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, downsllanting 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 autoimmmune 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 hypoxemia, 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 oedema, dry cough and progressive dyspnea reaching minimal efforts appeared. At admission severe anaemia (Hb 6.71 gr/dL) and leucopenia (2860 cels/mm3) were observed and prompted a peripheral blood and blood marrow asparate examination by the hematology department, founding mild global hypocellularity, leucopenia and granulocytic hypoplasia, and also...
notice the presence of LE cells in both direct marrow and peripheral blood smears. A serological test for HIV, 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-sparing. The nipples appears widely spaced and chest roentgenogram shown a moderate 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.

### Table 1: Laboratory Data.

| Variable                           | During Hospitalization | Reference Range |
|-----------------------------------|-----------------------|-----------------|
| White-cell count (per mm³)        | 2860                  | 4500-1000       |
| Lymphocytes (%)                   | 16                    | 22-44           |
| Hemoglobin (g/dl)                 | 6.7                   | 12.0-16         |
| Platelet count (per mm³)          | 234,000               | 150,000-400,000|
| Erythrocyte sedimentation rate (mm/hr) | 18                  | 1-20            |
| C-reactive protein (mg/dl)        | 0.5                   | <1.0            |
| Haploglobin (mg/dl)               | 12                    | 30-200          |
| Direct Coomb Test                 | Positive 3 +          | Negative        |
| Aspartate aminotransferase (U/liter) | 97                   | 9-32            |
| Alanine aminotransferase (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 (U/ml)   | 42                    | <5.5            |
| Anti-thyroid peroxidase antibodies (U/ml) | 1850              | <5              |
| Anti-thyroglobulin antibodies (U/ml) | 340                   | 0-100           |
| Thyrotropin (U/ml)                | 4.4                   | 0.5-4.7         |
| Thyroxine (free) (ng/dl)          | 2.2                   | 0.8-2.8         |

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.
patients but pericardial disease is usually asymptomatic. It is generally of the disease. Pericarditis may be the initial manifestation in SLE the form of effusion occurs in over 50% of SLE patients at some point pointed out that SLE observed in patients with an early diagnosis of SLE. In a recent article, Bader-Meunier et al. [13] case. The homogeneous pattern reflects antibodies to the DNA-histone prevalent pattern observed in three patients including the present or some nuclear antigens. The homogeneous staining was the most 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 RASopathies 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 diseases and multiple antibodies reported by Quaio et al. a high prevalence of autoimmune diseases (14%) fulfilling specific criteria including SLE, antiphospholipid syndrome [5,6,15]. In a recent large cohort of NS patients [14].

| 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 Thyrogblobulin 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 | Quiao CR et al (Ref 16) |
| F   | 3 y / 18 y                   | Short stature, facial dysmorphism, pectus excavatum, hypertrophic cardiomyopathy, psychomotor retardation | Polyarthritis, papillary RASH on lower limbs, Coombs positive hemolytic anemia, lymphopenia, thrombocytopenia, ANA >1:40, high anti dsDNA Ab and IgM anticardiolipin. | None | KRAS | Leventopolous 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 1:840 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 hyperextensibility, 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, hepatop – esplenomegaly, epilepsy, mental retardation | Arthrogrias, lymphopenia, hemolytic anemia, ANA 1:540 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 stranded 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.
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 immune systems 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 high risk of lupus, but only about 15% of the heritability of SLE to be explained by those loci. Some rare monogenic disorders has been reported including gene mutations in PTPN11, and a null mutation in the gene in the Arab population [22].

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 ophathies including NS and related disorders. The hypothesis of a common origin is strength for the linkage of a susceptibility gene for SLE to an area that is also directly involved in the occurrence of RAS ophathy, although no definite study has yet been performed. Until that happens clinicians should be alert about the molecular mechanisms that underlies RAS ophathy may predispose to the development of SLE.

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