Clinical Pediatrics

AN 9610313604
AB Presents an update on the **Noonan syndrome.** History; Genetics; Incidence; Diagnosis; Prenatal history; Early infancy; Development; Growth; Eye findings; Orthopedic problems; Genitourinary problems; Neurologic problems; Skin and hair; Hematology; Lymphatics.
JN Clinical Pediatrics
TI **Noonan syndrome.**
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IS 0009-9228
NT 11bw
PB Westminster Publishing
PD Sept94
VO 33
PG p548, 8p
FT Magazine: Clinical Pediatrics, September, 1994

NOONAN SYNDROME

An Update and Review for the Primary Pediatrician

Introduction

Noonan syndrome[1] is a relatively common multiple congenital anomaly **syndrome**, with an estimated incidence of between one per 1,000 and one per 2,500 live births.[2] Affected individuals have characteristic facial features, are usually short in stature with a chest deformity, and about half have a congenital cardiac abnormality. Autosomal dominant inheritance, with variable expression, has been documented in a number of families. Many cases, however, appear to be sporadic. The diagnosis rests solely on clinical criteria, and so far, the underlying cause or genetic defect is unknown.

The natural history of this **syndrome** is still being defined. Children with **Noonan syndrome** have a large number of potential health problems, making it essential for the primary-care pediatrician to be aware of this **syndrome**, so that the special needs of such children may be met.

History

In 1883, Kobylinski[3] reported a 20-year-old male with clinical features compatible with what is now called **Noonan syndrome**. Many early publications reported both males and females with a webbed neck, small stature with low-set ears, micrognathia, and other anomalies which probably represented a number of different syndromes including **Noonan syndrome**. In 1930, Ullrich[4] described a number of patients with webbed neck and short stature, some of whom represented Turner **syndrome** and, no doubt, some **Noonan syndrome**. While Ullrich was intrigued primarily by the webbed neck, in 1938, Turner[5] described a number of patients with sexual infantilism who also had a webbed neck and short stature. Turner **syndrome** was later recognized as a sex chromosome abnormality with either the absence or an abnormality of one of the X chromosomes. Ullrich was intrigued by the work of a mouse geneticist, Bonnevie, who had bred a mutant strain of mice with a webbed neck and swelling of the limbs. In 1949, Ullrich[6] speculated on the possible similarity between his patients and the mice bred by Bonnevie. The term Bonnevie-Ullrich **syndrome** became popular, particularly in Europe, and was used to describe children, some of whom would now be recognized as having **Noonan syndrome**. In 1943, Flayell[7] reported a male who had a phenotype

similar to that reported by Turner, and he used the term "male Turner" **syndrome**. In 1963, **Noonan** and Ehmke[8] reported nine patients--six males and three females, with short stature and characteristic facies including hypertelorism, ptosis, and low-set ears -- whom we felt represented a distinct **syndrome**. Several of the males had undescended testes. Chest deformities were frequent, and all had valvular pulmonary stenosis. Chromosome studies were normal. Dr. John Opitz[9] suggested the eponym **Noonan syndrome** be used to describe such patients. He felt my observation that this **syndrome** occurred in both males and females was not associated with chromosomal abnormalities and could be inherited justified the eponym. For a number of years, the term Turner phenotype persisted, but in 1968, the eponym **Noonan syndrome** appeared in print for the first time. Thereafter, Dr. Victor McKusick listed **Noonan syndrome** as a hereditary congenital disorder of the cardiovascular system. Since the eponym **Noonan syndrome** is relatively recent, many pediatricians have only a limited knowledge of this condition. This review is intended to be an update and review for the primary pediatrician.

