GENETIC DRIFT
Mountain States Regional Genetic Services Network

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Management of Common Genetic Disorders

From the Editor and Authors:

The summer 1998 *Genetic Drift* is a compilation of health supervision guidelines for the diagnosis and management of six common genetic disorders. Individual guidelines have been set forth by the American Academy of Pediatrics (AAP), Committee on Genetics, and are referenced at the conclusion of each article. Our intent here is to offer this invaluable information in a single publication, for easy access by primary care and specialty providers. The authors have also incorporated additional current management suggestions for selected disorders. Please contact the Editor if you would like to learn of more extensive resources available regarding these conditions. Syndrome specific web sites are featured on page 12.

This issue was spearheaded by Peggy Pearson, MD (AZ), with contributions from her colleagues on the MSRGSN Clinical Services Committee: Joanne Milisa, MS (NM), Janet Stewart, MD (CO), Louise Gane, MS (CO) and Kirk Aleck, MD (AZ).

Carol L. Clericuzio, MD (NM), Editor

In This Issue

Achondroplasia

Introduction

Achondroplasia is the most common skeletal dysplasia with an incidence of 1/15,000 to 1/77,000 live births. It is an autosomal dominant disorder with complete penetrance and occurs in all ethnic groups. Eighty to 90% of cases are new mutations and advanced paternal age has been associated with de novo cases. An affected individual has a 50% risk to transmit the disorder to his/her child. The recurrence risk for two unaffected parents is less than 1%, although instances of gonadal mosaicism have been reported. If both parents are affected, there is a 25% risk for their child(ren) to be homozygous for the achondroplasia allele, resulting in a much more severe phenotype that is usually lethal within the first year of life. Achondroplasia is caused by a mutation in

fibroblast growth factor 3 (FGFR3) on chromosome 4, causing a defect in the maturation of chondrocytes in the cartilage growth plate. Direct mutation analysis is available for prenatal diagnosis or confirmation of equivocal cases.

Clinical Features

The clinical features of achondroplasia include disproportionate short stature with a normal trunk length and rhizomelic shortening of the extremities, macrocephaly, frontal bossing with a depressed nasal bridge, bowing of the lower extremities, trident hands, lumbar lordosis, infantile hypotonia with motor delays, and normal intelligence. Average adult height is 51 inches (130 cm) in males and 48.5 inches (123 cm) in females. The skeletal features of achondroplasia may lead to neurologic, respiratory, orthodontic, skeletal, and psychosocial problems.

Common Medical Complications

Neurologic complications include cervicomedullary junction compression, communicating hydrocephalus, spinal stenosis, and infantile hypotonia. The foramen magnum is relatively small in achondroplasia and may lead to a variety of neurologic abnormalities including apnea, paraparesis or quadriparesis, hydrocephalus, or sudden death. Therefore, it is critical to provide adequate neck support during the first year of life and to perform a thorough neurologic examination at each medical encounter. Infants should be referred to a pediatric neurosurgeon if there is any evidence of central apnea, reflex asymmetry, extreme hypotonia, or early hand preference. Only on very rare occasions is decompression of the foramen magnum necessary.

Megalencephaly with enlarged ventricles is common in achondroplasia due to anatomic abnormalities of the skull, however, symptomatic hydrocephalus requiring shunting is uncommon. Nonetheless, the head circumference should be measured monthly during the first year of life. A head ultrasound should be obtained if there is an unusually large fontanel, rapidly increasing head circumference, or other signs or symptoms of increased intracranial pressure develop, with referral to a pediatric neurosurgeon as necessary.

Spinal cord compression due to lumbosacral spinal stenosis is the most common neurologic complication of adolescents and adults with achondroplasia. It is exacerbated by lumbar lordosis and may present with a variety of neurologic signs and symptoms including weakness, paresthesias, pain, claudication, urinary or fecal retention or incontinence, abnormal deep tendon reflexes, or sensory loss. It is usually treatable with laminectomy if diagnosed early. Therefore, a thorough neurologic history and examination is required at each medical encounter. Maneuvers which may prevent or delay the development of this complication include discouragement of early sitting in infancy, avoidance of curled up positions, avoidance of gymnastics and contact sports, and correct posture. Epidural or spinal anesthesia is contraindicated.

The midface hypoplasia, short cranial base, and small foramen magnum characteristic of achondroplasia can lead to a number of respiratory complications including apnea, upper airway obstruction, otitis media, sinusitis, and dental malocclusion. Upper airway obstruction may manifest as excessive sweating, snoring, retractions, compensatory sighs, or choking. The development of any of these signs should be evaluated with sleep studies, sensory evoked responses, and/or MRI. Nasal CPAP, tonsillectomy and adenoidectomy, and weight loss have been beneficial in reducing upper airway obstruction.

