cardiomyocyte hypertrophy. Pharmacological studies showed that postnatal treatment of NSML-associated Pptn11Y279C/+ mice with rapamycin, a mTOR inhibitor, prevented the development of HCM and associated increase in cardiomyocyte hypertrophy due to increased AKT activity [79]. PTPN11Q510E mutation that represents a NSML RASopathy who exhibited severe HCM was treated with a mTOR inhibitor, everolimus improved heart failure and decreased the levels of the HCM marker, brain natriuretic peptide. Unlike in the Ptpn11Y279C/+ mice, everolimus treatment in this patient did not reverse the HCM, which could imply that earlier intervention prior to irreversible cardiac remodeling would have been more effective [80].

Src Family Tyrosine Kinase Pathway Inhibition by prenatal and postnatal treatment with low-dose dasatinib in mice also successfully rescued the HCM phenotype [81].

C-Type Natriuretic Peptide Analogues

Achondroplasia is caused by a gain-of-function mutation in the fibroblast growth factor receptor 3 (FGFR3) gene, a member of the tyrosine kinase family, resulting in prolonged activation of RAS/MAPK and alteration of chondrocyte proliferation and differentiation at the growth plate level. An analogue of CNP that is resistant to proteolytic degradation (BMN111/vosoritide; BioMarin) significantly improved growth plate abnormalities and bone growth by reducing RAS/MAPK activation [82].

Statins

Statins were first investigated in the treatment of cognitive impairment in NF1 and lovastatin was shown to improve synaptic plasticity as well as attention and memory in NF1 patients, but not with simvastatin [83-85]. Although they are contraindicated during pregnancy, the clinical effects of statins in pregnant women through an interactive review by the analysis of fifteen original articles within five years demonstrate that statins have not been associated with the development of fetal malformations and it is useful in preventing unfavorable cardiovascular outcomes, with the potential to reduce oxidative stress and angiogenic dysfunction [86]. However, the use of statins to prevent pre-eclampsia in humans has not been properly clarified. Statins may be safe when used during pregnancy since there was no association with congenital anomalies, but caution is needed because of an increased risk of low birth weight and preterm labor [87,88].

An important issue is the optimal age for starting treatment. In several animal studies, MEK (Mitogen-Activated Protein Kinase) inhibitor treatment was initiated during embryonic development (by exposing the pregnant mothers to the MEK inhibitor) and continued after birth. MEK inhibition prevented the various developmental defects (i.e. craniofacial, cardiac, and growth defects) when started prenatally, whereas this treatment did not ameliorate these defects when started after weaning [89]. Another issue is the duration of treatment and therapy aimed at allowing normal growth and cognitive development should probably be maintained throughout childhood.

Gene Editing

In utero gene editing has the potential to treat genetic diseases prenatally. Clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR-associated 9 (CRISPR-Cas9) or base editor 3 (BE3) in utero, seeking therapeutic modification of Pcsk9 or Hpd in wild-type mice or the murine model [90]. Intronic CRISPR repair is a therapeutic strategy to treat NS (Noonan Syndrome)-associated hypertrophic cardiomyopathy [91]. A CRISPR-based epigenetic repression system downregulating MAP2K1 and MAP2K2 expression for the treatment of RASopathies was proposed in animal models [92].

Discussion

In utero manifestations of RASopathies are less well characterized and approximately half of RASopathy variants being inherited in postnatal series [93]. The Noonan syndrome has been well established in its association with NIHF (Nonimmune hydrops fetalis), defined by the presence of fetal ascites, pleural or pericardial effusions, skin edema, cystic hygroma, increased thickness of nuchal translucency (≥3.5 mm), or a combination of these conditions. Pregnant women with fetuses that have NIHF are also at risk for complications resulting from a form of preeclampsia called mirror syndrome [94,95]. Some genetic disorders underlying NIHF portend mild long-term outcomes, whereas others are lethal despite treatment [96,97]. Increased index of suspicion of Costello syndrome (CS) in newborn is shown in Table 2.