Genetics

Because of the superficial resemblance between patients with **Noonan syndrome** and those with Turner **syndrome**, an abnormality of the X chromosome has been suspected. Thus far, no consistent chromosomal abnormality has been found. A number of patients have had **Noonan** phenotype as well as neurofibromatosis, and for that reason, there was speculation that the genetic defect in **Noonan syndrome** might be linked to the same chromosome, 17,[10] as in neurofibromatosis. So far, although a genetic abnormality is suspected, neither the affected chromosome nor the genetic abnormality has been found. There are clearly a number of patients with autosomal dominantly inherited **Noonan syndrome** through three generations. Since males with **Noonan syndrome** often have un-descended testes and are sometimes infertile, it is not surprising that more reports of mother-to-child transmission have been reported than father-to-child (Figure 1). There appears to be great variability in expression, a feature common in dominantly inherited disorders, making it difficult to identify mildly affected individuals who still carry the gene. In 1985, Allanson et al[11] reported that the phenotype in **Noonan syndrome** changes between birth and adulthood. Thus, a parent may not resemble the affected young child with **Noonan syndrome**, but review of past photographs of a parent will often show a surprising resemblance of the parent at the same age as the child. Careful examination of both parents, other siblings, and review of family pictures at various ages should be done in order to evaluate whether the child is truly a sporadic case or an example of a familial case with a mildly affected parent. A truly sporadic case should not increase the risk of **Noonan syndrome** in future offspring, but if a parent of a patient with **Noonan syndrome** is affected, there is a 50% risk that a subsequent offspring will also be affected. Reliable prenatal diagnosis of **Noonan syndrome** is not possible, although several authors[12,13] have reported in utero fetal edema and cystic hygroma in patients who subsequently develop **Noonan syndrome**.

Incidence

Although Nora et al[2] have estimated the frequency of **Noonan syndrome** to be one per 1,000 to one to 2,500 live births, Mendez and Opitz[14] feel the frequency is higher -- namely one per 1,000 of severely affected and one per 100 of mild expression. There appears to be no racial predilection, and cases have been reported worldwide. The variability of the **syndrome** is so wide that mild cases appear as a normal variant while only the severe are recognized as abnormal. A number of other syndromes focusing on heart and skin called cardio-facio-cutaneous syndromes[15] have been reported, including Watson **syndrome**[16] and LEOPARD **syndrome**.[17] Such patients may be indistinguishable from those with **Noonan syndrome**, and I would include some of these patients

as examples of **Noonan syndrome** until specific diagnostic tests become available.

Among children with congenital heart disease, **Noonan syndrome** is the most common nonchromosomal **syndrome** noted. Kramer et al[18] reported a frequency rate of 1.4% of **Noonan syndrome** among 1,016 children with the variety of congenital cardiac defects. Roberts et al[19] noted a high frequency of **Noonan syndrome** among children requiring surgery for pulmonary stenosis. At their hospital, of 297 children undergoing pulmonary valvotomies between 1958 to 1969, 16, or nearly 7%, had **Noonan syndrome**.

Diagnosis

The diagnosis of **Noonan syndrome** is based on clinical findings. The characteristic facies are very helpful in diagnosis, but as mentioned earlier, they change with age. In the newborn, **Noonan syndrome** is difficult to diagnose by facial appearance (Figure 2). The forehead is often sloping and broad and the ears may be thick and angulated posteriorly. Apparent ocular hypertelorism, anti-mongoloid slant of the palpebral fissures, and a deep philtrum -- as well as mild retrognathia -- may also be present. Newborns may have marked edema with excess nuchal skin and, if female, must be distinguished from Turner **syndrome**. In those newborns without edema, the diagnosis of **Noonan syndrome** is usually not suspected in the neonatal period.

In infancy, from neonatal to age 2 years, the head often appears relatively large. The malar eminences are flat and the eyes prominent and round. The nasal bridge is depressed, and the neck appears short but is no longer webbed. By 12 to 24 months, the body appears more stocky and the chest deformity becomes more prominent. In childhood, the facial appearance shows coarse features but. becomes more triangular as the chin lengthens. The eyes become less prominent and ptosis more apparent. The neck appears longer and the low hairline and webbing may become more obvious. In the teenager and young adult, the triangular facial features become sharper. The nose has a pinched root and a thin, high bridge. The older adult has prominent nasolabial folds, high anterior hairline, and transparent wrinkled skin (Figures 3 and 4).

