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Case Report Open Access

Noonan Syndrome and Systemic Lupus Erythematosus: Association or Risk Factor?

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Abstract

Aim: The *RAS/MAPK* signaling pathway proteins with germline mutations in their respective genes are associated with several disorders such as Noonan, LEOPARD, neurofibromatosis type 1, Costello and cardio-facio-cutaneous syndromes. Some monogenic conditions are associated with the development of systemic lupus erythematosus (SLE), in medical literature are few reports that describe the association of *RAS* opathies and autoimmune disease. Our aim was to describe the clinical picture of a patient with diagnosis of Noonan and SLE.

Methods: We report a clinical case of a 24-year-old woman with Noonan syndrome who developed SLE according to American College of Rheumatology criteria for the classification of SLE. The patient had arthritis, serositis, lymphopenia, proteinuria, high levels of antinuclear antibodies and anti-ds DNA positive. This rare association then driven to search the medical literature for English articles on the subjects of Noonan and SLE in Pubmed.

Results: Our patient had oligoarthritis, serositis, lymphopenia, ISN/RPS Class IV lupus nephritis, ANA 1:1280 homogeneous pattern and anti-dsDNA antibodies very similar to the 8 patients already reported in literature.

Conclusion: There are nine cases reported with the association of two rare diseases, Noonan syndrome and SLE, this connection could suggests that *RAS* opathies may be a risk factor to the development of autoimmune disorders.

Introduction

In 1962, Jacqueline Noonan, a pediatric cardiologist, presented at the Midwest Society for Pediatric Research a clinical study describing nine patients who shared distinctive facial features including hypertelorism, downslanting palpebral fissures, low set posteriorly rotated ears, ptosis and malar hypoplasia. In addition short stature, pulmonary stenosis, cryptorchidism and chest deformities were observed. A few years later, in 1968, Dr Noonan published additional 10 patients descriptions being the first to indicate that this disorder associated with congenital heart defects occurred in both genders, was associated with normal chromosomes [1].

Noonan syndrome (NS) is a relatively common congenital genetic disorder with an estimated prevalence of 1 in 1000 to 1 in 2500 live births. It is an autosomal dominant disorder with complete penetrance but variable expressivity. Until recently, diagnosis was based solely on clinical findings, but a genetic mutation is identifiable in 61% of the patients [2].

NS is genetically heterogeneous, and nine genes that participate in the rat sarcoma/mitogen-activated protein kinases (*RAS/ MAPK*) pathway (*PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF, SHOC2, MEK1* and *CBL*) have been causally linked to this trait or closely related conditions. These diseases have been grouped into a single family, which has been termed the neuro-cardio-facial-cutaneous syndrome family (or, alternatively, the *RAS*-opathies) [3].

Systemic lupus erythematosus (SLE) is the prototypic systemic autoimmune disease characterized by heterogeneous, multisystem involvement and the production of an array of serum autoantibodies. Clinical features in individual patients can be quite variable, ranging from mild joint and skin involvement to severe, life-threatening internal organ disease. In the last decade, several studies support the role of multiple susceptibility genes in the development of SLE [4].

The association of NS and autoimmune disorders, such as thyroiditis, vasculitis, vitiligo, celiac disease or anterior uveitis, and SLE has been reported in isolated cases or case series in the past decades [5,6].

As far as we know there are eight reported patients with NS and SLE in the literature, we report the case of a young woman with a concomitant diagnosis of NS and LES serving to further investigations to identify an increasingly recognizable association between NS and other autoimmune diseases including SLE.

Case Report

A 24-year-old woman was admitted to the Internal Medicine Department for the management of anemic syndrome. Three months before admission she presented hiporexia, headache and exertional dyspnea, intermittent fever and a loss of 22 pounds (about 10 kilograms) was estimated since the beginning of her symptoms. Two weeks before admission bilateral knee pain, ankle oadema, dry cough and progressive dyspnea reaching minimal efforts appeared. At admission severe anaemia (Hb 6.71 gr/dL) and leucopenia (2860 cels/mm^3) were observed and prompted a peripheral blood and blood marrow aspirate examination by the hematology department, founding mild global hypocellularity, leucopenia and granulocytic hypoplasia, and also

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notice the presence of LE cells in both direct marrow and peripheral blood smears. A serological test for HVI, hepatitis B and C viruses were negative.

