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Research Letter

Systemic Lupus Erythematosus and Other Autoimmune Disorders in Children With Noonan Syndrome

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To the Editor:

Noonan syndrome (NS) [OMIM 163950] was first described by Noonan and Ehmke [1963]. It has an estimated frequency of between 1:1,000 and 1:2,500 live births [Noonan, 1994, 1999]. The diagnosis of NS is made on the basis of clinical criteria including characteristic facial traits such as long forehead, hypertelorism, downslanting palpebral fissures, ptosis, low-set, posteriorly angulated ears, short neck with excess nuchal skin, low posterior hair line, short stature, delayed puberty, congenital heart defects, and other congenital anomalies. At least 50% of cases of NS have been found to have a mutation in the *PTPN11* gene [Tartaglia et al., 2001; Zenker et al., 2004].

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by widespread inflammation of blood vessels and connective tissues, in association with the presence of antinuclear antibodies (ANA), particularly antibodies to double-stranded DNA. The incidence of SLE in children has been reported at approximately 0.36 per 1,00,000 children per year [Malleson et al., 1996]. It is very rare in children under the age of 5 years, with the annual incidence increasing throughout childhood, reaching a peak of about 7.6 per 1,00,000 in adulthood [Petri, 2002].

Three cases of NS with SLE are reported [Martin et al., 2001; Amoroso et al., 2003; Alanay et al., 2004]. Another report from Yamashita et al. [2004] details a patient with NS, Moyamoya vascular changes, and antiphospholipid syndrome with positive testing for anticardiolipin antibody, ANA, and lupus anticoagulant. In addition there are numerous reports of NS patients with various types of autoimmune disorders [Chaves-Carballo and Hayles, 1966; Vesterhus and Aarskog, 1973; Berberich and Hall, 1976; Sharland et al., 1992]. We report on a 5-year-old girl with NS and SLE, the youngest child described to date with both disorders serving to identify further an increasingly recognizable association between NS, SLE, and potentially other auto-immune mediated diseases.

Our patient was born normally at 38 weeks of gestation. Birth weight was 3.6 kg (50%). The pregnancy was uncomplicated. Review of the family history showed that her parents were nonconsanguineous. The rest of the family history was unremarkable and careful examination of the parents did not show any manifestation of NS.

The diagnosis of NS in our patient was made at age 3½ years based on characteristic facial appearance, small stature, concentric left ventricular hypertrophy, and mild developmental delay (Fig. 1). Karyotype was normal (46,XX) at 450–550 band resolution. At age 5 she presented with lethargy, decreased appetite, hematuria, proteinurea, arthritis of the right knee, peripheral edema, ascites, mild respiratory distress, a small left pleural effusion, hypertension, and pancytopenia. Initial concerns about malignancy prompted a bone marrow aspiration that showed signs suggestive of peripheral consumption of platelets and neutropenia. A renal biopsy showed diffuse proliferative lupus glomerulonephritis (WHO class IV). Magnetic resonance angiography showed equivocal signs of cerebral vasculitis; however, conventional cerebral angiography was normal. She fulfilled 1997 ARC classification criteria for SLE with glomerulonephritis, Coombs positive hemolytic anemia (Hb 69 gm/L), thrombocytopenia (100×10^9/L), high titre ANA (>1:1,280), and raised antibodies to DNA (15 kU/L) and anticardiolipin antibodies (IgG 36.2 MOM). Her latest EKG showed sinus rhythm with axis slightly rightward with no definite ventricular hypertrophy. Her echocardiogram shows mils septal thickening. She is presently stable on her current treatment regimen.

Physical examination at age 5 years (Figs. 1 and 2) showed a height of 102 cm (<5%), weight of 17.4 kg (5%), and OFC of 51 cm (50%). She had a normal shaped head, fine curly hair with widow's peak, and centrally placed hairwhorl. Her neck was short with no webbing. She had a myopathic facial appearance, downslanting palpebral fissures, and bilateral ptosis. Her ears were posteriorly angulated with thickened helices. She had a highly arched palate. Her chest was shield-like with mild pectus, wide-spaced nipples, and a short sternum. Cardiac auscultation revealed a mid-systolic grade 1/6 murmur. She had flared lower ribs and her abdominal findings were unremarkable. She had mild hypotonia. She had mild lumbar lordosis, bilateral genu valgus with bilateral calcaneovalgus deformity of the ankles, pes planus, and tight heel cords. She had prominent finger pads of D1–10. Ophthalmologic examination showed intermittent exotropia.

