CASE REPORT

Noonan Syndrome With Tuberous Sclerosis Complex; A Rare Co-occurrence

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ABSTRACT

Noonan Syndrome (NS) and Tuberous Sclerosis Complex (TSC) are rare genetic disorders with distinct clinical manifestations. NS is characterized by facial features, developmental delays, short stature, congenital heart defects, and renal abnormalities. Mutations affecting the RAS-MAPK pathway are responsible for NS. Meanwhile, TSC is a neurocutaneous disease, typically present with seizures, intellectual disability, and angiofibroma. TSC is caused by mutations in TSC1 and TSC2 genes, leading to inhibition of the mTOR signalling cascade. We would like to present a rare instance of a 4-year-old girl who was initially diagnosed with NS, later also found to have features of TSC, subsequently confirmed by mutation of PTPN11 - c.922A>G (p.Asn308Asp) and TSC2 - c.3693_3696del (p.Ser1232Thrfs*92). The intricate interaction between the RAS–MAPK and mTOR pathways, involving shared upstream signalling, convergence on AKT as a common effector, and the role of RAS proteins in PI3K activation, may underlie the observed clinical manifestations.
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Keywords: Noonan syndrome, Tuberous sclerosis complex, Genetic disorder, Neurocutaneous disease

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INTRODUCTION

Noonan Syndrome (NS) is a genetic multisystem disorder distinguished by distinct facial features, developmental delays, short stature, congenital heart defects and renal abnormalities. The mutations responsible for NS affect genes that encode proteins involved in the RAS-MAPK pathway, resulting in the dysregulation of this pathway. It is inherited as an autosomal dominant trait, with an incidence of one in 1,000 to 2,500 children (1). Comparatively, tuberous sclerosis complex (TSC) is a rare neurocutaneous disease with a classical triad of seizures, intellectual disability, and angiofibroma. However, this combination is observed in just 29% of TSC patients. TSC is caused by mutation of TSC1 and TSC2 gene; TSC1 on chromosome 9 encoding hamartin, and TSC2 on chromosome 16 encoding tuberin. This genetic mutation will cause loss of inhibition of the mammalian target of rapamycin (mTOR) signalling cascade (3). According to epidemiologic studies, TSC prevalence varies between one in 6,000 to 12,000 individuals and does not vary based on gender or race, although the symptoms tend to be milder in women (3). To the best of our knowledge, the pathogenesis of NS and TSC seems to be distinct. Here, we reported a very rare case of a 4-year-old-girl initially followed up for NS and later also diagnosed to have TSC after developing a series of seizures and distinctive skin features, which was further confirmed by genetic study.

CASE REPORT

A 4-year-old girl, the only child of a non-consanguineous marriage, was born at term with a birth weight of 2.8kg and normal anthropometry (15th–50th percentile). She experienced growth failure after three months old, dropping below the 3rd percentile (-2SD) (Figure 1). At 2.5 years, she presented with unprovoked seizures. Clinically, she had a thin build, short stature, dysmorphic features (relative macrocephaly, triangular facies, prominent forehead, downslanted eyes with ptosis, hypertelorism, epicanthal folds, micrognathia, low-set ears) (Figure 2), and neurocutaneous lesions (hypopigmented skin lesions, Ash-Leaf macule, Shagreen patches) (Figure 3). Systemic examinations were unremarkable.

Interictal EEG showed occasional polyspike wave discharges over the left frontal region, and brain MRI revealed subcortical nodules and subependymal nodules (Figure 4). Echocardiogram and cardiac MRI were normal, with no cardiac masses or pulmonary valve stenosis. Additional screenings (chest radiograph, abdominal ultrasound, hearing, ophthalmological assessments) were unremarkable.

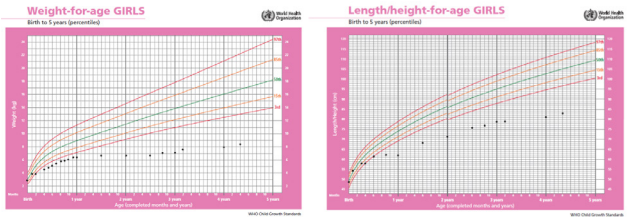

Figure 1: Growth chart of the patient

Figure 2: Facial features of the patient showing features of NS

Next generation sequencing (NGS) identified few genetic mutations; PTPN11 - c.922A>G (p.Asn308Asp), TSC2 - c.3693_3696del (p.Ser1232Thrfs*92), and PTS - c.166G>A (p.Val56Met), which fits into patient's phenotype for NS and TSC. Parental testing showed the father is only a carrier for the PTS gene mutation, while the mother is negative for any genetic mutations.