A Rheumatologist assessment was requested because of anemia, lymphopenia, bilateral knee arthritis and the presence of LE cells. The patient was a previously healthy young pleasant woman. The family history did not reveal any known genetic or rheumatologic disorder. The past medical history also reveals hair loss during the last three months but no other dermatologic lesion was observed by the patient. In addition to moderate painful arthritis of the knees, the physical examination was relevant to demonstrate multiple phenotypic traits and a Geneticist evaluation was also requested. No similar phenotypical abnormalities were observed in parents or first degree relatives through direct observation or by photography means. She was born from a nine-month normal fifth pregnancy by vaginal delivery. The growth and development was normal, with secondary sex characteristics and menarche appearances at the usual age. No intellectual disabilities were observed, although not tested, the patient appeared to have normal intelligence. The physical examination reveals short stature (with <3 centile of height achieved at age 19 years recorded in a vaccine-immunization schedule), slightly curly hair with a high hairline giving the appearance of a broad forehead, mild low-set ears implantation, sparse eyebrows, bilateral telecanthus with no deviation of the palpebral fissure, mild bilateral ptosis, broad short neck with mild bilateral neck-webbing, deep groove philtrum, high arched palate, micrognatia, absent uvula and lingual frenulum and crowded teeth. The nipples appears widely spaced and a chest roentgenogram shown a moderate pectus excavatum. No morphological abnormalities were apparent in the upper and lower extremities, or genitalia. An electrocardiogram shown sinus tachycardia and left axis deviation. A transthoracic echocardiography reported mild mitral and tricuspid insufficiency with mild pulmonary arterial hypertension and small pericardial effusion without hemodynamic repercussion. A chromosomal analysis demonstrated a normal 46 XX karyotype and the diagnosis of Noonan syndrome was made on the basis of clinical findings according to the criteria proposed by van der Burgt et al. [7]. At the same time an extensive laboratory assessment was taken (Table 1). Posteroanterior chest X-ray shown bilateral pleural effusion with posterior aspirate liquid analysis being exudative one.

The patient was diagnosed with SLE according to the American College of Rheumatology classification criteria (arthritis, serositis, lymphopenia, proteinuria greater than 0.5 gr per day, high levels of antinuclear antibodies and anti-ds DNA) [8]. We performed real-time ult*RA*Sound-guided renal biopsy revealing Class IV International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification lupus nephritis [9]. The patient was treated with 1000 mgs metylprednisolone pulses for three consecutive days followed by prednisone 1 mg/kg/day with tapered indication after few weeks plus 0.75 g/m^2 of cyclophosphamide on day one. The blood cell count started to rise soon after the treatment has begun and the pleural effusions resolved without any other particular treatment. The patient is actually receiving monthly high dose cyclophosphamide.

Discussion

The heterogeneous clinical features of NS are characterized by distinctive facial features, short stature, chest deformity, congenital heart disease, other malformations and variable levels of mental retardation. It is important to notice that even when the phenotype becomes very striking in early childhood, with advancing age, it may again become quite subtle [2]. The variable phenotypic expression and correlation between disease phenotype and genetic heterogeneity have been well established and less severe cases may go unnoticed for many years as in our reported patient.

The first evidence for autoimmunity in patients with NS was described by Vesterhus et al. who reported an increased prevalence of autoimmune thyroiditis in patients with NS [10]. Since the first report of NS and SLE in a 20-year-old patient was reported by Martin et al. [11] some other reports for this association has been recognized in the last decade (Table 2). A slightly predominance of female patients with NS and LES (5 female/4 male) has been observed which is below the female-to-male ratio reported in children, adults, and older people.

