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CASE REPORT

Noonan syndrome associated with systemic lupus erythematosus

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Noonan syndrome (NS) is a developmental disorder characterised mainly by cardiac defects and craniofacial dysmorphia. An association between NS and some autoimmune diseases, such as thyroiditis and systemic lupus erythematosus (SLE), has been suggested. We report the case of a 28-year-old man with a diagnosis of NS and autoimmune hypothyroidism who developed symptoms and immunologic features of SLE. *Lupus* (2009) **18,** 267–269.

Key words: autoimmune thyroiditis; Noonan syndrome; systemic lupus erythematosus

Introduction

Noonan syndrome (NS) is a relatively frequent congenital disorder phenotypically characterised by variable craniofacial malformations, hypogonadism and cardiac defects among other anomalies.[1] This condition is an autosomal dominant disorder in 50% of cases although autosomal recessive forms or sporadic cases also occur. A gene mutation in the PTPN11 gene of the 12q24.1 locus has been described.[2]

The association of NS and autoimmune disorders, such as thyroiditis, vasculitis, vitiligo, celiac disease or anterior uveitis, has been reported in isolated cases. The coexistence of several autoimmune disorders is far less frequent.

We report the case of a young man with NS and primary autoimmune hypothyroidism who also developed systemic lupus erythematosus.

Case report

A 28-year-old man presented to our outpatient rheumatology unit in October 2005 complaining of polyarthritis. He had been diagnosed with NS according to the criteria proposed by van der Burgt, *et al.*[3] as the patient showed characteristic facial dysmorphia (hypertelorism, pterygium colli, ptosis, low-set dysmorphic ears), pulmonary valve stenosis, pectus excavatum and bilateral cryptorchidism. The chromosomal analysis was normal, with a 46 XY karyotype. There was no familial history of NS, systemic lupus erythematosus (SLE) or other autoimmune conditions.

At the age of 15, the patient was treated with growth hormone for 2 years because of stature retardation, achieving a height of 158 cm and developing puberty signs. At the age of 17, testosterone depot therapy was added due to primary hypogonadism. When he was 19 years old, his height was 169 cm and showed an adequate development of sexual characteristics but was implanted a testicular prosthesis at the age of 20 due to persistence of left cryptorchidism.

In 2001, routine analysis detected autoimmune primary hypothyroidism (thyroid stimulating hormone, TSH 8.8 μU/mL [N = 0.4–4 μU/mL], free T4 0.92 ng/dL [N = 0.8–1.8 ng/dL]), thyroid antiperoxidase antibodies 439 AU/mL (N = 0–15 AU/mL) and antithyroglobulin antibodies 524 U/mL (N = 0–100 U/mL); the patient required levothyroxine therapy 2 years later.

In October 2005, the patient was referred to our rheumatology unit for a 3-month history of symmetric polyarthritis affecting wrists, metacarpophalangeal joint (MCP) and proximal interphalangeal joint (PIP) joints and morning stiffness lasting more than 1 hour. He had a normal complete blood count and biochemistry but elevated acute phase reactants (ESR = 36 mm/first h, CRP = 1.3 mg/dL). Rheumatoid factor and anticyclic citrullinated peptide antibodies were negative, and the antinuclear antibodies titer was 1/80. Hand and feet radiographs showed no evidence of erosions or other abnormalities.

Therapy with prednisone, non-steroidal anti-inflammatory drugs (NSAIDs) and methotrexate was started following a clinical diagnosis of seronegative

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rheumatoid arthritis, with methotrexate dose progressively increased up to 20 mg per week because of persistent synovitis. Leflunomide of 20 mg/d was added due to persistent active disease.

Over the following months, persistent lymphopenia ($<1 \times 10^9$/L), a progressive elevation of antinuclear antibodies titer (up to 1/640, speckled pattern), low complement levels and positive RNP antibodies were detected. No erosive joint disease was detected in yearly radiographs. A routine chest radiograph showed cardiomegaly; the patient did not have fever, cough, dyspnea or chest pain. A high-resolution computed tomography and transesophageal ultrasound showed the presence of an important pericardial effusion without haemodynamic instability. Steroid therapy was started with resolution of the pericardial effusion.

The patient was diagnosed with SLE as he fulfilled four of the American College of Rheumatology (ACR) criteria (nonerosive polyarthritis, pericarditis, lymphopenia and positive antinuclear antibodies).

