A BRIEF REVIEW ON COHEN SYNDROME

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ABSTRACT

Cohen syndrome is a hereditary condition with a wide range of symptoms, including hypotonia (decreased muscle tone), abnormalities of the head, face, hands, and feet, abnormalities of the eyes, and non-progressive intellectual incapacity. The majority of those who are affected have microcephaly, a condition that shows that the head circumference is smaller than would be reasonable given the infant's age and gender. Obesity is prevalent in many older individuals, especially in the torso and is linked to skinny arms and legs. Some affected people have a reduced level of certain white blood cells called neutrophils (neutropenia) from birth. The VPS13B/COH1 gene is mutated in the autosomal recessive genetic disorder known as Cohen syndrome. This review summarizes regarding Causes, Symptoms, Clinical Description, Diagnosis and Treatment of Cohen syndrome.

Key words: Cohen syndrome, Hereditary, Neutropenia, Obesity.

INTRODUCTION

Cohen syndrome is an extremely rare autosomal recessive genetic condition also known as Pepper syndrome or Cervenka syndrome. The Cohen syndrome was first identified in three infants who had a distinctive facial appearance along with mental impairment, hypotonia, joint laxity, obesity that started in middle childhood, and ocular defects in 1973 by Cohen *et al*. Since then, more than 100 cases have been documented globally. In 1984, Norio colleagues expanded the definition of Cohen syndrome to include microcephaly, neutropenia, and particular ophthalmic abnormalities, such as severe myopia and retinal dystrophy. They did this by reporting on a small group of Finnish patients. An autosomal recessive pattern of inheritance was supported by the reported families' consanguinity. A cohort of 29 Finnish individuals was later defined, and this revealed a remarkably homogenous clinical profile with recurrent ophthalmological and hemological problems. The Cohen syndrome gene, COH1, has one significant location on the long arm of chromosome 8 in this cohort, according to molecular genetics research. The majority of Finnish patients were explained by a common ancestral mutation, according to haplotype analysis, which revealed a substantial founder impact. [1-2]

CAUSES OF COHEN SYNDROME

Cohen syndrome is brought on by mutations or alterations in the COH1 gene. The VPS13B gene is another name for this one. In order to make proteins, which are essential to numerous bodily processes, genes supply instructions. The protein product may be flawed, ineffective, or nonexistent when a gene is altered. The effects on various body organ systems will depend on how the protein operates.

Researchers have determined that the protein product of the *COH1* gene is involved in glycosylation, the process by which sugar 'trees' (glycans) are created, altered and chemically attached to certain proteins or fats (lipids). When these sugar molecules are attached to proteins, they form glycoproteins; when they are attached to lipids, they form glycolipids. Glycoproteins and glycolipids have numerous important functions in all tissues and organs. Glycosylation involves many different genes, encoding many different proteins such as enzymes. A deficiency or lack of one of these enzymes can lead to a variety of symptoms potentially affecting multiple organ systems, and there is nearly always an important neurological component. Symptoms can vary in severity.

The autosomal recessive inheritance pattern for Cohen syndrome. An individual develops a recessive genetic condition when they inherit a defective gene from both parents. A person will be a carrier for the disease if they have one healthy gene and one disease-causing gene, although they often won't exhibit any symptoms. With each pregnancy, there is a 25% chance that two carriers will pass the defective gene and result in an afflicted child. With each pregnancy, there is a 50% chance that the child will carry the same gene as one of the parents. A child has a 25% chance of inheriting normal genes from both parents. Both men and women are at the same level of danger. [3]

SIGNS AND SYMPTOMS

Patients with Cohen syndrome frequently have abnormalities in the morphology of their eyelashes and eyelids, teeth, lingual aplasia or hypoplasia, arachnodactyly, chorioretinal dystrophy, downslanted palpebral fissures, gingival overgrowth, global developmental delay, a high and narrow palate, maxillary hypoplasia, zygomatic bone hypoplasia, hypotonia, intellectual disability, Other symptoms that are frequently noticed include abnormal skin pigmentation, a cat cry, cubitus valgus, decreased foetal movement, delayed puberty, failure to thrive in infancy, feeding issues in infancy, syndactyly, genu valgum, intrauterine growth retardation, joint hyperflexibility, macrodontia, narrow palm, obesity, short stature, thick hair, and a weak cry. [2]

CLINICAL DESCRIPTION

Clinical signs differ from family to family. Since the distinctive facial characteristics are not yet developed, babies appear normal at delivery, albeit neutropenia may be present. Feeding issues, hypotonia, microcephaly, delayed developmental milestones (rolling over, sitting independently), and joint hypermobility are among of the initial symptoms. The majority of patients are short-statured, with smaller-than-normal hands and feet, as well as truncal obesity in adolescence. The development of distinctive facial characteristics, such as high-arched or wave-shaped eyelids, thick hair, a low hairline, a short philtrum and long, thick eyelashes, a prominent nasal root, and upper central incisors, begins at the age of five and intensifies between the ages of seven and fourteen, continuing into adulthood. Speech takes longer to develop. In certain people, aphthous ulcers are present. [4]