Because the diagnosis of **Noonan syndrome** must rely on clinical judgment, in 1981 Duncan et al[20] developed a scoring system to evaluate **Noonan syndrome** by attributing scores for the presence or absence of the most characteristic findings usually present in **Noonan syndrome**. Use of this table is helpful to the clinician, but without a reliable diagnostic test, the diagnosis will remain somewhat subjective. A careful history to eliminate the possibility of alcohol abuse in the mother or the use of other teratogens, such as anticonvulsants, as well as normal chromosome studies, are useful in distinguishing **Noonan syndrome** from other conditions which must be considered in the differential diagnosis.

Prenatal History

Although the majority of patients with **Noonan syndrome** have an unremarkable prenatal history, Sharland et al[21] reported that in one third, the pregnancy was complicated by polyhydramnios. With increasing use of fetal ultrasound, a number of fetuses have been reported with cystic hygroma or fetal edema who subsequently developed **Noonan syndrome**. The excessive weight loss in the first week following delivery suggests some degree of fetal edema may be quite common.

Early Infancy

After an apparently normal birth history, many patients develop feeding problems in early infancy. Sharland et al[21] reported 39% of 144 cases had no or mild feeding difficulties, while 39% had moderate problems, mainly vomiting. In 24%, severe feeding problems were present, often requiring tube feedings for 2 weeks or longer. In my experience, a number of young infants have been hospitalized with lethargy, poor feeding, and vomiting, with the diagnosis of suspected sepsis.

Development

In general, the feeding problems resolve later-on in infancy, although some children are subjected to many diagnostic procedures for failure to thrive, and these procedures are usually nonrevealing. **Noonan syndrome** should be suspected in a dysmorphic-appearing infant with some hypotonia, poor feeding, and failure to thrive.

Development

In general, patients with **Noonan syndrome** demonstrate mild motor delay, which may be partly attributed to muscular hypotonia. In the study of Shatland et al,[21] the mean age for sitting was 10 months, walking alone 21 months, and talking 31 months. Although mental retardation is usually mild, it is not always present and is by no means constant. In their study from England, Shatland et al[21] noted the following: of 100 children of school age,84 were attending regular school, five were in physically handicapped classes, and only 11 children required special education. The overall experience suggests that at least one third of children will have some degree of mental retardation or learning disabilities. Graduation from college and achievement of Ph.D. degrees, however, are reported, and mental retardation is not a constant feature. Conductive hearing loss is frequent. All children with **Noonan syndrome** should have a hearing evaluation.

Eye Findings

Lee et al[22] reported on the ocular manifestations of **Noonan syndrome** in 58 consecutive patients. Only three of the 58 had an entirely normal eye examination. Hypertelorism was present in 74%, ptosis in 48%, epicanthal folds in 39%, and an antimongoloid slant in 38%. Refractive errors were present in 61%, strabismus in 48%, and amblyopia in 33%. Other findings included some anterior segment changes, such as prominent corneal nerves, in 63%. Twenty percent had fundal changes. Several children with colobomas -including one of our own (Figure 5) -- have been described. Light blue or light green irides are also frequent. Obviously, with the high frequency of ocular changes, all children with **Noonan syndrome** should have a complete eye examination.

Growth

Weight and length are usually normal at birth. However, short stature is present in 80%, with height often less than weight. In general, there is an average 2-year delay between bone age and chronologic age. As a result, continued growth occurs up to the early 20s so that at adult maturity, the mean height for males is about 2 standard deviations below average. Adult height is affected somewhat by parental height. Most females achieve a height of about 5 feet, while males achieve a height of about 5 feet 5 inches. There is obviously wide variation. In general, the mean adult height for females is 1 standard deviation higher than those with Turner **syndrome.** For the most part, there is no evidence of growth hormone deficiency, but growth hormone treatment has been used to accelerate height in patients with **Noonan syndrome.** As expected, growth hormone treatment accelerates growth with but so far, there is no evidence that the final adult height is increased.