Discussion

The prevalence of NS, also known as Ullrich syndrome, is approximately 1/2000 births.[1] It was first described by Noonan and Ehmke in 1963 in nine cases with pulmonary valve stenosis associated with facial dysmorphism, short stature and other features similar to those of Turner syndrome.[4]

NS shows an autosomal dominant inheritance in half of cases, but variable phenotypic expression and genetic heterogeneity are well established and mild cases may go unnoticed. A responsible gene named PTPN11 has been recently identified in chromosome 12q24.1, which encodes the tyrosine phosphatase SHP-2.[2,5] Among other functions, this enzyme has a role in cardiac valve development and acts as a mediator of intracellular signalling of B and natural killer (NK) cells[2,6,7] and possess an autoregulatory mechanism in the SHP-2 N-terminal domain. Mutations in this domain are associated with an overexpression of SHP-2 and have been reported in about 50% of cases of NS. This could explain the frequent association of heart valve disease, especially pulmonary stenosis[8] and several autoimmune diseases such as autoimmune thyroiditis,[9] vitíligo,[10] vasculitis,[11] celiac disease,[12] anterior uveitis[13] and SLE.

SLE is a multisystem autoimmune disease of unknown aetiology. There are some features that point to a genetic influence in the development of SLE, such as family aggregation, concordance in monozygotic greater than in dizygotic twins, a higher prevalence in some ethnic groups and its association with some hereditary immunodeficiencies.

In the last decade, several studies support the role of multiple susceptibility genes in the development of SLE.[14] Nath, *et al.*[15] have showed that a region of chromosome 12 (12q24) contributes to the development of SLE, especially in Hispanic and Caucasian families. Further studies focusing on this region could help explain the association of NS with SLE.

To our knowledge, only four cases (two of them in adults) of the NS and SLE association have been reported (Table 1).[12,16–18] SLE in these patients was characterised by the presence arthritis and serositis (generally mild), haematologic abnormalities and positive antinuclear and DNA antibodies. The absence of serious features could explain underdiagnosis and the relative scarcity of cases reported. Another feature of these four cases, also present in our patient, is the development of SLE at an early age (two children and three young patients; Table 1); this fact could support a relatively higher influence of genetic compared with environmental factors in these patients.

The coexistence of several autoimmune disorders is even more infrequent, with only one case previously

Table 1 Previously reported cases of Noonan syndrome and SLE

Reference	*Sex/age*	*Noonan syndrome features*	*SLE features*
Martin, *et al.*[16]	M/20 y	Short stature, facial dysmorphism, pectus excavatum, mental retardation, mitral valve disease	Nonerosive polyarthritis, aphthous disease, serositis, anaemia, renal insufficiency, antinuclear antibodies 1/2560
Amoroso, *et al.*[12]	F/26 y	Short stature, facial dysmorphism, pectus carinatum, cardiac abnormalities, epilepsy, mental retardation	Arthralgia, serositis, antinuclear antibodies 1/2560, anti-dsDNA, anti-Sm, anticardiolipin and lupus anticoagulant positive, Coombs-positive haemolytic anaemia, lymphopenia, thrombocytopenia
Alanay, *et al.*[17]	M/11 y	Short stature, facial dysmorphism, mental retardation, pulmonary stenosis	Arthritis, lupus nephritis, aphthous disease, antinuclear antibodies 1/40, anti-dsDNA, anticardiolipin antibodies positive, thrombocytopenia
Lopez-Rangel, *et al.*[18]	F/5 y	Short stature, facial dysmorphism, sternum deformation, mental retardation, hypertrophic cardiopathy	Arthritis, serositis, lupus nephritis, antinuclear antibodies 1/1280, pancytopenia, Coombs-positive haemolytic anaemia, anti-dsDNA, anti-Sm and anticardiolipin antibodies positive
Lisbona, *et al.*	M/28 y	Short stature, facial dysmorphism, pectus excavatum, pulmonary stenosis, crytorchidism	Nonerosive polyarthritis, pericarditis, antinuclear antibodies 1/640, anti-RNP antibodies, lymphopenia

reported of a patient with NS with autoimmune thyroiditis, celiac disease and SLE.[12] Autoimmune hypothyroidism was associated to SLE in our patient with NS. Fifteen cases of autoimmune thyroiditis in patients with NS have been reported. The estimated prevalence of antithyroid antibodies in patients with NS ranges between 20% and 60%, but most cases are subclinical.[8,9] Some authors have showed that the prevalence of antithyroid antibodies increases with age and suggest that thyroid function should be regularly monitored in these patients from the age of 12.[19]

In summary, the association of NS and SLE or other autoimmune disorders is not frequent. However, NS may not be diagnosed in patients with less apparent phenotypic expression. We should be alert of the diagnosis of NS in the presence of SLE in young patients with cardiac defects or facial abnormalities. In these patients, we should also be vigilant of thyroid function. However, physicians following patients with NS should be attentive to the development of autoimmune disorders in order to achieve early diagnosis and avoid complications.