Variable	During Hospitalization	Reference Range
White-cell count (per mm^3)	2860	4500-1000
Lymphocytes (%)	16	22-44
Hemoglobin (g/dl)	6.7	12.0-16
Platelet count (per mm^3)	234,000	150,000-400,000
Erythrocyte sedimentation rate (mm/hr)	18	1-20
C-reactive protein (mg/dl)	0.5	<1.0
Haptoglobin (mg/dl)	12	30-200
Direct Coomb Test	Positive 3 +	Negative
Aspartate aminotransfe*RA*Se (U/liter)	97	9-32
Alanine aminotransfe*RA*Se (U/liter)	32	7-30
Lactate dehydrogenase (U/liter)	1000	110-210
Complement C3 (mg/dl)	49	88-200
Complement C4 (mg/dl)	6.4	12-70
Rheumatoid Factor	Negative	Negative
Urine protein 24 hr	980	<150 mg/24 hr
Antinuclear antibody (Hep2 cells substrate)	1:1280 homogenous pattern	Negative at 1:40 dilution
Anti-double-stranded DNA (UI/ml)	42	<5.5
Anti-thyroid peroxidase antibodies (UI/ml)	1850	<5
Anti-thyroglobulin antibodies (IU/ml)	340	0-100
Thyrotropin (μU/ml)	4.4	0.5-4.7
Thyroxine (free) (ng/dl)	2.2	0.8-2.8

Table 1: Laboratory Data.

Sex	Age at NS diagnosis/SLE onset	Noonan Syndrome Features	SLE features	Other autoimmune manifestations	Affected Gene	Reference
F	24 y / 24 y	Short stature, facial dysmorphism, cardiac abnormalities	Oligoarthritis, serositis, lymphopenia, ISN/RPS Class IV lupus nephritis, ANA 1:1280 homogeneous pattern and anti-dsDNA Ab	Anti-TPO and anti thyroglobulin Ab	NT	Present Case
M	10 y / 13 y	Short stature, facial dysmorphism, darkly pigmented skin and sparse hair	Polyarthritis, serositis (pericardial), ANA 1:800, positive anti-ds DNA Ab and lupus anticoagulant	Massive lymphadenopathy and hepatosplenomegaly	SHOC2	Bader-Meunier B et al (Ref 13)
F	Not reported / 32 y	Not reported	Photosensitivity, arthritis, lymphopenia and ANA 1:320 homogeneous pattern	Autoimmune hypothyroidism	*PTPN11*	Quaio CR et al (Ref 16)
F	3 y / 18 y	Short stature, facial dysmorphism, pectus excavatum, hypertrophic cardiomyiopathy, psychomotor retardation.	Polyarthritis, papillary *RAS*h on lower limbs, Coombs positive hemolytic anemia, lymphopenia, thrombocytopenia. ANA >1:40, high anti dsDNA Ab and IgM anticardiolipin.	None	K*RAS*	Leventopoulus G et al (Ref 28)
M	Not reported / 28 y	Short stature, facial dysmorphism, pectus excavatum, pulmonary valve stenosis, bilateral cryptorchidism	Polyarthritis, lymphopenia, serositis (pericardial), ANA 1:640 speckled pattern	Autoimmune primary hypothyroidism	NT	Lisbona MP et al (Ref 27)
F	3 ½ y / 5 y	Short stature, facial dysmorphism, shield-like chest with mild pectus, multiple long bone deformities, mild septal cardiac thickening, cognitive function in the low borderline range	Arthritis, serositis, thrombocytopenia, Coombs positive hemolytic anemia, WHO Class IV lupus nephritis, ANA 1:1260, raised anti-dsDNA Ab and IgG anticardiolipin Ab.	None	*PTPN11* test was negative. Rest NT.	Lopez-Rangel E. et al (Ref 26)
M	8 y / 8 y	Short stature, facial dysmorphism, short webbed neck, joint hiperextensibility, pulmonary valve stenosis, mild mental retardation	Arthritis, oral ulcers, thrombocytopenia, ANA 1:40, anti-dsDNA Ab, elevated IgG anticardiolipin Ab, WHO Class I lupus nephritis	None	NT	Alanay Y et al (Ref 25)
F	Infancy / 26 y	Short stature, facial dysmorphism, pectus carinatum, cardiac abnormalities, hepato – esplenomegaly, epilepsy, mental retardation	Artharlgias, lymphopenia, hemolytic anemia, ANA 1:640 homogeneous pattern, positive anti-dsDNS Ab, anti-SM, Lupus anticoagulant and IgG and IgM anticardiolipin Ab	Autoimmune thyroiditis, celiac disease.	NT	Amoroso A et al (Ref 6)
M	20 y / 17 y	Short stature, facial dysmorphism, pectus excavatum, poorly developed secondary sexual characteristics, mitral valve disease.	Polyarthritis, oral ulcers, serositis (pericardial and pleural), renal insufficiency, ANA 1:2560 peripheral pattern.	None	NT	Martin DM et al (Ref 11)