Table 2: Features to Suspect CS in Newborn

1.	**Fetal atrial tachycardia**
2.	**Increased birth weight and head circumference**
3.	**Neonatal hypoglycemia**
4.	**severe feeding difficulties**
5.	**Urinalysis for hematuria – embryonal rhabdomyosarcoma**
6.	**Loose, redundant skin on the hands and feet seen in newborns – key role in clinical suspicion of CS**

Prenatal diagnosis of HCM is critical, as it enables the clinicians to anticipate potential complications such as LVOTO (Left ventricular outflow tract obstruction), arrhythmias, and heart failure, which may manifest shortly after birth [98]. Interventricular septal thickness measured during fetal life is a reliable predictor of postnatal outcomes, with a threshold of ≥4.5 mm is associated with higher risk of perinatal morbidity and mortality [99]. Long-term outcomes of fetal HCM are influenced by underlying etiology. Parasternal long axis view showing “ventriculomegaly” (massive RVH and LVH) as shown in Figure 9 is well tolerated in a 9-year-old boy with Costello syndrome as in Figures 10 and 11 with increased RV pressure as in Figure 12

due to increased capillary growth along with the hypertrophied muscle [100-102].

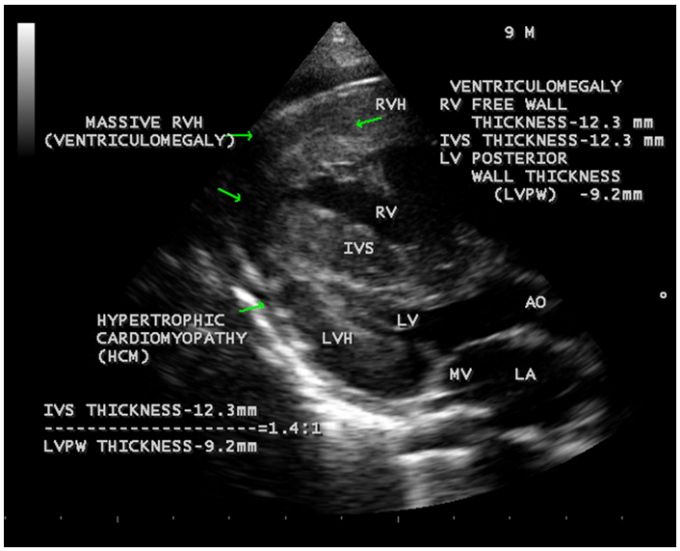

Figure 9: Showing Biventricular Hypertrophy (Ventriculomegaly) in a 9-Year-Old Boy with Costello Syndrome

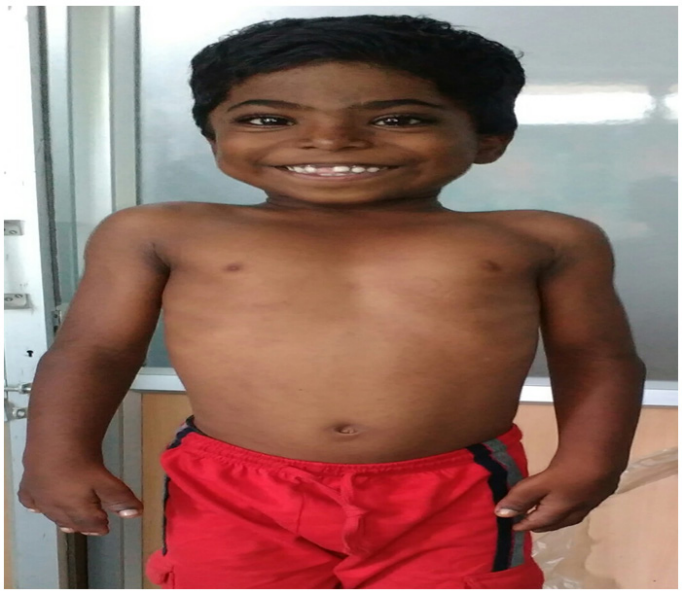

Figure 10: Radiant Smile, Warm, Sociable Personality and Skin Folding below the Lower eyelids of Costello Syndrome in a 9-Year-Old Boy