Developmentally our patient manifested speech and developmental delay. Psychological assessment showed a scattered

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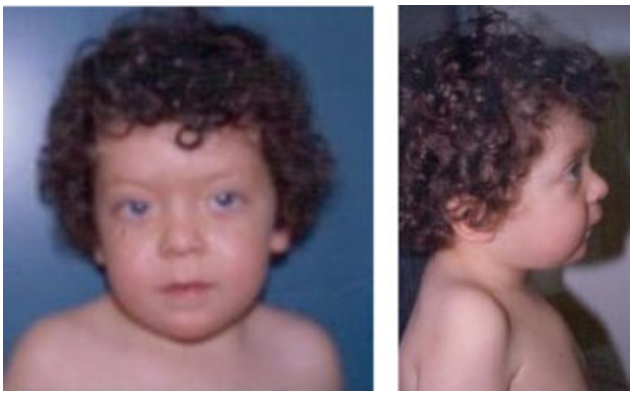

Fig. 1. Our patient at 4 years of age.

performance with cognitive functioning in the low to borderline range. At age 8 she functions at the level of a 5–6 years old.

PTPN11 mutation testing was performed on genomic DNA from this patient by direct bidirectional sequencing of the entire coding sequence exons 1–15. PCR primers were used to amplify the *PTPN11* gene coding region (exons 1–15 with flanking intronic sequences) [Maheshwari et al., 2002]. Each amplification product was sequenced in both the forward and reverse directions. The sequence analysis did not identify a mutation in the *PTPN11* gene coding region of this patient.

Autoimmune disorders are not a common manifestation in NS. However, there have been several reports of NS patients with several different autoimmune disorders (Table I). The incidence of autoimmune disorders as a group in the general population is very hard to determine but there are published incidences for specific autoimmune disorder such as chronic arthritis (26.3%), connective tissue diseases (6.5%), and all forms of vasculitis (6.1%) [Malleson et al., 1996]. The incidence of autoimmune disorders in NS has not been established but is increasingly being reported.

The strength of the association between autoimmune-mediated thyroiditis and NS is difficult to interpret as Hashimoto thyroiditis occurs with an incidence of 1.3% in the general population [Dayan and Daniels, 1996]. Anti-thyroglobulin and anti-thyroid peroxidase antibodies have been detected in 20% and 10% of NS patients, yet also in 14% and 6% of unaffected control individuals, thus such findings may not be significant. However, the report by Dayan and Daniels [1996] also found that raised autoantibody titres, although rare in patients with NS below the age of 12, increased after that age, suggesting that adolescents with NS should be monitored regularly for positive thyroid autoantibodies linked with autoimmune thyroiditis [Svensson et al., 2003].

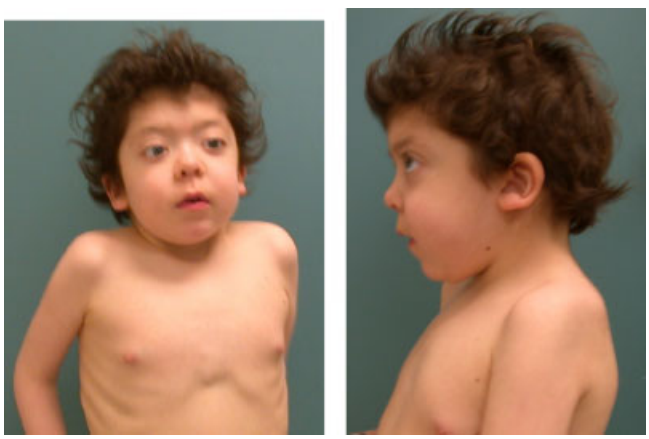

Fig. 2. Our patient at 7 years of age. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The association between SLE and NS was described previously in three separate publications (Table II). All had the characteristic phenotype of NS and fulfilled the American College of Rheumatology Classification Criteria (ACR) for the diagnosis of SLE.