The role of the PTPN11 gene and SHP-2 in the modulation of the immune response in patients with NS and their roles in the association with autoimmune disease warrant investigation.

References

1 Nora JJ, Nora AH, Sinha AK, Spangler RD, Lubs HA. The Ullrich-Noonan syndrome (Turner phenotype). *Am J Dis Child* 1974; **127**: 48–55.
2 Tartaglia M, Mehler EL, Goldberg R, *et al*. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet* 2001; **29**: 465–468.
3 van der Burgt I, Berends E, Lommen E, van Beersum S, Hamel B, Mariman E. Clinical and molecular studies in a large Dutch family with Noonan syndrome. *Am J Med Genet* 1994; **53**: 187–191.
4 Noonan JA, Ehmke DA. Associated noncardiac malformations in children with congenital heart disease. *J Pediatr* 1963; **63**: 468–470.
5 Jamieson CR, van der Burgt I, Brady AF, *et al*. Mapping a gene for Noonan syndrome to the long arm of chromosome 12. *Nat Genet* 1994; **8**: 357–360.
6 Yoshida R, Hasegawa T, Hasegawa Y, *et al*. Protein-tyrosine phosphatase, nonreceptor type 11 mutation analysis and clinical assessment in 45 patients with Noonan syndrome. *J Clin Endocrinol Metab* 2004; **89**: 3359–3364.
7 Jongmans M, Sistermans EA, Rikken A, *et al*. Genotypic and phenotypic characterization of Noonan syndrome: new data and review of the literature. *Am J Med Genet A* 2005; **134A**: 165–170.
8 Sharland M, Burch M, McKenna WM, Paton MA. A clinical study of Noonan syndrome. *Arch Dis Child* 1992; **67**: 178–183.
9 Vesterhus P, Aarskog D. Noonan's syndrome and autoimmune thyroiditis. *J Pediatr* 1973; **83**: 237–240.
10 Yalcin B, Tamer E, Gür G, Oztas P, Polat MU, Alli N. Neurofibromatosis 1/Noonan syndrome associated with Hashimoto's thyroiditis and vitiligo. *Acta Derm Venereol* 2006; **86**: 80–81.
11 Berberich MS, Hall JG. Noonan syndrome-an unusual family with above average intelligence, a high incidence of cancer and rare type of vasculitis. *Birth Defects Orig Artic Ser* 1976; **12**: 181–186.
12 Amoroso A, Garzia P, Vadacca M, *et al*. The unusual association of three autoimmune diseases in a patient with Noonan syndrome. *J Adolesc Health* 2003; **32**: 94–97.
13 Elgohary MA, Bradshaw P, Ahmad N. Anterior uveitis and congenital fibrosis of the extraocular muscles in a patient with Noonan syndrome. *J Postgrad Med* 2005; **51**: 319–321.
14 Harley JB, Alarcón-Riquelme ME, Criswell LA, *et al*. International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN). Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. *Nat Genet* 2008; **40**: 204–210.
15 Nath SK, Quintero-Del-Rio AI, Kilpatrick J, Feo L, Ballesteros M, Harley JB. Linkage at 12q24 with systemic lupus erythematosus (SLE) is established and confirmed in Hispanic and European American families. *Am J Hum Genet* 2004; **74**: 73–82.
16 Martin DM, Gencyuz CF, Petty EM. Systemic lupus erythematosus in a man with Noonan syndrome. *Am J Med Genet* 2001; **102**: 59–62.
17 Alanay Y, Balci S, Ozen S. Noonan syndrome and systemic lupus erythematosus: presentation in childhood. *Clin Dysmorphol* 2004; **13**: 161–163.
18 Lopez-Rangel E, Malleson PN, Lirenman DS, Roa B, Wiszniewska J, Lewis ME. Systemic lupus erythematosus and other autoimmune disorders in children with Noonan syndrome. *Am J Med Genet A* 2005; **139**: 239–242.
19 Svensson J, Carlsson A, Ericsson UB, Westphal O, Ivarsson SA. Noonan's syndrome and autoimmune diseases. *J Pediatr Endocrinol Metab* 2003; **16**: 217–218.