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Brief Clinical Report

Systemic Lupus Erythematosus in a Man With Noonan Syndrome

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Noonan syndrome is a multiple congenital anomaly condition characterized by craniofacial anomalies, short stature, cardiac malformations, and normal peripheral blood karyotype analysis. Prior reports of individuals with Noonan syndrome have revealed an association with several autoimmune diseases, including vasculitis and anterior uveitis, but no reports of systemic lupus erythematosus (SLE). Here we present the first case report of a 21-year-old man with a clinical diagnosis of Noonan syndrome and a recent history of mitral valve dysfunction and systemic lupus erythematosus. We discuss his findings in the context of known features of Noonan syndrome and propose that individuals with Noonan syndrome be regularly monitored for associated autoimmune phenomena. © 2001 Wiley-Liss, Inc.

KEY WORDS: Noonan syndrome; lupus; autoimmune disease

INTRODUCTION

Noonan syndrome was first recognized in 1963 as a distinct syndrome characterized by short stature, characteristic face, and cardiac disease [Noonan and Ehmke, 1963]. Since this original description, additional reports have been published to further delineate the cardinal features of Noonan syndrome and to broaden the spectrum of less common manifestations. Autoimmune dysfunction, although not considered a cardinal feature of Noonan syndrome, has been reported in various forms, such as autoimmune thyroiditis, vasculitis, vitiligo, and anterior uveitis [Sharland et al., 1992]. We report a 20-year-old man with Noonan syndrome and seropositive systemic lupus erythematosus (SLE), and provide a brief overview of other types of autoimmune dysfunction in Noonan syndrome for comparison.

CLINICAL REPORT

A 20-year-old man presented to the Medical Genetics inpatient consultation service after admission to the general medical ward for management of dyspnea, peripheral edema, and decreased exercise tolerance. He had a history of multiple congenital anomalies without an underlying diagnosis to explain his features. His medical history was remarkable for a diagnosis of SLE 3 years prior at age 17, based on the presence of recurrent fever of unknown origin, progressive nonerosive polyarthritis primarily involving the small joints of the hands and knees, generalized alopecia, oral ulcers, pericarditis, pleuritis, renal insufficiency, anemia, and a positive ANA at a titer of 1:2,560 in a peripheral pattern. He required chronic steroid therapy. He had a 1-year history of mitral valve regurgitation and stenosis with congestive heart failure.

Review of his birth history revealed an uncomplicated, full-term gestation, absence of teratogen exposures, normal spontaneous vaginal delivery, and average growth parameters at birth. Dysmorphic facial features (small, slit-like palpebral fissures, epicanthus inversus, strabismus, and nasal tip hypoplasia) were noted immediately at birth (Fig. 1). Cardiac arrhythmia of uncertain origin was present at birth, with follow-up evaluations normal. Peripheral blood karyotype done at 1 month of age revealed normal 46,XY chromosomes. Postnatal course was complicated by growth delays. His childhood was significant for tachyarrhythmia that spontaneously resolved, mild cognitive delays requiring special education classes, and ptosis and strabismus necessitating surgical repair at age 10. He graduated from high school at age 18 and worked at a grocery store

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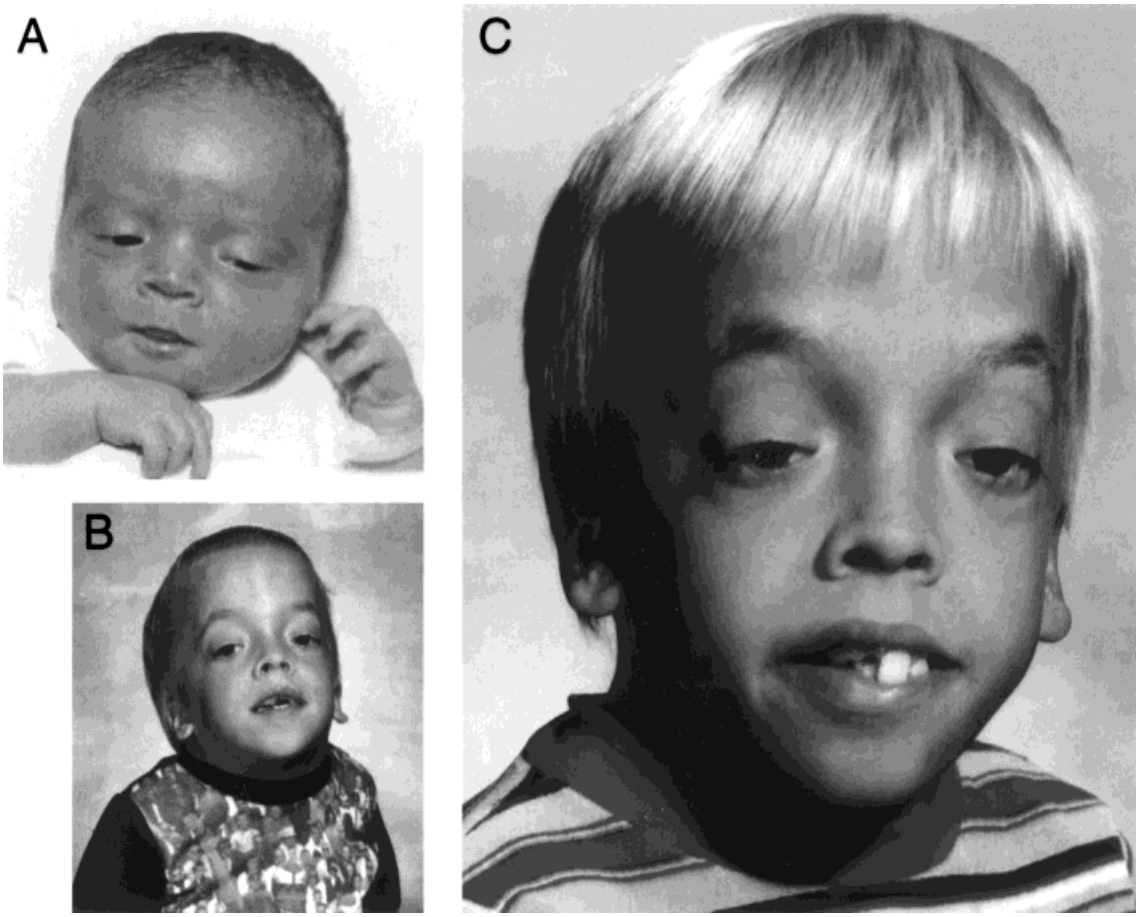