Orthopedic Problems

Over 90% of patients with **Noonan syndrome** have a chest deformity, such as a pectus carinatum or pectus excavatum. Scoliosis occurs in 10% to 15%, and talipes equinovarus in 10% to 15%. A small percentage have radio-ulnar synostosis, cervical spine fusion, or joint contractures. More than half have somewhat hyperextensible joints, and muscle hypotonia is common. In general, hypotonia improves with time. There is often an increased carrying angle at the elbow and sometimes a curved fifth finger. The chest is often shield-like, with apparently wide-spaced nipples.

Genitourinary Problems

Over half the males with **Noonan syndrome** have one or both testes undescended. A delay in puberty is common, corresponding to the delay in bone age of about 2 years. Females often have a delay in puberty, but normal sexual development is usual. Females appear to have normal fertility. Among males with undescended testes, there is sometimes the expected decrease in fertility. Renal abnormalities are seen, but they are generally of little clinical consequence and occur in about 10% of children.

Neurologic Problems

Recurrent seizures were reported in 13% of the patients of Sharland et al.[21] Unexplained peripheral neuropathy has been seen, and a patient of mine with a mild myelomeningocele has had several recurrences of tethered cord. Other neurologic complications have included spina bifida occulta, subarachnoid hemorrhage from aneurysm, and syringomyelia. Several patients with associated neurofibromatosis have had optic glioma and medulloblastoma. In addition, malignant schwannoma has been reported,[23] and one of my patients had several benign schwannomas. Hypotonia is frequent. Poor coordination is reported by some parents. This may be attributable to a combination of hypotonia and visual problems.

Cardiac Problems

About 50% of patients have a cardiac problem. A dysplastic, often stenotic, pulmonary valve is the lesion most characteristic of **Noonan syndrome**, but virtually every type of cardiac defect has been described. Atrial septal defect, branch pulmonary artery stenoses, ventricular septal defect, and tetralogy of Fallot are among those more frequently seen. Valvar aortic stenosis, subaortic stenosis, patent ductus arteriosus, and coarctation of the aorta have all been reported. In addition, hyper-trophic cardiomyopathy--both obstructive and nonobstructive--occurs in 20% to 30% of patients. Myocardial hypertrophy may be noted at birth or may develop in later infancy or in later childhood. Unlike the nonsyndromic hyper-trophic cardiomyopathy, patients with **Noonan syndrome** frequently have involvement of both the right ventricle and left ventricle. Microscopic examination, however, reveals similar findings in both forms --namely muscle disarray[24] and thick-walled coronary arteries. In addition to a dysplastic pulmonary valve, all valves may be dysplastic. Mittal vane prolapse is relatively common, occurring with other cardiac defects or as an isolated finding.

An unusual electrocardiogram with an indeterminant or left-axis deviation and a dominant S wave over the entire precordium is frequent but not clearly related to any specific cardiac malformation. The cause of this electro-cardiographic finding is unknown, but it is a helpful sign, supportive of the diagnosis of **Noonan syndrome**. Cardiac ultrasound is very helpful in diagnosing the cardiac abnormalities present. All patients with **Noonan syndrome** should undergo an initial cardiac evaluation, as well as periodic follow-up, since myocardial disease may develop on later follow-up.

Treatment of the heart disease depends on the severity and symptomatology. If the dysplastic pulmonary valve is obstructed, treatment may be indicated. Although balloon valvuloplasty is now the preferred treatment for pulmonary stenosis, the results of balloon valvuloplasty are less successful if the valve is dysplastic.[26] However, balloon valvuloplasty may be tried, and if not successful, surgery is an option. Sometimes the pulmonary valve may need to be completely resected to relieve the obstruction. The other kinds of congenital heart disease may be repaired in the usual fashion. Hypertrophic cardiomyopathy is more difficult to treat, but the same treatment options used for the nonsyndrome hypertrophic cardiomyopathy are appropriate. The natural history and prognosis of cardiomyopathy in **Noonan syndrome** is not yet well-defined. A few children with **Noonan syndrome** and severe cardiomyopathy have undergone cardiac transplantation.