There is an increased incidence of serous otitis media in achondroplasia due to short eustachian tubes. Therefore, an ear examination should be done with each upper respiratory infection and otitis media should be treated as necessary. Hearing should be tested annually and a formal speech evaluation should occur by two years of age. Sinusitis is also common in achondroplasia due to midface hypoplasia. It should strongly be considered in the differential diagnosis of the febrile child and treated if present.

Other skeletal complications of achondroplasia include low thoracic/high lumbar gibbus, lumbar lordosis, external rotation of the hips, joint stress, leg bowing, disc herniation, osteophyte formation, and short stature. The gibbus abnormality may be prevented by avoiding curled up positions and providing proper back support throughout life. The lumbar lordosis can be minimized by emphasizing correct posture beginning in early childhood. External rotation of the hips usually resolves spontaneously within six months of weight bearing. Leg bowing occurs due to

fibular overgrowth but usually does not require treatment. If it interferes with walking, an orthopedic referral may be indicated.

Other Medical Considerations

Short stature is the most significant problem for people with achondroplasia. Achondroplasia growth charts are available. Experimental limb lengthening procedures and growth hormone therapy have been tried in some patients, however, most people learn to adapt their environment to foster independence. Adaptations include lowering faucets and light switches, use of a step stool to keep feet from dangling when sitting, use of step stools, an extended wand for toileting, and adaptations of toys for short limbs.

Obesity occurs in approximately one-third of patients with achondroplasia and often develops by mid to late childhood. It may exacerbate lumbar lordosis, spinal stenosis, obstructive apnea, and other respiratory problems. A person with achondroplasia may only need half of the calories of an average-size individual of the same age. Nutritional counseling and regular exercise should begin in early childhood.

While achondroplasia does not affect fertility, pregnant women are considered high risk. Respiratory compromise is common during the third trimester and baseline pulmonary function studies should be done before pregnancy to aid in evaluation and management. Pelvic insufficiency necessitates Cesarean section under general anesthesia since the epidural approach is contraindicated.

Conclusion

The vast majority of people with achondroplasia have normal intelligence and lead healthy, independent, and productive lives. However, the presence of short stature can cause a number of psychosocial problems. Many families find it beneficial to interact with other families and children with achondroplasia through local and national support groups. Two national support groups are:

Little People of America
P.O. Box 9897
Washington, D.C. 20026
(888) LPA-2001
or (214) 388-9576

The Billy Barty Foundation
929 W. Olive Ave.,
Suite C
Burbank, CA 91506
(818) 953-5410

Reference:

Health Supervision for Children With Achondroplasia. Committee on Genetics. Pediatrics 95 (3): 443-451, 1995

Contributed by Joanne Milisa, MS (NM) and Peggy Pearson, MD (AZ)

Down Syndrome/Trisomy 21

Introduction

Trisomy 21 is the most common autosomal chromosome abnormality with an incidence of 1/800 live births. It occurs in all ethnic groups. Ninety-five percent are due to meiotic non-disjunction. Most of the time the extra chromosome is of maternal origin and the risk increases with increasing maternal age. A translocation is seen in 3-4% of cases, about half of which are de novo and half familial. Mosaicism is seen in 1-2% of children and the clinical picture correlates somewhat with the percentage of normal cells. The recurrence risk depends upon the etiology. In cases with non-disjunction and de novo translocations, the risk is about 1% plus the maternal age risk. Familial 21/21 translocations have a 100% recurrence risk. Other translocations have a lower recurrence risk with a 2-5% risk if the carrier is the father and a 10-15% risk if the mother is the carrier.

Clinical Features

Individuals with Down syndrome have characteristic facies and typical minor anomalies. Most striking in the newborn are the upslanting palpebral fissures, protruding tongue, abnormal palmar creases, and hypotonia. Once the diagnosis is suspected, it should be confirmed by a chromosomal analysis on cultured lymphocytes. The family should be referred for genetic counseling to discuss the diagnosis, the recurrence risks, and the options for prenatal diagnosis (amniocentesis, chorionic villus sampling, maternal serum triple screen, and/or ultrasound) in future pregnancies.

Common Medical Complications

The child with trisomy 21 is at risk for other abnormalities and complications. The most common is congenital heart disease, typically a ventricular septal defect although endocardial cushion defects are also common in Down syndrome. Cardiac defects require SBE prophylaxis for dental work or other invasive procedures. An echocardiogram is recommended for all infants with Down syndrome. The presence of Down syndrome per se does not adversely affect the outcome of surgery in the absence of pulmonary hypertension. Gastrointestinal anomalies are present in about 12% of individuals with Down syndrome including duodenal atresia/stenosis, tracheoesophagel fistula, Meckel diverticulum, Hirschsprung disease, imperforate anus and omphalocele. Hypotonia can lead to poor suck as well as constipation. Genitourinary involvement can include renal malformations, hypospadias, micropenis and undescended testes. The risk for leukemia is 10 to 30% higher than the general population risk, but is less than 1%. Neonatal leukemoid reactions are common.