The minimum incidence rate for SLE per 100,000 children at risk per year calculated from the Canadian Pediatric Rheumatology Association Disease SLE Registry is 0.36 (95% CI 0.23, 0.61) [Malleson et al., 1996]. The occurrence of SLE in children under 5 years of age is extremely rare [Lehman et al., 1989] and females are considerably more frequently affected than males (female to male ratio 4.3:13.6) [Petri, 2002]. In view of the relative rarity of each respective disorder and increasing observations of NS and SLE co-morbidity, including two cases in young children, we hypothesize that SLE may be an important risk of NS.

The etiology of SLE remains unknown and is postulated to be due to complex genetic inheritance. Evidence of linkage to disease susceptibility loci on a variety of different chromosomes has been reported [Gaffney et al., 2000; Tsao et al., 2002; Cantor et al., 2004]. It is noteworthy that in one half of cases NS is due to gene mutations in *PTPN11* at the 12q24 locus, a locus also concordant with recent linkage study reports of SLE in Hispanic and European American families [Nath et al., 2004]. The reported candidate interval region for SLE susceptibility spans approximately 15 Mb from 12q24.1 (D12S070) to 12q24.3 (D12S2078) and includes the *PTPN11* gene at 12q24 between D12S84 and D12S134 [Nath et al., 2004]. The linkage of a susceptibility gene for SLE to 12q24 further heightens the prospect of a proposed association between NS and SLE.

Missense mutations in *PTPN11* have been identified in 50% of studied Noonan cases [Schollen et al., 2003]. The gene encodes SHP-2 (Src homology 2 domain-containing tyrosine phosphatase 2), a nonreceptor protein tyrosine phosphatase that acts in signal transduction downstream to growth factor hormone and cytokine receptors [Fragale et al., 2004]. All *PTPN11* missense mutations reported so far are clustered in the interacting portions of the amino N-SH2 domain and the phosphotyrosine phosphatase (PTP) domains, which are involved in switching the protein between its inactive and active conformations [Tartaglia et al., 2001]. These mutations in PTPN11 are gain-of-function mutations, and are found not only in NS but also in Leopard syndrome and in myeloid malignancies [Tartaglia et al., 2004]. Leopard syndrome is rare, however autoimmune disorders have not been reported for this condition.

As far as we are aware SHP-2 has not been reported, either in humans or in experimental models, in association with autoimmune disease. However, SHP-2 acts as an intracellular pathway regulator that interacts with the adaptor proteins grb2 and gp130 both known to be involved in B cell function [Wu et al., 1998]. SHP-2 acts as a regulator of NF-Kappa B activation [Kapoor et al., 2004], and in concert with SHP-1 inhibits NK cell activation [Yusa and Campbell, 2003]. As both of these are important in immune function, it is possible that gain-of-function mutations of *PTPN1*1 could contribute to the development of autoimmunity.

Our patient was tested and did not show a *PTPN1*1 mutation identified by sequence analysis of the coding region. No studies have been done looking for large intragenic deletions or duplications, whole gene deletion, changes in the 3′UTR, promoter or enhancer regions of the *PTPN1*1 gene. There is one reported case of a 3 bp deletion of exon 3 in the *PTPN1*1 gene in a child with severe NS who presented with hydrops fetalis and juvenile myelomonocytic leukemia. This deletion is thought to also lead to gain of function [Yoshida et al., 2004]. Our

TABLE I. Previously Reported Cases of Patients with Noonan Syndrome (NS) and Autoimmune Disorders

