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Review Article

A Unique Case of Gorlin-Goltz Syndrome with Associated Soto Syndrome: A Review Article

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ABSTRACT

Gorlin Goltz syndrome is a hereditary condition, with complete penetrance and variable expressivity characterized by a wide range of developmental abnormalities and a predisposition to neoplasms. Soto syndrome is another hereditary syndrome with variable features. Clinical diagnosis of such syndromes relies on specific criteria. Gene mutation analysis confirms the diagnosis and genetic counseling is mandatory. Antenatal diagnosis is feasible by means of ultrasound scans and analysis of DNA extracted from fetal cells. This review considers the importance of genetic aspect of above said syndromes and how they can impact the treatment plan and follow up considerations of individuals suffering from these syndromes.

Keywords: Gorlin Goltz syndrome; Soto syndrome; Genetics; Genetic counselling

INTRODUCTION

Gorlin-Goltz syndrome also known as Bifid Rib Syndrome, Hermans-Herzberg Phakomatosis, Basal Cell Nevus Syndrome and Multiple Basal Cell Carcinoma Syndrome often presents itself in an early age. Main hallmarks of this syndrome are multiple basal cell carcinomas and multiple parakeratinized odontogenic keratocyst; however, there are other manifestations that are grouped into the five categories, namely cutaneous anomalies, dental and osseous anomalies, ophthalmic anomalies, neurological anomalies and sexual anomalies [1].

Many affected individuals will develop basal cell carcinomas which is a type of skin cancer. Basal Cell Carcinomas may appear as brownish, flesh-colored, or orange spots on the skin. They can also appear as red patches of skin or scars. The number of Basal Cell Carcinomas that can develop ranges from only a few spots to thousands of lesions. These lesions can vary in size from less than 1 millimeter to approximately 10 millimeters. The face, nape of the neck, back, and chest are most commonly affected. Sun-exposed areas of the skin are affected more often than areas that are not commonly exposed to the sun. Basal Cell Carcinomas do not usually spread to other areas of the body, but they can become aggressive and invade local tissue. Localized infection can develop and these lesions can crust, bleed and ulcerate. If left untreated Basal Cell Carcinomas can cause disfigurement, especially if located on the face. The appearance and behavior of basal cell carcinomas in this syndrome do not differ in any way from sporadic Basal Cell Carcinomas. The term, "nevoid" reflects the multiplicity, but not the characteristics, of the Basal Cell Carcinomas.

Gorlin Goltz Syndrome affected individuals may develop multiple distinctive small pits on the palms of the hands and the soles of the feet (palmar-plantar pits). These pits are present in about 65% of the patients. These are asymmetrical, ranging from 2-3 millimeters in diameter & 1-3 millimeters in depth. These pits develop late in the second decade but could be seen in patients as young as 5 years of age. They are caused by partial or complete absence of dense keratin in sharply defined areas. They can be seen much more clearly after soaking the hands or feet in warm water for approximately 10 minutes. Deepa et al. [2-4] Basal cell carcinomas may arise from these pits [4].

Dental anomalies like multiple odontogenic keratocyst are found in patients affected with Gorlin Goltz Syndrome. Woolgar et al. [5] and Dominiguez et al. [6] found significant differences between syndrome keratocysts and single keratocysts. Syndrome

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keratocysts were found to have a markedly increased number of satellite cysts, solid islands of epithelial proliferation, odontogenic rests within the capsule, and mitotic figures in the epithelial lining of the main cavity. There are immunochemical differences between syndromal and solitary keratocysts. Woolgar et al. noted that syndrome keratocysts tend to occur at a much earlier age than single keratocysts [7].

A variety of skeletal abnormalities may also be associated with Gorlin Goltz Syndrome including fused, splayed or missing ribs, abnormal curvature of the spine (scoliosis), extra fingers or toes (polydactyly), webbing of the fingers or toes (syndactyly), and Sprengel deformity, a condition characterized by elevation and/or underdevelopment of the shoulder blade (scapula), limited movement of the arm on the affected side, and the development of a lump at the base of the neck due to elevation of the shoulder blade. Affected individuals may exhibit a sunken chest (pectus carinatum) or a chest that protrudes outward (pectus excavatum).

Approximately 1% to 5% of affected individuals develop a medulloblastoma, the most common type of malignant brain tumor in children. Childhood medulloblastoma are also called primitive neuroectodermal tumor. Symptoms associated with a medulloblastoma can include headaches in the morning that improve as the day goes on, recurrent vomiting and difficulty walking and with balance. Medulloblastomas can spread to affect other areas of the central nervous system. Medulloblastomas associated with Gorlin Goltz Syndrome tend to occur around the age of 2, younger than in children without Gorlin Goltz Syndrome (isolated medulloblastoma). In addition, when associated with Gorlin Goltz Syndrome, this tumor is generally less aggressive than the isolated form.