Skin and Hair

Prominent fetal pads on the fingers and toes are common. Curly hair is often a feature, but in some, both hair and eyebrows are sparse. Nevi and freckles are common and, as mentioned earlier, a number of patients have been seen with findings characteristic of both neurofibromatosis and **Noonan syndrome** (Figure 6). Keratosis pilaris[27] is often associated with **Noonan syndrome**. When prominent, the cutaneous findings in **Noonan syndrome** may lead to the diagnosis of LEOPARD or Watson syndromes, both of which cannot be distinguished from **Noonan syndrome** at the present time. In my experience, these children have a tendency to form extensive keloids following surgical procedures. This should be kept in mind when surgery is recommended.

Hematology

Hepatosplenomegaly, usually unexplained, is present in about 25% of patients. Bleeding problems and easy bruising have been noted fairly frequently. In a multicenter study by Wittet al,[28] a variety of bleeding problems, including factor XI deficiency, Von Willebrand's disease, thrombocytopenia, and platelet function defects were identified among 19 patients with **Noonan syndrome**. If there is any suspicion of a bleeding problem, a prothrombin time, partial thromboplastin time, bleeding time, and platelet count should be obtained and aspirin or aspirin-containing products avoided.

One of my first patients had persistent thrombocytopenia in childhood and died as an adult from aplastic anemia. A report by Piombo et al[29] described two patients with previously unrecognized **Noonan syndrome** among 307 consecutive patients with acute lymphatic leukemia, and they noted a previous reported case of acute lymphatic leukemia. Further long-term follow-up studies will be required before it is possible to determine whether or not there is an increased risk of malignancy in patients with **Noonan syndrome**.

Lymphatics

Lymphatic abnormalities occur in less than 20% of patients with **Noonan syndrome**. Lymphangiography[30] has demonstrated hypoplasia or absence of superficial lymphatic channels. Several fetuses have been reported with cystic hygroma who, on later follow-up, have findings characteristic of **Noonan syndrome**.[12,13] Puffy hands and feet are relatively common in severely affected newborns. This edema generally subsides but in some, lymphedema develops in late childhood or as adults. Intestinal lymphangiectasia leading to protein-losing enteropathy was first reported by Vallet et al.[31] In 1975, Baltaxe et al[32] reported pulmonary lymphangiectasia, and Smith and associates[33] described a patient with both chylothorax and protein-losing enteropathy in 1979. Spontaneous chylothorax has been reported,[34] and chylous effusion following cardiac surgery is a known risk in patients with **Noonan syndrome** (Figure 7).

Parental Concerns

Labeling a child as having **Noonan syndrome** should not be made without careful thought and evaluation. The word **syndrome** is frightening to parents. It suggests something abnormal, different, or imperfect. I prefer to suggest such children are special and have special needs. Parents are concerned about their children's futures and issues such as long-term complications and their ability to function in an adult world. In this review, I have tried to discuss the wide variety of problems that may occur in a child with **Noonan syndrome**. Fortunately, many children are very mildly affected and may essentially be treated as "normal." Because of the high incidence of abnormal eye and cardiac findings, these children should have careful eye and cardiac evaluations. In addition, hearing should be tested. Careful developmental assessment should be carried out before the child begins school, so that any potential learning disabilities can be recognized early, before the child develops any school problems.

A pamphlet on **Noonan syndrome** for parents has been produced by the Southeast Regional Genetics Group. For information, contact the Division of Genetics and Dysmorphology, Department of Pediatrics, University of Kentucky Medical Center, 800 Rose Street, Lexington, Kentucky 40536.