Fig. 1. Proband at birth (**A**), 7 years (**B**), and 10 years (**C**). Note bilateral ptosis, epicanthus inversus, strabismus, and nasal tip hypoplasia.

until his medical condition declined. Family history was negative for Noonan syndrome, SLE, short stature, learning disability, mental retardation, structural cardiac disease, arthritis, or chromosomal anomalies. Detailed examination of his mother and sister did not reveal any features suggestive of Noonan syndrome. Father and brothers were not available for examination, but review of their photographs, medical histories, and stature did not suggest characteristic features of Noonan syndrome.

Physical examination at age 20 years during our inpatient consultation was notable for weight 44.4 kg (less than 3rd centile), and height 142 cm (less than 3rd centile). Craniofacial features (Fig. 2) included generalized alopecia, prominent forehead, flattening of the occiput, a low posterior hairline, mild midfacial hypoplasia, hypertelorism, bilateral ptosis with severe limitation of upward gaze, triangular jawline with mild micrognathia, high palate, prominence and tenting of the upper lip, and slightly protruding, midline tongue. Ears were low-set, posteriorly rotated, and 5.4 cm in vertical dimension (10th percentile) bilaterally. His neck was short with mild webbing. Thorax was notable for small, widely spaced nipples, superior prominence of the sternum and an inferior pectus excavatum deformity (Fig. 2). Cardiac examination was remarkable for a left ventricular heave and laterally displaced point of maximal impulse with third heart sound. A small umbilical hernia and hepatosplenomegaly were noted. Genitourinary examination was notable for poorly developed secondary sexual characteristics and bilaterally high testes with scrotal edema. Complete subluxations at the proximal interphalangeal joints with both hands were present (Fig. 2). Cranial nerves were intact; diffuse, generalized hypotonia and muscle wasting were present. Skin examination revealed a facial café au lait macula, and normal dermatoglyphics with no unusual patterns. Repeat peripheral blood karyotype at age 20 was normal. We diagnosed him at age 20 with Noonan syndrome on the basis of short stature, characteristic craniofacial features, short webbed neck, pectus deformity, and normal cytogenetic analyses.

DISCUSSION

We have described a 20-year-old man with postnatal short stature, characteristic craniofacial features, short neck, cognitive delays, broadly spaced nipples, pectus deformity, and a normal karyotype who we diagnosed with Noonan syndrome based on clinical criteria. He was in good health until age 17 when he developed SLE.