Case	Sex	Age at time of diagnosis	Autoimmune conditions	Reference
5 years old	Female	5	SLE	Our case
11 years old	Male	6	SLE ITP	Alanay et al. [2004]
20 years old	Male	17	SLE	Martin et al. [2001]
26 years old	Female	18	SLE Celiac disease Thyroiditis	Amoroso et al. [2003]
7 cases (antimicrosomal antibodies were measured in 23 consecutive asymptomatic NS and found positive in 7)	Unknown	Unknown	Thyroiditis	Sharland et al. [1992]
1 case	Unknown	Unknown	Vasculitis	
1 case	Unknown	Unknown	Vitiligo	
1 case	Unknown	Unknown	Anterior uveitis	
1 case	Male	Unknown	Degos disease (malignant	Berberich and Hall
1 case	Female	Unknown	atrophic papulosis)Polyserositis of unknown etiology possibly Degos disease	[1976]
8 years old	Male	Unknown	Thyroiditis w/hypothyroidism	Vesterhus and Aarskog [1973]
7 years old	Male	Unknown	Thyroiditis	
17 years old	Male	Unknown	Thyroiditis w/hypothyroidism	
11 years old	Female	Unknown	Thyroiditis	
4 years old	Male	Unknown	Thyroiditis	
5 years old	Female	Unknown	Thyroiditis	
11 years old	Male	11	Thyroiditis	Chaves-Carballo and Hayles [1966]

patient's phenotype is mild, thus, a deletion of *PTPN1*1 seems unlikely. However, the possibility of a contiguous gene deletion involving *PTPN11* and a second locus for SLE susceptibility must be considered. It has also been suggested that a mutation in the promoter/enhancer region of *PTPN11* may be responsible for the phenotype in some cases of NS [Allanson, 2002].

Similar genotype–phenotype correlations between NS patients with and without a *PTPN1*1 mutation have shown that patients without a PTPN11 mutation have a significantly higher prevalence of hypertrophic cardiomyopathy [Tartaglia et al., 2002; Zenker et al., 2004]. Our patient has confirmed hypertrophic cardiomyopathy and was not found to have a *PTPN11* mutation in keeping with past reports. These and other rare associations may prove to be considerable help in identifying other gene mutations associated with NS.

It is clear that more research is needed to clarify the incidence and association of SLE and other autoimmune disorders with NS and to increase awareness of clinicians and caregivers. This would establish an important new risk factor for improving the anticipatory care and clinical care guidelines for individuals with NS, their family, and caregivers. It is also important to explore the potential role of the *PTPN11* gene and SHP-2 protein expression in modulating

TABLE II. Features of SLE in Three Patients

Patient	NS features	SLE features
5 years old (our patient)	Short stature, dysmorphic features: myopathic facies, wide spaced eyes with downslanting fissures and mild ptosis, low set posteriorly rotated ears, curly hair, mild pectus excavatum, hypotonia, mild cognitive delay, mild concentric left ventricular hypertrophy	Nephrotic syndrome, arthritis of her right knee, peripheral edema, ascites, serositis, hypertension, pancytopenia, C3, C4 low, CH50 absent, Coombs test positive, ANA positive, SSA antibodies positive, Sm/RNP antibodies positive, anticardiolipin antibodies positive, VWF positive, platelets 100
11 years old Alanay et al. [2004]	Short stature, dysmorphic features: frontal bossing, bilateral ptosis, downslanting palpebral fissures, high arched eyebrows, posteriorly rotated ears with thickened helices, webbed neck and wide chest, mild cognitive delay, systolic ejection murmur	Arthralgias, epistaxis, ITP, oral aphtous lesions, positive ANA and anti-DNA hypertension, elevated ESR, Normal renal function, complement C3 and C$
20 years old Martin et al. [2001]	Short stature, dysmorphic features: prominent forehead, midface hypoplasia, bilateral ptosis, small palpebral fissures and short neck with mild webbing, pectus excavatum, mild cognitive delay	Recurrent fever, polyarthritis, alopecia, oral ulcers, pericarditis, pleuritis, renal insufficiency, ANA positive, hepatosplenomegaly
26 years old Amoroso et al. [2003]	Short stature, dysmorphic features: flat forehead, wide set eyes, downslanting palpebral fissures and mild ptosis, curly hair Webbed neck, chest deformity, CHD: Pulmonary stenosis, atrial septal defect, mitral valve prolapse mutlivalvular insufficiency, mental retardation	ESR 64 mm/h, Hb 9.5 g/dL, lymphocyte 550/mm^3, platelet count 35,000/mm^3, Coombs test positive, ANA positive, anti-dsDNA positive, anti-Sm positive, LAC positive, C3, C4 low, seizures, artralgias, serositis, hepatosplenomegaly

normal and aberrant immune responses both in patients with NS with and without a *PTPN11* mutation.

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