SLE: Systemic Lupus Erythematosus; ANA: Antinuclear Antibodies; Anti-dsDNA: Anti-double strained DNA; Ab: Antibodies; Anti-TPO: Anti Thyroid Peroxidase; ISN/RPS: International Society of Nephrology/Renal Pathology Society; NT: Not Tested

Table 2: Description of Noonan syndrome patients with associated SLE diagnosis.

The age at SLE onset in the published cases including our patient has been in the range of 5-26 years and in six patients the diagnosis was made in the peak incidence age reported for SLE (sixty-five percent of patients with SLE have disease onset between the ages of 16 and 55) [12]. In almost half of the reported cases lupus nephritis was observed. In one case a WHO Class I lupus nephritis was observed which is rarely, if ever, diagnosed because these patients typically have a normal urinalysis, no or minimal proteinuria, and a normal serum creatinine. In the remaining two patients with biopsy proven lupus nephritis including our case, diffuse glomerulonephritis were observed (WHO class IV or ISN/RPS class IV) which is the most common and most severe form of lupus nephritis. Antinuclear antibodies can produce different staining patterns reflecting the presence of antibodies to one or some nuclear antigens. The homogeneous staining was the most prevalent pattern observed in three patients including the present case. The homogeneous pattern reflects antibodies to the DNA-histone complex. It is believed that these antibodies are responsible for the LE phenomenon which was observed in the present case and prompted to an early diagnosis of SLE. In a recent article, Bader-Meunier et al. [13] pointed out that SLE observed in patients with *RAS* opathies may differ from "classic" SLE in part because of the high frequency of pericarditis (4/8 patients) observed in the former cases. Pericardial involvement in the form of effusion occurs in over 50% of SLE patients at some point of the disease. Pericarditis may be the initial manifestation in SLE patients but pericardial disease is usually asymptomatic. It is generally diagnosed by echocardiography performed for some other reason, such as suggestive electrocardiographic abnormalities or because as in the present case, a high prevalence of cardiac abnormalities observed in NS patients [14].

Interestingly a growing number of cases linking autoimmune disorders other than SLE with NS have been described including: celiac disease, vitiligo, autoimmune thyroiditis, anterior uveitis and antiphospholipid syndrome [5,6,15]. In a recent large cohort of NS patients and related disorders evaluated for autoimmune disases and multiple antibodies reported by Quaio et al. a high prevalence of autoimmune diseases (14%) fulfilling specific criteria including SLE, autoimmune thyroiditis, celiac disease, primary antiphospholipid syndrome, autoimmune hepatitis and vitiligo were reported. This represents a two to threefold increase in frequency when compared with normal population (5-8%). They also observed autoimmune antibodies in 52% of the patients without clinical findings correlation in some patients [16]. In the present case high levels of antinuclear antibodies and anti-DNA were founded and we can classify the patient as having SLE according to ACR criteria. Anti-thyroglobulin and anti-thyroid peroxidase antibodies have been detected in 20% and 10% of NS patients with an increased prevalence in older age [10]. Three of the previously 8 reported patients with NS and SLE has autoimmune hypothyroidism. In the present case we founded high levels of thyroid autoantibodies without clinical or functional correlation until now. We suggest that patients with NS and SLE show be monitored regularly for autoimmune thyroiditis.