There is an active parent support group in England which also publishes a newsletter. (Contact the **Noonan Syndrome** Foundation, 27 Pin Fold Lane, Chelsey Hay.) In addition, there is a **Noonan syndrome** support group in San Jose, California, at 1278 Pine Avenue, San Jose, CA 95125.

Conclusion

Children with **Noonan syndrome** are special. They usually have a pleasant personality, although they may be a little immature because of their small size. The great majority will grow up and function normally in the adult world. However, they need to be counseled that there is a 50% chance that their offspring may be affected. These offspring may be only mildly affected or may have a more severe form of **Noonan syndrome**. It is important that we continue to learn more about the natural history of **Noonan syndrome** as well as to continue research into the underlying basic defect. Once a genetic defect is identified, a specific diagnostic test will likely become available and it will be possible to do prenatal testing.

PHOTO (BLACK & WHITE): Figure 1. Mother with **Noonan syndrome** and affected infant.

PHOTO (BLACK & WHITE): Figure 2A. Newborn with **Noonan syndrome**.

PHOTO (BLACK & WHITE): Figure 2B. Redundant nuchal skin.

PHOTO (BLACK & WHITE): Figure 3A. Patient with **Noonan syndrome** from Figures 2A and 2B shown here at 2 1/2 months.

PHOTO (BLACK & WHITE): Figure 3B. Same patient at 10 months of age.

PHOTO (BLACK & WHITE): Figure 3C. Same patient at 19 years of age.

PHOTO (BLACK & WHITE): Figure 4. Adult with **Noonan syndrome** who has an affected son.

PHOTO (BLACK & WHITE): Figure 5. **Noonan syndrome** with coloboma.

PHOTO (BLACK & WHITE): Figure 6. **Noonan syndrome** male showing webbed neck, chest deformity; and a few nevi.

PHOTOS (BLACK & WHITE): Figure 7. Chest ra-diograph showing dilated lymphatics and right chylous effusion in a postoperative patient with **Noonan syndrome**: (A) posterior-ante-rior view, (B)lateral view.

REFERENCES

1. **Noonan** JA. Hypertelorism with Turner phenotype. Am J Dis Child. 1968;116:373-380.

2. Nora JJ, Nora AH, Sinka AK, et al. The Ullrich-**Noonan Syndrome** (Turner phenotype). Am J Dis Child. 1974;127:48-55.

3. Kobylinski O. Ueber Eine Flughoutahnbiche Ausbreitung. Am Halse Arch Anthropol. 1883;14:342-348.

4. Ullrich O. Uber typische kombinationbilder multiper abanturgen. Z Kinderheilkd. 1930;49:271-276.

5. Turner HH. A **syndrome** of infantilism, congenital webbed neck, and cubitus valgus. Endocrinology. 1938;25:566-574.

6. Ullrich O. Turner's **syndrome** and status Bonnevie-Ullrich; a synthesis of animal phenogenetics and clinical observations on a typical complex of developmental anomalies. Am J Hum Genet 1949; 1:179202.

7. Flavell G. Webbing of the neck with Turner's **syndrome** in the male. Br J Surg. 1943;31:150-153.

8. **Noonan** JA, Ehmke DA. Associated noncardiac malformations in children with congenital heart disease. J Pediatr. 1963;468-469.

9. Opitz JM. Editorial comment: the **Noonan syndrome**. Am J Med Genet. 1985;21:515518.

10. Sharland M, Taylor R, Patton MA, Jeffrey S. Absence of linkage of **Noonan syndrome** to the neurofibromatosis type I locus. J Med Genet. 1992;29:188-190.

11. Allanson JE, Hall JG, Hughes M. **Noonan syndrome**: The changing phenotype. Am J Med Genet. 1985;21:507-514.

12. Bowie EV, Black V. Non-immune hydrops fetalis in **Noonan**'s **syndrome**. Am J Dis Child. 1986; 140:758-760.

13. Donnenfeld AE, Nazir MA, Sindoni F, Libviggi RJ. Prenatal sohographic documentation of cytic hygroma regression in **Noonan syndrome**. Am J Med Genet. 1991;39:461-465.