GENETIC ORIGIN

Most cases of Gorlin Goltz Syndrome are caused by changes (mutations) in the *PTCH1* gene, but some rare patients that have no detectable mutation in *PTCH1* have been found to have mutations in *PTCH2*, a gene that is very similar to *PTCH1* while some have been found to have mutations in *SUFU*, and these can cause a similar set of characteristics (phenotype). All three genetic forms of the disorder are inherited in an autosomal dominant pattern. However, sporadic cases due to new mutations are common.

The *PTCH1* gene is as a tumor suppressor gene. A tumor suppressor gene is a gene that slows down cell division, repairs damage to the DNA of cells, or tells cells when to die, a normal process called apoptosis. The *PTCH1* gene creates (encodes) a protein that is involved in the sonic hedgehog pathway. This pathway involves a number of complex interactions that are critical for normal human development. These interactions involve the activation or repression of certain other genes. Impairment (dysregulation) of this pathway leads to human disease including cancer. *SUFU*, is another hedgehog pathway gene that works in concert with *PTCH1* to control cell growth and development. Symptoms like intellectual disability is unusual in patients with mutations limited to the PTCH1 gene and is often related to deletions or other chromosome rearrangements that affect PTCH1 along with surrounding genes.

Mutation of one of an individual's two copies of the *PTCH1* gene is believed to be sufficient to cause many of the developmental abnormalities associated with Gorlin Goltz Syndrome such as rib/vertebrae abnormalities or macrocephaly. However, cancer development in affected individuals is believed to follow the "two-hit" theory. This theory states that a second hit, damage to the normal copy of the *PTCH1* gene, is required before cancer can develop. This second hit can occur at any point after conception (somatically).

DIFFERENTIAL DIAGNOSIS

Several rare congenital disorders are characterized by the combination of macrocephaly with developmental defects and distinctive facial features. Such disorders include Beckwith-Wiedemann Syndrome (BWS), Sotos syndrome, and Bannayan-Riley-Ruvalcaba Syndrome (BRSS). These disorders are associated with signs and symptoms that can differentiate them from Gorlin Goltz Syndrome.

Sotos syndrome is an OverGrowth-Intellectual Disability (OGID) syndrome caused by a gene deletion with an autosomal dominant pattern of inheritance and characterized by cerebral gigantism, hypotonia, and joint hyperextensibilty. Other associated clinical features include large size, a large head (dolichocephaly), intellectual impairment, and distinctive facial features including a prominent forehead, widely spaced eyes, a high narrow palate, a pointed chin and a long face, scoliosis, seizures, renal anomalies, and cardiac anomalies.

There are several extremely rare disorders that are associated with basal cell carcinomas including Bazex syndrome and Muir-Torre syndrome. Bazex syndrome is characterized by multiple Basal Cell Carcinomas, milia, reduced sweating (hypohidrosis), abnormal loss of hair (hypotrichosis), and follicular atrophoderma, a skin condition involving breakdown of the follicles of the skin and causing lesions, especially on the arms and legs. Muir-Torre syndrome is characterized by a predisposition to skin cancer, including Basal Cell Carcinomas and sebaceous tumors, and gastrointestinal malignancies. This syndrome is a variant of Lynch syndrome and is usually caused by mutations in the *MSH2* gene, an established Lynch syndrome gene.

DIAGNOSIS

The diagnosis of Gorlin Goltz Syndrome is established in a proband with the following findings:

- Two major diagnostic criteria and one minor diagnostic criterion or one major and three minor diagnostic criteria by Evans et al. [1,8]. A similar series of diagnostic criteria was proposed by Kimonis et al. [9]. No study has been able to assess which combination of diagnostic criteria represents the best differentiation between sensitivity and specificity.

- Identification of PTCH1 or SUFU pathogenic variant on molecular genetic testing.

Molecular testing approaches can include

Serial single-gene testing,

Multigene panel, and Genomic testing.

Serial single-gene testing has the following suggested order:

1. Sequence analysis of PTCH1

2. Gene-targeted deletion/duplication analysis of PTCH1

3. Sequence analysis of SUFU

4. Gene-targeted deletion/duplication analysis of SUFU

5. RNA analysis of PTCH1

An important fact is that SUFU molecular testing should be considered first in families with medulloblastoma and without jaw keratocysts [10].