Eight genes in the *RAS-MAPK* signalling pathway cause Noonan syndrome or closely related conditions. (*PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF, SHOC2*, and *CBL*). In 50% of cases, Noonan syndrome is caused by missense, gain of function mutations in the *PTPN11* region which encodes the protein SHP2 and has been linked to the chromosomal band 12q24.1. [17]. At least 107 *PTP* family members has been recognized and their function (dephosphorylate tyrosine residues) is a key regulatory mechanism for numerous physiological processes, including many that are crucial for the immune system. Severe phenotypes are also observed in many *PTP* knock-out mice, and in many cases, the immune system is affected. The SHP2 enzyme has positive role in lymphocyte activation, augments *ERK* activation that is crucial for lymphoid development [18]. Among other functions the product of *PTPN11* is important for the maintenance of resting lymphocytes and regulation of the transcription factor NF-kB, which plays a fundamental role in antibody production and natural killer cells activation [19].

The humoral and cellular immunities play roles in SLE pathogenesis. Many clinical features of SLE result from loss of B-cell tolerance, leading to the development of autoantibodies targeting self-antigens to induce tissue damage. A genetic contribution to human lupus is well established. The strong genetic contribution to the development of SLE is supported by the high heritability of the disease (>66%), a higher concordance rate for SLE in monozygotic twins than in dizygotic twins or siblings (24–56% versus 2–5%, respectively) which was observed over 30 years ago, and the high sibling recurrence risk ratio of patients with SLE (between eightfold and 29-fold higher than in the general population) and up to 10% of SLE patients have a relative with lupus [20]. Another *PTP* family member, *PTPN22* is a negative regulator for T-cell signal transduction in cellular immunity. It is considered to be the strongest common genetic risk factor for human autoimmunity besides the major histocompatibility complex (MHC) and as an important candidate gene in SLE [21].

Several studies have founded single nucleotide polymorphisms associated with SLE, but only about 15% of the heritability of SLE to be explained by those loci. Some rare monogenic disorders has been associated with a high risk of SLE, especially pediatric-onset SLE including Aicardi-Goutieres syndrome, spondylenchondrodysplasia, congenital complement deficiencies, chronic granulomatosis disease and a null mutation in the *DNASE1L3* gene in the Arab population [22].

Besides *PTPN22* known association with autoimmunity, the high frequency of autoimmunity and alterations in the level of immunoglobulins observed in patients harbouring mutations in *PTPN11* may, as suggested by Quaio et al. the involvement of other *PTP*Ns, an association that needs to be confirmed [16]. Several studies in animal and human immunologic models have pointed to the complex role of *RAS/MAPK* signaling pathway in general immunity. *RAS* is a GTP-binding protein that plays multiple roles in the proliferative and inflammatory responses crucial for the maintenance of immune tolerance. Even when the product of *PTPN11*, SHP2 has not been reported to be associated with autoimmune diseases, SHP-2 acts as a regulator of NF-Kappa B activation, and in concert with SHP1 inhibits NK cell activation, it is possible that mutations of *PTPN11* as the observed in NS could contribute to the development of autoimmunity [23]. Linkage analysis on SLE susceptibility loci has been reported including gene mutations in *PTPN11* at the 12q24 locus in Hispanic and European American families [24].

Noonan syndrome is a relatively common autosomal dominant disorder, which makes very likely that most doctors will encounter NS patients during their career, a diagnosis that might be overlooked because presentation can be mild and phenotypical traits can be subtle with age. The association between NS and SLE and other autoimmune diseases has been described in a few cases in the medical literature. The understanding of the molecular genetics causes of NS has experienced enormous progress in the past decade recognizing mutations in the *RAS/MAPK* as the signaling system involved in NS. T lymphocytes play a critical role in SLE pathogenesis. Since *RAS* is an essential protein for normal T lymphocyte function, it is not surprising that dysregulated *RAS* signaling participates in the genesis of autoimmune diseases reported in patients with *RAS* opathies including NS and related disorders. The hypothesis of a common origin is strengthen for the linkage of a susceptibility gene for SLE to an area that is also directly involved in the occurrence of *RAS* ophaty, although no definite study has yet been performed. Until that happens clinicians should be alert about the molecular mechanisms that underlies *RAS* opathy may predispose to the development of SLE.

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