14. Mendez HM, Opitz JM. **Noonan syndrome**: A review. Am J Med Genet. 1985; 21:493-506.

15. Fryer AE, Holt PJ, Hughes HE. The cardio-facio-cutaneous **syndrome** and the **Noonan syndrome**: are they the same? Am J Med Genet. 1991;38:548-551.

16. Watson GH. Pulmonary stenosis, cafe-au-lait spots and dull intelligence. Arch Dis Child. 1967;42:303-307.

17. Gorlin RJ, Anderson RC, Blaw M. Multiple lentigenes **syndrome**. Am J Dis Child. 1969;117:652-662.

18. Kramer HH, Majewski F, Trampisch HJ, et al. Malformation patterns in children with congenital heart disease. Am J Dis Child. 1987; 141:789-795.

19. Roberts N, Deverall P, Stark J. In: Bergsma D, ed. The Cardiovascular System, Part E Baltimore, MD: Williams and Wilkins; 1972;5:122-123.

20. Duncan WJ, Fowler RS, Farkas LG, et al. A comprehensive scoring system for evaluating **Noonan syndrome**. Am J Med Genet. 1981; 10:37-50.

21. Sharland M, Burch M, McKenna WM, Patton MA. A clinical study of **Noonan syndrome**. Arch Dis Child. 1992;67:178183.

22. Lee NB, Kelly K, Sharland M. Ocular manifestations of **Noonan syndrome**. Eye. 1992;6:328-334.

23. Kaplan MS, Opitz JM, Cosset FR. **Noonan's syndrome**: a case with elevated serum alkaline phosphatase levels and malignant schiwannoma of the left forearm. Am J Dis Child. 1968;116:359-366.

24. Burch M, Mann J, Sharland M, et al. Myocardial disarray in **Noonan syndrome**. Br Heart J. 1992;68:586-588.

25. Burch M, Sharland M, Shinebourne E, et al. Cardiologic abnormalities in **Noonan syndrome**: phenotypic diagnosis and echocardiographic assessment of 118 patients. J Am Coll Cardiol. 1993;22:11891192.

26. Marantz PM, Huhta JC, Mullins CE, et al. Results of balloon valvuloplasty in typical and dysplastic pulmonary valve stenosis: Doppler echocardiographic follow-up. J Am Coll Cardiol. 1988;12:476-479.

27. Pierini DU, Pierini AM. Keratosis pilaris atrophicans facei (ulerythema ophryogenes): A cutaneous marker in the **Noonan syndrome**. Br J Dermatol. 1979; 100:409-416.

28. Witt DR, McGillioray BC, Allanson JE, et al. Bleeding diathesis in **Noonan syndrome**: a common association. Am J Med Genet. 1988;31:305-317.

29. Piombo M, Rosanda C, Pasino M, et al. Acute lymphoblastic leukemia in **Noonan syndrome**: report of two cases. Med Pediatr Oncol. 1993;21:454-455.

30. Hoeffel JC, Juncker P, Remy J. Lymphatic vessel dysplasia in **Noonan syndrome**. Am J Roentgenol 1980;134: 399-401.

31. Vallet HL, Holtzapple PG, Eberlein WR, et al. **Noonan syndrome** with intestinal lymphangiectasisa. J Pediatr. 1972; 80:269-274.

32. Baltaxe HA, Lee JG, Ehlers KH, Engle MA. Pulmonary lymphangiectasia demonstrated by lymphangiography in 2 patients with **Noonan syndrome**. Radiology. 1975;115:149-153.

33. Smith S, Schulman A, Weir EK, et al. Lymphatic abnormalities in **Noonan syndrome**. S Aft Med J. 1979;56:271274.

34. Goens MB, Campbell D, Wiggins JW. Spontaneous chylothorax in **Noonan syndrome**. Treatment with prednisone. Am J Dis Child. 1992;146:1453-1456.

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