DISCUSSION

In NS, the most common genetic mutations are PTPN11(50%), SOS1(10%), RAF1(10%), and less than 1-2% for KRAS and NRAS. Other mutations include BRAF, MEK2, RRAS, RASA2, A2ML1, SOS2, SHOC2 and CBL genes. Studies suggest that 50% of cases of NS are caused by missense, gain of function mutation in PTPN11; a gene located on chromosome 12 (1).

TSC is an autosomal dominant disorder, but around two-thirds of the cases are sporadic (3). Among familial cases of TSC, there is an equal distribution of mutations among TSC1 and TSC2. While, among the sporadic cases, TSC2 mutations are much more frequent than TSC1 mutations. On average, sporadic patients with TSC2 mutations have more severe disease and organ involvement with a significantly earlier presentation of epilepsy compared to TSC1 mutations.

Majority of NS patients possess at least one cardiovascular involvement throughout their life; in which about 80% are classified as congenital heart disease (CHD) while the rest are hypertrophic cardiomyopathy (HCM). The commonest CHD manifested includes pulmonary valve stenosis (PVS) as high as 40%, followed by atrial

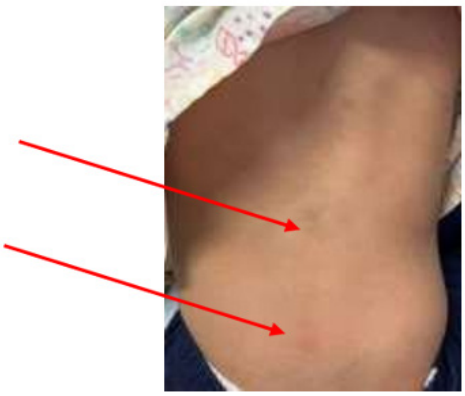

Figure 3: Patient's back showing Ash-Leaf macules and Shagreen patch

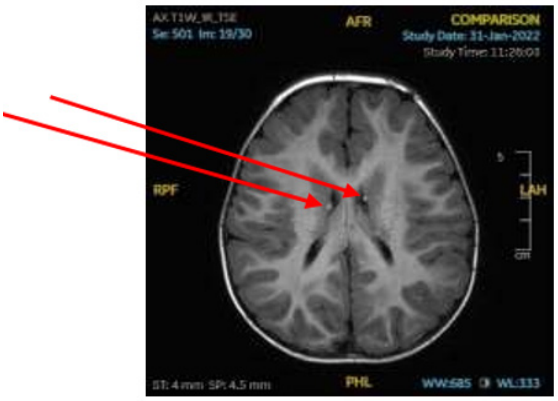

Figure 4: MRI brain (axial T1W) showing subependymal nodules

(8%) or ventricular septal defect, as well as atrioventricular canal defects (AVCDs) (2).

As for TSC, cardiac rhabdomyomas are seen in approximately 50% of children with TSC (3). Rhabdomyomas can enlarge significantly in size later in gestation, possibly because of the influence of maternal hormones during pregnancy. Majority remain asymptomatic, but they can be clinically significant depending on their location and size, and they tend to occur as multiple in numbers in 90% of cases. Large majority of patients with cardiac rhabdomyomas regress spontaneously during the first year of life, showing a decreasing frequency in patients with TSC after 2 years of age (3). As in our case, she remains asymptomatic of heart condition.

Patients with Noonan syndrome (NS) typically present with characteristic craniofacial features such as a short neck, low-set ears, epicanthal folds, hypertelorism, ptosis and a low posterior hairline, often accompanied by cardiac involvement including pulmonary valve stenosis and hypertrophic cardiomyopathy; neurodevelopmental impairment is usually mild to moderate with developmental delay and intellectual disability, and seizures are uncommon. In contrast, tuberous sclerosis complex (TSC) is characterised by distinctive cutaneous manifestations (hypomelanotic macules, facial angiofibromas, ash-leaf macules and shagreen patches), frequent central nervous system involvement with seizures,

developmental delay, cognitive impairment and autism spectrum disorder, as well as multisystem tumour formation (hamartomas) affecting organs such as the brain, heart, kidneys, lungs and retina. (3).