Children should be referred for an ophthalmologic examination by 9 months of age. Common eye problems include congenital nystagmus or alternating esotropia (which often resolves), congenital cataracts, glaucoma, strabismus, refractive errors, and nasolacrimal duct obstruction.

The incidence of hearing loss approaches 75% with most cases being conductive due to serous otitis media. However, there may also be middle ear anomalies and/or sensorineural hearing loss. Therefore, all children should have formal audiograms by 6 months of age and hearing should be monitored at each office visit. In addition to otitis media, there is also a higher incidence of sinusitis and obstructive sleep apnea.

The major musculoskeletal abnormalities are hypotonia and hyperextensibility which contribute to gross motor delays. Atlantoaxial instability is seen on X-ray in 14% but only 1-2% develop signs of cord compression. Lateral neck films are recommended at 3 to 5 years of age (before participating in Special Olympics), before engaging in contact sports, or if symptoms of spinal cord compression develop. It is important to remember, however, that individuals can be symptomatic with normal neck films and, therefore, a thorough neurologic examination should be done at each office visit.

A variety of endocrine abnormalities may occur in Down syndrome. Thyroid dysfunction develops in 15% of children with Down syndrome and the signs and symptoms can mimic trisomy 21. Therefore, Down syndrome individuals should be screened at birth, 6 months, 12 months, and then annually. Sexual maturation is essentially normal with 15-30% of females being fertile. Appropriate contraceptive counseling should be given as the risk of having a child with Down syndrome is 50%. Males are usually infertile. In monitoring growth, it is important to use Down syndrome growth charts. Obesity becomes a problem with age and nutritional counseling and an activity program should be started early to keep weight under control.

Routine dental care is also important as crowding, periodontal disease, and caries can develop.

Other Medical Considerations

The major question raised by families has to do with the intellectual potential of a child with Down syndrome. The average IQ is 40-77, but this is a poor indication of their ability to function in society. Early developmental intervention and appropriate therapies are recommended. In general, children with Down syndrome are better with visual processing and right brain functions. Many are capable of working and living semi-independently. There have been a variety of controversial therapies which have been advocated, but none have been scientifically validated. Such therapies include sicca cell therapy, patterning treatment and craniosacral manipulation. The latter is potentially harmful if there is any vertebral subluxation. The most wide-spread nontraditional therapy includes vitamin and mineral supplementation as well as piracetam. Also controversial is plastic surgery to "normalize" facial features.

Although the life span for an individual with trisomy 21 is less than the general population, many are living into adulthood and present some unique health problems. In general, they have an accelerated aging process. Both hearing and vision should be tested annually because of the incidence of high frequency hearing loss and cataracts. Annual thyroid screening should also continue as 40% of adults with Down syndrome have thyroid dysfunction. There should be clinical monitoring for mitral valve prolapse and aortic regurgitation with an echocardiogram as indicated. SBE prophylaxis should continue in

patients with cardiac defects. The major concerns with aging are related to dementia and an Alzheimer-like picture. Nearly all Down syndrome adults over 40 years of age have increased senile plaques and neurofibrillary tangles. By 50 years of age, about 25% of adults with trisomy 21 will have some signs of dementia. Seizures may also begin as early as the third decade. Psychiatric disorders, particularly depression, can occur and need to be differentiated from dementia. In addition, routine medical and dental care is needed to monitor weight, nutrition, physical activity, socialization, and vocational placement.

Conclusion

The overall outlook for individuals with Down syndrome has changed markedly over the past 25 years. They are healthier, have increased longevity, are better integrated into society, and may be cared for in all types of medical settings.

References:

Health Supervision for Children with Down Syndrome. Committee on Genetics. Pediatrics 93 (5): 855-859, 1994

AAP issues guidelines on health supervision for children with Down syndrome. Am Fam Physician 50(3):695-697, 1994

Contributed by Janet Stewart, MD (CO)

Fragile X Syndrome

Introduction

Fragile X syndrome is the most common cause of inherited mental retardation with an incidence of approximately 1 in 2,000 male, and 1 in 2,500 female, live births. The carrier frequency in females is 1/259 and in males is 1/755. Fragile X syndrome is an X-linked disorder and occurs with equal frequency in all ethnic groups. Fragile X syndrome is responsible for approximately 10% of all cases of inherited mental retardation and 30% of cases of X-linked mental retardation.

The gene responsible for fragile X syndrome is located on the X chromosome and is known as the Fragile X Mental Retardation 1 (FMR1) gene. Within the FMR1 gene is a specific region of CGG repeats. Individual with fewer than 40 repeats are not at risk to pass on fragile X syndrome to their offspring. Individuals with 55 to 200 repeats are said to carry the FMR1 premutation. Male individuals with more than 200 repeats have fragile X syndrome. Females with more than 200 repeats have a 50-70% risk to have a low or borderline IQ and a 30-50% chance to have a normal IQ. Approximately 60% of females with more than 200 repeats and a normal IQ have learning problems and emotional or behavioral difficulties. There are a few reports in the literature documenting fragile X syndrome due to deletions of the FMR1 gene, but the vast majority of cases are the result of expansion of the CGG triplet repeat within the FMR1 gene. Expansion occurs when the gene mutation is passed from the mother to the child. If a mother carries the gene mutation, she is at a 50% risk to pass the gene mutation on to her child. If a father carries the gene premutation, he will pass the gene mutation on to his daughters in the premutation state. None of his sons will inherit the gene mutation.