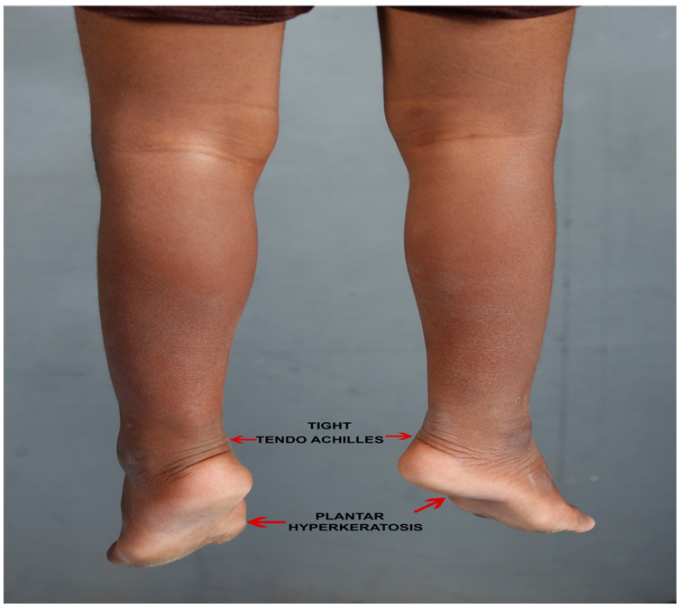

Figure 11: Tight Tendoachilles and Plantar Hyperkeratosis in a 9-Year-Old Boy with Costello Syndrome

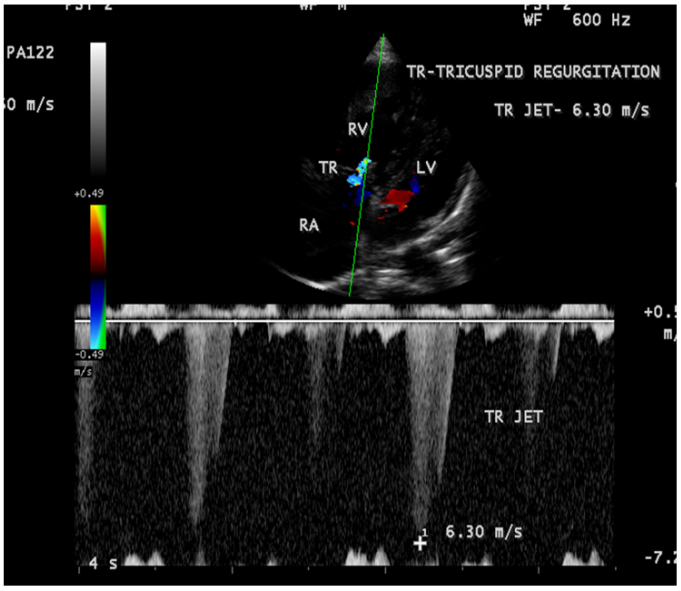

Figure 12: Apical 4 Chamber View – CW Doppler showing High Velocity TR (Tricuspid Regurgitation) Jet with Early Peaking Suggesting High RV Pressure at Suprasystemic Levels-165 mmHg

Conclusion

Rasopathy testing is recommended when the fetus shows an isolated increased NT ≥5.0 mm or when NT of ≥3.5 mm and at least one of the following ultrasound anomalies is present: distended JLS (Jugular Lymphatic Sacs), hydrops fetalis, polyhydramnios, pleural effusion, ascites, cardiac defects and renal anomalies [103]. Invasive prenatal testing is proposed for fetuses with NT values above 2.5 mm. Rapid screening for chromosomal aneuploidy (13, 18, 21, X, and Y), chromosomal microarray (CMA), and sequencing of the genes involved in Noonan syndrome and RASopathies are routinely performed. Whole genome sequencing identified two compound heterozygous variants in the NUP107 gene in fetuses [104]. Rigosertib, a novel dual Ras/MAPK and PI3K/AKT pathway inhibitor, reverses Hypertrophic

Cardiomyopathy in RAF1-Associated Noonan Syndrome [105]. The MEK inhibitor trametinib was an effective drug therapy for cardiac hypertrophy in NS mice with heterozygous LZTR1 (Leucine-zipper–like posttranslational regulator 1) mutation [106]. More than half of the RASopathy cases in utero manifests during the first trimester and a cutoff value of NT ≥ 6 mm missed 45% of cases during this period. Exome sequencing is a preferable option due to its efficiency within the limited timeframe in prenatal settings [107].

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