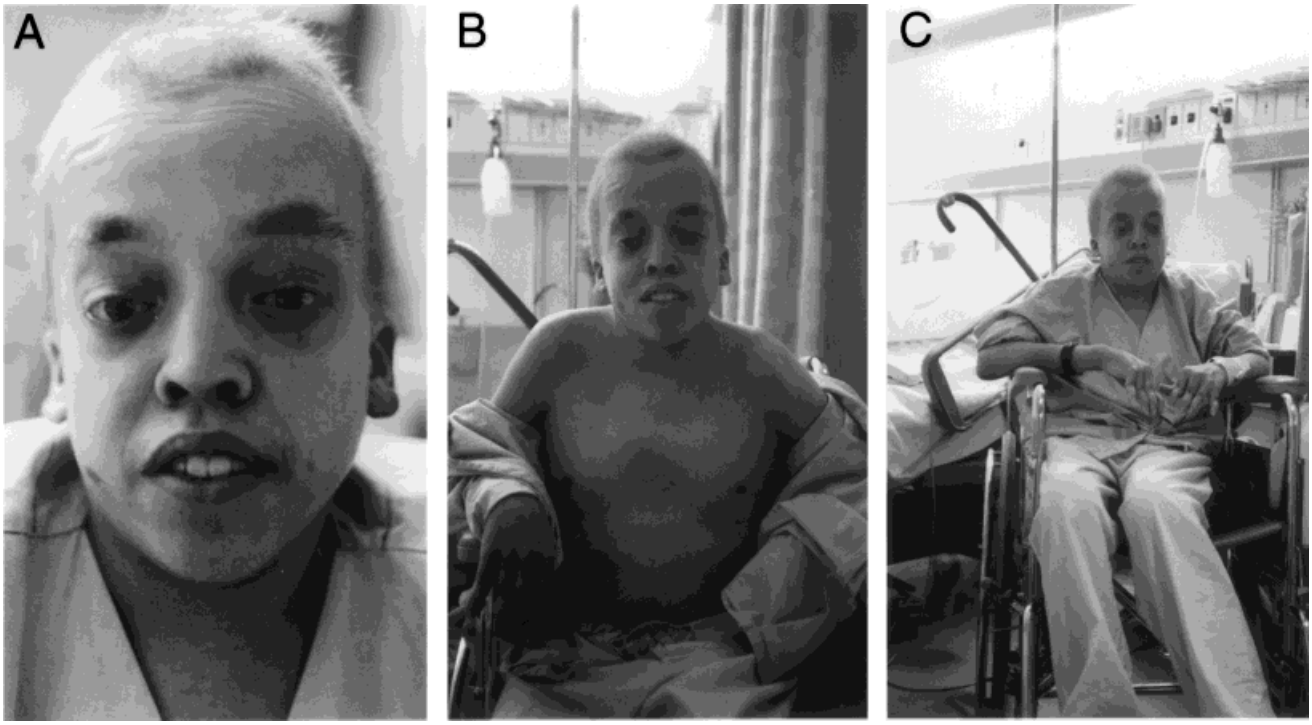

Fig. 2. Proband at 20 years. Note (**A**) characteristic craniofacial features, (**B**) pectus deformity, and (**C**) subluxations at the PIP joints bilaterally.

Approximately 3 years later, severe mitral valve disease developed. Echocardiogram at age 20 demonstrated mitral regurgitation, mild mitral stenosis, and an ejection fraction of 63%. Subsequent to our evaluation, he underwent mitral valve replacement. Most individuals with Noonan syndrome have right-sided cardiac defects, such as pulmonic stenosis [Marino et al., 1999; Noonan, 1999]. Left-sided defects have been reported [Danetz et al., 1999], with mitral valve abnormalities present in about 5.8% of individuals with Noonan syndrome [Marino et al., 1999]. The mitral valve abnormalities present in our patient were not detected until 3 years later after he developed SLE, making it unlikely that his mitral regurgitation was related to the diagnosis of Noonan syndrome.

Noonan syndrome, first described in 1963 [Noonan and Ehmke, 1963] is a clinical diagnosis made by the presence of clinical criteria. The estimated frequency of Noonan syndrome is between 1:1,000 and 1:2,500 live births [Noonan, 1994, 1999]. In some cases, candidate loci have mapped to 12q22 [Jamieson et al., 1994, Brady et al., 1997], however, in most cases the responsible genes or gene regions are not known. We are not aware of any autoimmune disorders that map to 12q22. We provide the first report of an individual with Noonan syndrome manifesting SLE.

The combination of SLE in an individual with Noonan syndrome raises questions about a causal relationship between these two conditions. Noonan syndrome has been associated with hematologic malignancies [Bader-Meunier et al., 1997; Choong et al., 1999] and bleeding diatheses [Massarano et al., 1996; Singer et al., 1997]. It is possible that SLE occurred in our patient as a separate event, unrelated to his underlying Noonan syndrome, as approximately one in 31 adult Americans have an autoimmune disease [Jacobson et al., 1997]. Nevertheless, his medical course, therapy, and prognosis are influenced by the co-existence of Noonan syndrome and SLE, and SLE may represent a rare feature of Noonan syndrome. Other forms of autoimmune dysfunction including thyroiditis, vasculitis, pericarditis, and uveitis have been reported, but the actual incidence of autoimmune diseases in this population has not been established [Sharland et al., 1992]. Our report, along with these other reports of autoimmune dysfunction in Noonan syndrome suggests that there may be an association between Noonan syndrome and SLE or other autoimmune disorders. As more individuals with Noonan syndrome are identified and followed, increased knowledge about the spectrum of medical problems associated with this condition will be realized.

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