The FMR1 gene produces the FMR1 protein (FMRP). In individuals with more than 200 repeats, the gene usually becomes methylated resulting in the gene being turned off. When the FMR1 gene is turned off, FMRP is not produced. It is the lack of FMRP that causes the cognitive features and connective tissue findings of fragile X syndrome.

Clinical Features

The physical features for males with fragile X syndrome include prominent ears, macrocephaly, hyperextensible joints, a long face, prominent forehead, high arched palate, macroorchidism, hand calluses, pectus excavatum, scoliosis, and flat feet. However, many of these features develop with age and are not easily distinguishable in young children. The physical features for females with fragile X syndrome include a long face, prominent forehead, hyperextensible finger joints, double jointed thumbs, mitral valve prolapse, soft skin, and flat feet. These characteristics are usually more prominent when an intellectual deficit is present.

Most males with fragile X syndrome have moderate mental retardation with an IQ ranging from 40 to 60. However, 13% of males with the full mutation have been reported to have an IQ above 70 (non retarded range). Young boys typically present with hypotonia, multiple ear infections, delayed language development, attention deficit disorder with or without hyperactivity, hand flapping, hand biting, gaze avoidance, and perseveration in speech and behavior. They may also present with a history of tantrums, irritability, sleep

problems, and hyperarousal to a variety of stimuli. Approximately 20% of individuals with fragile X syndrome experience partial or generalized seizures. Severely affected young girls with fragile X syndrome may present like the boys. Others may have more subtle features including emotional difficulties such as extreme shyness and poor eye contact, social anxiety, selective mutism, mood swings, and have attention problems, problems with math, and tactile defensiveness. Some fragile X syndrome girls experience precocious puberty.

Common Medical Complications

Each child with fragile X syndrome should be monitored carefully for otitis media, as many require tympanostomy tubes. Regular audiological exams should be done. A pediatric ophthalmologic exam is recommended to rule out strabismus, nystagmus, or myopia. Neurological evaluation may be warranted if seizures develop. A cardiology evaluation is indicated if there are signs or symptoms of mitral valve prolapse with insufficiency.

Young girls with fragile X syndrome present with a wide spectrum of findings which may include mental retardation and autistic like features, extreme shyness and anxiety which occasionally leads to selective mutism. In addition, they may have connective tissue problems similar to those found in males, such as scoliosis and mitral valve prolapse. Even those with normal IQ may have learning disabilities related to executive function deficits. This may lead to attention problems, poor topic maintenance, tangentiality in speech, and impulsivity.

Individuals with fragile X syndrome may benefit from a multidisciplinary approach to intervention. This includes specific medications for ADHD, occupational therapy with an emphasis upon sensory integration therapy, speech and language therapy, augmentative communication or assistive technology aids, and partial or full inclusion in the regular classroom.

Adolescents and adults with fragile X syndrome have unique problems that need to be addressed through ongoing medical and therapeutic approaches. These may include an increase in aggressive behavior, development of psychosis, heightened anxiety, sexuality issues, and difficulties around separation from parents. Often individuals dealing with these issues will benefit from counseling intervention provided by a professional who is experienced with working with those who have disabilities. In addition, specific medications are helpful in addressing these problems. Vocational planning is also important in the adolescent years as is transition into the workplace during young adulthood. The strengths of affected individuals (good memory, aptitude for rote and repetitive tasks, social skills, sense of humor, and computer skills) can be used for vocational planning.

Conclusion

Lifelong monitoring of health status, including mental health, for all patients diagnosed with fragile X syndrome is suggested. Life span is usually normal for these individuals. With changes occurring in society which promote inclusion of persons with disabilities, individuals with fragile X syndrome are likely to be cared for in a wide variety of medical settings.

References:

Fragile X Syndrome: Diagnosis, Treatment, and Research. Second Edition. Johns Hopkins University Press, 1996. Edited by Randi Jenssen Hagerman, M.D. and Amy Cronister Silverman, M.S

Health supervision for children with fragile X syndrome. Committee on Genetics. Pediatrics 98(2): 297-300, 1996

Contributed by Louise Gane, MS (CO)

Marfan Syndrome

Introduction

Marfan syndrome is an autosomal dominant, highly penetrant, disorder of connective tissue with extremely variable clinical expression. The frequency is 1 to 10 per 100,000 live births. About 15% of individuals with Marfan syndrome have new mutations; the rest are familial. It is caused by a defect in the fibrillin-1 gene (FBN1) on chromosome 15. Many different mutations of FBN1 have been identified, which may contribute to the variability seen in the disorder. Currently, no single gene probe or group of probes can detect most FBN1 mutations. Sequencing the entire gene for mutations is tedious, and often detects mutations that may represent normal variation, resulting in both false positives and false

negatives. Immunohistological evaluation of skin for abnormal fibrillin has been reported but is not widely available. For now, diagnosis of Marfan syndrome remains a clinical one.