A recent review of 182 genotyped individuals with Gorlin Goltz syndrome found that individuals with PTCH1-related syndrome were more likely to be diagnosed earlier (p=0.02), have jaw cysts (p=0.002), and have bifid ribs (p=0.003) or any skeletal abnormality (p=0.003), than individuals with no identified pathogenic variant [11]. It has been reported that approximately 90% of individuals with PTCH1-related Gorlin Goltz Syndrome develop multiple odontogenic keratocysts. Jaw cysts have not been reported in individuals with SUFU-related Gorlin Goltz Syndrome [10]. A rare malignant transformation of a keratocyst called ameloblastoma has been reported in individuals with Gorlin Goltz Syndrome at least six times [12]. Ovarian fibromas occur with both SUFU and PTCH1- related Gorlin Goltz syndrome and may be more common in individuals with SUFU-related Gorlin Goltz Syndrome [12]. The risk for medulloblastoma in PTCH1-related syndrome was lower than 2% [13].

SUFU-related Gorlin Goltz syndrome is associated with a high risk for medulloblastoma of up to 33% and a high meningioma risk post radiation. Facial features are likely more subtle in individuals with an SUFU pathogenic variant. Overall, clinical features are milder in individuals with SUFU-related Gorlin Goltz syndrome; these individuals are reported with less Basal Cell carcinomas, and no jaw cysts [12].

Major features of Sotos syndrome include behavioral problems, advanced bone age, cardiac anomalies, cranial MRI/CT abnormalities, joint hyperlaxity/pes planus, neonatal jaundice, neonatal hypotonia and renal anomalies. The risk for sacrococcygeal teratoma and neuroblastoma is slightly increased. The diagnosis of Soto syndrome is established in a proband by identification of a heterozygous NSD1 pathogenic variant or a deletion encompassing NSD1 on molecular genetic testing. Sotos syndrome is inherited in an autosomal dominant manner with more than 95% of individuals having a *de novo* pathogenic variant.

Gorlin Goltz syndrome and Soto syndrome both have different genetic origin but only one case report has described the occurrence of these two syndromes simultaneously in a single individual. It describes the overlapping clinical features of both syndromes and with accompanying distinctive features to differentiate the two [1].

TREATMENT

The importance for early diagnosis and multi-disciplinary approach on treatment of this syndrome is of utmost importance to prevent life-threatening complications of this disease. Frequent follow up and genetic counselling should be provided.

FDA has approved two targeted drugs that specifically counteract the effect of PTCH1 mutations. Sonidegib and vismodegib specifically inhibit the hedgehog pathway. Both can be used for the treatment of adults with advanced basal cell carcinoma that has spread to other parts of the body or that has recurred following surgery. Vismodegib has also been used for treatment of medulloblastoma. These drugs may become first-line agents for treatment of Basal Cell Carcinomas with additional research and experience in clinical trials. A specific type of surgery called Mohs micrographic surgery may be recommended for some individuals with Basal Cell carcinomas. With this surgery, a surgeon uses a precise technique to remove diseased tissue one layer at a time. Other treatment modalities are cryotherapy, electrodessication, curettage and laser vaporization.

Individuals with SUFU mutations are not optimal candidates for the existing hedgehog pathway inhibitors because these inhibitors act upstream of the SUFU protein. Novel inhibitors that work downstream from SUFU are in development. These novel inhibitors should be effective in patients with PTCH1 or PTCH2 mutations as well.

Follow up of head circumference should be done throughout childhood. Possibility of hydrocephalus should be ruled out in case of rapid enlargement of head circumference. Awareness of the risk of medulloblastoma in the first years of life is important and may justify developmental assessment and physical examination every six months. No evidence exists for the efficacy of regular neuroimaging; frequent computed tomography scans should be avoided because of risks associated with radiation sensitivity. A consensus meeting has suggested annual head MRI scans until age eight years in affected children [14], but this would require general anesthesia for many children and is probably not now justified in PTCH1-related Gorlin Goltz Syndrome with only a 2% risk [15]. However, it may well be justified in infants with SUFU pathogenic variants [13]. It has been supported by a consensus statement recommendation to "consider brain MRI every four months through age three years, then brain MRI every six months until the age five years" [15]. A baseline heart ultrasound examination in infants and ovarian ultrasound in women at age 18 have also been advised [15]. In order to identify jaw odontogenic keratocyst orthopantogram is indicated every 12-18 months in individuals older than age eight years [15]. Skin should be examined at least annually; some physicians recommend skin examination by a dermatologist every three to four months.

In general, regular multispeciality visits should be implied in such patients, protection from exposure to sun is vital and a periodic follow up at weekly interval followed by regular intervals of 6 months till 5 years, followed by once annually for the entire life should be practiced.

CONCLUSION

This review explores the genetic side of both Gorlin Goltz syndrome and Soto syndrome. The importance of preliminiary diagnosis and genetic counseling cannot be overstated. This knowledge, adequate treatment and follow up protocol can save the patient from avoidable complications. The spectrum of features shown in both syndromes can mislead one into making an incorrect diagnosis. Existence of both syndromes in a single patient can be appreciated in our case report but this has been devised based on clinical, radiographic and histologic features only. A genetics oriented approach is required towards such patients in order to contribute more to the already magnanimous list of features in these syndromes.

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