The co-existence of these two genetic disorders in one individual raises question about the potential interactions between the RAS-MAPK pathway in NS, and the mTOR pathway involved in TSC. The RAS-MAPK and mTOR are genetically interconnected at multiple levels (Figure 5). Firstly, both pathways are regulated by similar upstream signals like growth factors, nutrients, and cellular stress. Dysregulation in these upstream signals can lead to the activation of both pathways, contributing to tumorigenesis and developmental abnormalities. Secondly, both pathways share a common effector which is AKT. AKT is activated by RAS and, in turn, activates mTORC1 by inhibiting the TSC1/TSC2 complex. This creates a feedback loop between the RAS and mTOR pathways. AKT acts as a point of integration between these pathways, influencing cellular growth, survival and metabolism. Thirdly, RAS proteins can activate PI3K, which then activates AKT, an upstream activator of mTORC1. Thus, RAS signalling can both directly and indirectly stimulate mTOR activity through the PI3K-AKT-mTOR axis. Conversely, dysregulated mTOR due to mutations in TSC1/TSC2, might influence feedback loops that affect RAS-MAPK signalling. This biological crosstalk suggests that perturbations in one pathway could predispose or exacerbate dysfunction in the other (4).

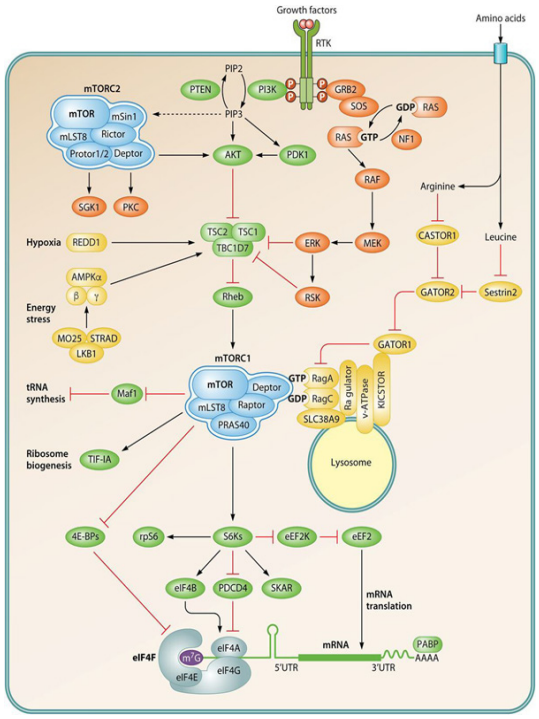

Figure 5: Schematic representation of signaling pathways regulating mRNA translation. Reproduced from Roux PP, Topisirovic I. Signaling Pathways Involved in the Regulation of mRNA Translation. Mol Cell Biol. 2018;38(12):e00070-18, published by the American Society for Microbiology, licensed under CC BY 4.0.

These two signalling pathways are both central to regulating cell growth, differentiation, survival, and metabolism. Dysregulation of these pathways at any genetic or molecular level can lead to disease manifestation, and influence one another, like NS and TSC as in our patient. On the other note, the interaction of RAS-ERK and PI3K-mTOR pathways can be explained by a few different possible mechanisms, mainly the negative feedback loop, cross-inhibition, cross-activation and pathway convergence. The strength of the stimulus and feedback loop regulate the intensity and duration of pathway activation. Only partial overlap of the agonists involved in the RAS-ERK activation with those that signal to PI3K-mTORC1 (5).

CONCLUSION

This case represents a rare co-occurrence of NS and TSC in a single individual, likely related to de novo mutation with atypical absence of cardiac involvement. This highlights the complex genetic interactions between the RAS-MAPK pathway in NS, and the mTOR pathway involved in TSC, which may contribute to variable phenotypic expression. Further studies at the molecular and genetic level are thus recommended.

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