Clinical Features

Marfan syndrome typically affects three major body systems: cardiovascular, skeletal, and ocular. Lungs and/or skin may also be involved.

Individuals with Marfan syndrome may be diagnosed at birth because of the presence of long thin, bones (dolichostenomelia). Others, however, are more subtle in their presentation and require years of close follow-up to diagnose. The diagnosis of Marfan syndrome is difficult due to extreme variability in presentation and the existence of several disorders similar to Marfan syndrome (e.g. homocystinuria). Detailed diagnostic criteria are now available. Diagnosis is based on manifestations in tissue and organ systems as well as family history. A series of major and minor criteria is used.

Skeletal System

Major Criteria: At least 4 of the following: 1) pectus carinatum, 2) pectus excavatum requiring surgery, 3) reduced upper-to-lower segment ratio or arm span to height ratio >1.05, 4) wrist and thumb signs, 5) scoliosis >20 degrees or spondylolisthesis, 6) reduced elbow extension (<170 degrees), 7) medial displacement of the medial malleolus causing pes planus, or 8) protrusio acetabulae (ascertained on radiographs).

Minor Criteria: Moderate pectus excavatum, joint hypermobility, high arched palate with dental crowding, or characteristic facial appearance.

Ocular System

Major Criterion: Ectopia lentis

Minor Criteria: Abnormally flat corneas, increased axial length of the globe, or hypoplastic iris or ciliary muscle causing miosis.

Cardiovascular System

Major Criterion: Dilatation of the ascending aorta involving at least the sinuses of valsalva or dissection of the ascending aorta.

Minor Criteria: Mitral valve prolapse, dilatation of the main pulmonary artery without valvular or peripheral pulmonic stenosis or other obvious cause before 40 years, or dilatation or dissection of the descending aorta before 50 years.

Pulmonary System

Major Criterion: None

Minor Criteria: Spontaneous pneumothorax and apical blebs.

Skin and Integument

Major Criterion: None

Minor Criterion: Striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy, or repetitive stress or recurrent or incisional hernias.

Dura

Major Criterion: Lumbosacral dural ectasia seen on CT or MRI imaging.

Minor Criterion: None

Family and Genetic History

Major Criteria: 1) A first degree relative who meets the criteria independently, 2) a mutation in FBN1 known to cause Marfan syndrome, or 3) a haplotpye around FBN1, inherited by descent, known to be associated with confirmed Marfan syndrome in the family.

Minor Criterion: None

Requirements for the Diagnosis of Marfan Syndrome

For the index case: If the family and genetic history is not contributory, major criteria in at least two different organ systems and involvement in a third system. If a mutation known to cause Marfan syndrome is present in other family members, major criterion in one organ system and involvement of another organ system.

Common Medical Complications

Cardiovascular abnormalities are the principle cause of mortality in Marfan syndrome. Dilatation of the aortic root can develop at any time and may result in death in the mid 30's without treatment. The use of β–blockers in patients with aortic dilatation and surgical repair of aortic aneurysms has increased life expectancy by at least 10 years. Patients need long-term cardiology follow-up and regular echocardiograms. Mitral valve prolapse requires antibiotic prophylaxis prior to dental or invasive procedures. Blood pressure should be monitored at each encounter and cardiac symptoms such as chest pain and syncope need further study. Non-strenuous exercise should be emphasized.

Eye abnormalities include myopia and subluxation of the lenses (ectopia lentis), but other findings such as sunken eyes (enophthalmos), down slanting palpebral fissures, and retinal detachments occur with increased frequency. Annual evaluation by an ophthalmologist is recommended. Ectopic lenses are of diagnostic significance and may cause visual impairment; myopia is usually treatable with refraction. The primary care physician should inquire about visual symptoms at each encounter and emphasize the importance of protective eyeware to prevent retinal detachment.

Skeletal complications include tall stature, scoliosis, pectus abnormalities, joint abnormalities, and malocclusion. Growth should be plotted on a Marfan syndrome growth curve. Rarely, hormone therapy may be used to accelerate puberty and limit height. Annual assessment of spine alignment, with referral to an orthopedist for rapid progression or curvature greater than 15 degrees, is indicated. Occasionally pectus anomalies compromise cardiac or respiratory function requiring surgical intervention during childhood. Cosmetic repair, however, should wait until at least mid-adolescence. Joint dislocations decrease with increasing muscle strength. Shoes with adequate arch supports are recommended for individuals with flat feet. Early orthodontic referral is beneficial.

The recurrence risk for Marfan syndrome is 50% for each pregnancy. Prenatal or preimplantation diagnosis are possible if the family's mutation is known. Affected women need a thorough cardiovascular evaluation before conception and those with an aortic root diameter <40 mm usually tolerate pregnancy well. Nonetheless, these women require close surveillance during pregnancy with echocardiography every 6 to 10 weeks. Delivery should be managed to minimize the second stage. There is an increased risk for aortic dissection for 6 to 8 weeks post partum.

References:

Rossiter JP, et al. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. Am J Obstet Gynecol 173(5):1599-1606, 1995

Shores J, et al. Progresssion of aortic dilitation and the benefit of long-term beta-adrenergic blockade in Marfan syndrome. N Eng J Med 330(19):1335-1341, 1994

Health Supervision for Children With Marfan Syndrome. Committee on Genetics. Pediatrics 98 (5): 978-982, 1996

Contributed by Kirk Aleck, MD (AZ)

Neurofibromatosis 1 (von Recklinghausen disease)

Introduction

Neurofibromatosis 1 (NF1) is a progressive multisystem disorder which affects approximately 1 in 3,000 individuals. NF1 is an autosomal dominant disorder with a high degree of penetrance, widely variable clinical expression, and a high frequency of new mutations, with only half of patients having an affected parent. Affected individuals have a 50% risk of transmitting the disorder to their children. However, parents of a child with a new mutation are not at an increased risk to have another affected child. The gene for NF1 is located on the long arm of chromosome 17 at band q11.2. It codes for a protein, called neurofibromin, which is thought to be a tumor suppresser. A number of point mutations and gene deletions have been identified in affected individuals. Commercial DNA testing for NF1 is offered as a protein truncation test, which does not detect all mutations. Due to controversy regarding the application of this test, the current standard of diagnosis remains clinical. In familial cases, prenatal diagnosis using DNA linkage analysis may be available.

Clinical Features

The diagnosis of NF1 requires the presence of 2 or more of the National Institutes of Health criteria including: 1) 6 or more cafe-au-lait spots of at least 5 mm. in diameter before puberty and 15 mm. in diameter after puberty; 2) 2 or more neurofibromata or one plexiform neurofibroma; 3) axillary or inguinal freckling; 4) optic glioma; 5) 2 or more Lisch nodules; 6) sphenoid dysplasia or cortical thinning of the long bones; or 7) a first-degree relative with NF1. Some of these features, such as size and number of cafe-au-lait spots, neurofibromata, freckling, and Lisch nodules, are age-dependent. Therefore, repeated examinations may be necessary to make the diagnosis in non familial cases.

Common Medical Complications

The incidence of complications in NF1 varies among studies and is generally overestimated. There is extreme variability in this disorder even within families. Approximately 1/3 have serious complications and 1/2 are only mildly affected.

The most serious complication of NF1 is an increased risk of malignancy. Fibrosarcomas are the most common tumors but other malignancies, such as central nervous system tumors and leukemia, also occur with increased frequency in NF1. The exact incidence of malignancy in NF1 is not known but is estimated to be approximately 5%. Therefore, each medical encounter should include evaluation for proptosis, increasing head size, focal neurological signs, pain or rapid growth of neurofibromata, and other signs and symptoms which could be indicative of malignancy. Treatment of malignancy in NF1 is no different than for the general population.

Various neurologic complications occur with increased frequency in NF1 including mental retardation, learning disabilities, speech delay, ADHD, seizures, and subtle neurologic abnormalities. Psychological and audiological assessments may be indicated prior to entering school. Early interventions should be initiated if abnormalities are present. Patients with seizures need to be evaluated for tumors of the central nervous system.

Optic gliomas occur with increased frequency in NF1 and may lead to blindness. Some authors advocate cranial imaging at the time of diagnosis to look for presymptomatic optic gliomas. However, the NIH Consensus Development Conference recommends cranial imaging only when clinically indicated. Patients with NF1 should have an annual ophthalmologic and neurologic evaluation to look for early signs of optic glioma or other CNS tumors.

Hypertension is common in NF1 and may be associated with renal artery stenosis, aortic stenosis, pheochromocytomas, adrenal tumors, or a variety of vascular hypertrophic lesions. Therefore, blood pressure should be monitored at every visit beginning in infancy.

A variety of skeletal changes may occur in NF1 including kyphosis, scoliosis, localized hypertrophy due to a plexiform neurofibroma, pseudoarthrosis, sphenoid dysplasia, and cortical thinning of the long bones. Each examination should include evaluation of asymmetry, deformity, and joint limitation and, if found, appropriate referrals should be made.

Gastrointestinal bleeding may occur due to a gastrointestinal neurofibroma. Referral to a gastroenterologist may be indicated.

Other Medical Considerations

Disfigurement may occur from the neurofibromata, especially if they are present on the face. In general, surgical removal of cutaneous neurofibromata is reserved for lesions which are very disfiguring or compromise function. Recurrence after removal is common.

Both precocious and delayed puberty are seen with increased frequency in NF1. In cases of precocious puberty, optic glioma or hypothalamic tumor should be ruled out. Puberty and pregnancy may cause cafe-au-lait spots and neurofibromata to increase in size and number.

Conclusion

In view of the complex nature of the disorder, all patients with NF1 should pursue surveillance of their health status every six to 12 months. A multidisciplinary team approach is recommended with the patient's primary care physician coordinating the care. Treatment of NF1 is primarily aimed at complications which are easier to manage when identified early. Each medical encounter should include evaluations of the skin, nervous system, skeletal system, and monitoring of blood pressure. If any abnormalities are detected, referral to the appropriate specialist should occur. Referral to local and national support groups may also be beneficial to the family.

References:

Gutmann DH, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 278(1):51-57, 1997

Health Supervision for Children with Neurofibromatosis. Committee on Genetics. Pediatrics 96 (2): 368-372, 1995

Riccardi VM. Von Recklinghausen neurofibromatosis. N Engl J Med 305(27):1617-1627, 1981

Contributed by Peggy Pearson, MD (AZ)

Turner Syndrome

Introduction

Turner syndrome is a condition in females characterized by short stature, gonadal dysgenesis, and a variety of other major and minor anomalies due to the lack of a normal second sex chromosome. It is the most common female sex chromosome abnormality, occurring in approximately 1/2,500 female live births. The remaining X chromosome is maternally inherited in two-thirds of girls with a 45,X karyotype. However, Turner syndrome is not associated with advanced maternal age.

Several cytogenetic abnormalities occur in Turner syndrome including 45,X, mosaicism with other cell lines, structural abnormalities of the second X chromosome, and/or cryptic Y mosaicism. Mosaicism for a normal cell line can be demonstrated in approximately 70% of Turner syndrome individuals. Low level mosaicism may be necessary for fetal survival since 1-2% of all conceptuses are 45,X but 99% of these abort spontaneously. Fifteen percent of spontaneous abortions have a 45,X karyotype.

Girls with a 45,X karyotype should have a sufficient number of cells analyzed to evaluate for low level mosaicism, and the use of fluorescent in situ hybridization using Y chromosome probes should be considered in the presence of a marker chromosome, ambiguous genitalia at birth, or virilization at puberty. There is a 15-25% risk of gonadoblastoma or dysgerminoma if Y chromosome material is present and, therefore, prophylactic gonadectomy is recommended by 6 years in these girls.

Clinical Features

The "classic" features of Turner syndrome include short stature, edema of the hands and feet, webbed neck or cystic hygroma, low posterior hair line, shield chest with wide spaced nipples, cubitus valgus, coarctation of the aorta, bicuspid aortic valve, horseshoe kidney, and lack of spontaneous secondary sexual development. However, these clinical features vary with patient age and are not present in all individuals with Turner syndrome. Only 15% of girls with Turner syndrome are diagnosed in the neonatal period. Over half of girls with Turner syndrome are not diagnosed until 12 to 14 years of age when they fail to develop secondary sexual characteristics.

Cardiovascular abnormalities are the primary cause of increased mortality in Turner syndrome. Consultation by a pediatric cardiologist is indicated at the time of diagnosis, and an initial echocardiogram should be obtained to evaluate the cardiac anatomy, especially for left-sided anomalies such as bicuspid aortic valve (50%) and coarctation of the aorta (20%). Prophylactic antibiotics for dental or surgical procedures, which may cause bacteremia, are recommended for all individuals with abnormal echocardiograms. Coarctation of the aorta requires surgical intervention, and individuals with bicuspid aortic valve are at increased risk to develop progressive aortic dilatation and/or dissection. Therefore, Turner syndrome patients with abnormal echocardiograms require ongoing cardiology management. The frequency of echocardiogram and consultation by a cardiologist in those patients whose initial evaluation was normal is not agreed upon. Some authors advocate annual echocardiograms, however, most pediatric cardiologists recommend consultation and echocardiography every five years in asymptomatic individuals to screen for aortic root dilatation or aneurysm.

Hypertension is a common feature of Turner syndrome due to cardiac and renal anomalies as well as idiopathic hypertension. Therefore, blood pressure and peripheral pulses should be assessed at each physical examination. Hypertension should be treated aggressively.

Renal anomalies are very common in Turner syndrome and a renal ultrasound should be obtained at the time of diagnosis. If a renal anomaly is detected, urinary tract infections may be more common and, therefore, should be strongly considered, and aggressively treated, in the febrile infant or young child.

Short stature is virtually universal in Turner syndrome, regardless of the karyotype. Turner syndrome girls may have some mild intrauterine growth retardation, but more typically have a normal growth rate until 2 years of age. A progressive deceleration in growth occurs from 2 to 11 years of age, and there is very slow growth during adolescence with an absence of a pubertal growth spurt. The average height in untreated adult women with Turner syndrome is 143 cm (4'8"). Individuals with Turner syndrome devel-

op progressive growth hormone deficiency and do not develop the normal pubertal increase in growth hormone and insulin-like growth factor. Turner syndrome girls should be treated with growth hormone when their height falls below the 5th percentile on the normal growth curve, usually between 2 to 5 years of age. Anabolic steroids may be added at 9 to 12 years. Therapy is continued until the bone age is greater than 15 years and the growth rate falls to less than 2 cm. per year. On this regimen, the final adult height is often greater than 150 cm (4'11").

After growth hormone therapy is completed, estrogen therapy is initiated to induce puberty, usually between 12 to 15 years of age. Estrogen therapy is continued throughout life to prevent osteoporosis and premature atherosclerotic heart disease. Progestin therapy is added 12 months after starting estrogen therapy to promote a normal menstrual cycle.

Other endocrine issues for Turner syndrome individuals include hypothyroidism, carbohydrate intolerance, osteoporosis, and infertility. Hypothyroidism, usually due to autoimmune thyroiditis, occurs in up to half of adult women with Turner syndrome. Annual thyroid screening with appropriate intervention is recommended.

Although the majority of adult women with Turner syndrome have an abnormal glucose tolerance test, due to mild insulin resistance, the incidence of diabetes mellitus is not increased. Therefore, routine glucose tolerance testing is not necessary. Obesity, which is present in about 40% of women with Turner syndrome, may increase insulin resistance and appropriate diet and exercise should be encouraged.

Premature osteoporosis is very common in Turner syndrome. Estrogen therapy may help to ameliorate the problem; however, adequate calcium intake and regular weight-bearing exercises are also recommended. Bone densitometry is recommended every 3 to 5 years, beginning at age 20.

Other Medical Considerations

The vast majority of women with Turner syndrome are infertile, although 2 to 5% have spontaneous menses due to residual ovarian function. Over 50 natural pregnancies have been reported in women with Turner syndrome. There appears to be an increased incidence of congenital anomalies, including chromosome abnormalities, spina bifida, and congenital heart defects. Turner syndrome patients with spontaneous pubertal development should be referred for genetic and reproductive counseling. For the remainder of women with Turner syndrome, in vitro fertilization with donor eggs is an option. Some centers have achieved pregnancy rates of 50 to 60% with this technique in Turner syndrome women. A thorough medical evaluation is strongly recommended prior to conception to rule out any contraindications such as cardiac or renal dysfunction.

Other issues that require monitoring by the primary care physician include an increased incidence of hearing loss and scoliosis. Otitis media and associated conductive hearing loss are common due to eustachian tube abnormalities. In addition, there is a high incidence of progressive sensorineural hearing loss. Therefore, annual hearing evaluations are recommended. Scoliosis occurs in about 10% of Turner syndrome girls, usually during adolescence. Careful monitoring and early intervention are recommended.

Conclusion

Intelligence is usually normal in individuals with Turner syndrome. However, many individuals with Turner have difficulty with visual-spatial relationships and there is an increased incidence of attention deficit disorder which may interfere with school performance. Therefore, it is recommended that a developmental evaluation be performed prior to starting school. Most women with Turner syndrome can expect to lead healthy and productive lives.

References:

Health Supervision for Children With Turner Syndrome. Committee on Genetics. Pediatrics 96 (6): 1166-1173, 1995

Saenger P. Turner's syndrome. N Engl J Med 335(23):1749-1754, 1996

Saenger P. Clinical review 48: The current status of diagnosis and therapeutic intervention in Turner's syndrome. J Clin Endocrinol Metab 77(2):297-301, 1993

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Web sites featuring professional medical advisory boards for specific disorders

National Down Syndrome Society	http://www.ndss.org/
The Turner's Syndrome Society of the US	http://turner-syndrome-us.org/
Fragile X Syndrome Information Resource	http://www.stayhealthy.com/hrdfiles/hrd00243.html
The National Neurofibromatosis Foundation	http://nf.org//
Little People of America	http://www-bfs.ucsd.edu/dwarfism//lpa.htm
National Marfan Foundation	http://www.marfan.org/

Announcement

Managed Care and Genetics Symposium
Wednesday, September 30, 1998; Microsoft Corporation, 2929 N. Central Ave., Suite 1200, Phoenix, AZ
Economic Realities and Perspectives in Managed Care and Genetic Services Delivery: A Dialog Between MCOs/HMOs and the Medical Scientific Communities.
This symposium, consisting of a panel of eight participants from the consumer, government, managed care and medical communities, is intended for medical and scientific professionals and consumers. The program, supported by a MSRGSN grant, will explore current and future options for the provision of genetics services in the context of managed care. Seating is limited to 70; the program will also be netcast on the Internet, and will allow for interactive discussion and questions. For more information, contact Susan Bryan, OmniTech, Inc. 5025 N. Central, Suite 177, Phoenix, AZ 85012; by email: omnitech@ww-web.com; or by phone at (602) 417-1573.

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