Some individuals also experience recurrent upper respiratory infections, which may be related to neutropenia. Although intellectual disability is observed, it is not progressive, and new ideas can be learned. Patients frequently have a positive outlook and are quite gregarious. In the majority of instances, retinochoroidal dystrophy symptoms are evident in adolescence along with myopia and strabismus. With time, nyctalopia and a condensed visual field appear, and after the age of 30, vision gradually starts to decline. Severe retinochoroidal atrophy and posterior subcapsular cataracts affect patients above the age of 45. Although severe, visual defects do not result in blindness. [4]

Characteristic clinical features of Cohen syndrome are well-described and involve multiple systems as discussed below [5-6]

Perinatal

Two of the three patients in the first study by Cohen et al. exhibited less foetal activity. As many as 50% of individuals had decreased foetal activity, which is a persistent observation. Although most babies are delivered at term, their weight and length at birth are frequently between the 10th and 25th percentile. Infancy can show signs of hypotonia, which can make

breathing and eating very difficult. According to some authors, a high-pitched cry may be brought on by laryngeal anomalies similar to those seen in 5p deletion (Cri-du-chat) syndrome.

Growth

Low birth weight and short stature are possible, although they are not necessary characteristics. Teenagers may experience true obesity. The term "obesity" has been suggested to be replaced with "abnormal truncal fat distribution" because these patients frequently have an enlarged waist circumference but a normal body mass index (BMI). According to functional research, the increased fat deposition in Cohen syndrome patients is caused by pre-adipocytes' higher propensity to develop into cells that store fat. Accelerated expression of some adipogenic genes is caused by an enhanced responsiveness of cells to insulin during early stages of differentiation.

Development

The development of motor milestones is significantly delayed, and independent walking typically appears between the ages of two and five. The first words often come out between one and five years old, however there could also be a language delay. Many people are unable to talk in complete phrases by the age of six. All Cohen syndrome patients have some degree of intellectual disability, and up to 22% of them have substantial delay. Disordered social interactions are frequent and include things like having trouble forming friends, communicating nonverbally, comprehending others' feelings, and sharing. Although afflicted people can typically eat and use the loo independently, patients may struggle with independence and self-help. Both males and females appear to be equally affected by these defects. Additionally, reports of a positive outlook, a kind attitude, and a high voice have been made. Behaviour that is antisocial, violent, destructive, rebellious, or unreliable is uncommon. There is a chance that some Cohen syndrome patients will also test positive for an autistic spectrum disorder. It is crucial to start early intervention programmes in speech/language therapy, physical therapy, and occupational therapy to treat motor deficits and hypotonia. Sign language can be used to communicate effectively in many situations.

Craniofacial abnormalities

Cohen syndrome has "typical facial characteristics," which include microcephaly, down-slanting palpebral fissures, wave-shaped palpebral fissures, hypertelorism, thick eyebrows, thick bushy hair, low hairline, long and thick eyelashes, very short philtrum, prominent upper central incisors, open mouth appearance because of a short upper lip, maxillary hypoplasia, micrognathia, and high and narrow palate. large nasal root, bulbous nasal tip, broad, improperly folded earlobes, or nonexistent or very little lobules.

Dentition

In addition to the characteristic prominent upper incisors, patients may have an early periodontal breakdown, extensive alveolar bone loss, and often harbor putative pathogens more likely to be associated with periodontitis. A critical concern in patients with Cohen syndrome is the possibility of a difficult airway caused by characteristic craniofacial deformities and prominent upper incisors. During procedural anesthesia, it may be prudent to have the equipment to manage a difficult airway and an otolaryngologist available to provide a surgical airway if needed.

Ophthalmologic

In addition to the early onset of high-grade myopia, which frequently requires corrective glasses as early as two years old, there is a steady decline in vision throughout life. By the second decade of life, visual function has deteriorated due to progressive contraction of the visual fields. Despite the rarity of total blindness, many affected persons have considerable vision impairment by the age of 40. As a result of dysgenesis and atrophy of the cornea, ciliary body, and iris, which results in iridial and zonular laxity and spherophakia, refractive myopia is most frequently of the high corneal and lenticular power variety.

Cohen syndrome has symptoms and characteristics that are similar to retinitis pigmentosa. Other findings include retinal macular pigmentation, microphthalmia, microcornea, strabismus, astigmatism, shallow anterior chamber, slow pupillary response, retinal degeneration, bull's eye maculopathy, optic nerve atrophy, chorioretinal dystrophy, peripapillary macular atrophy, periorbital extrinsic atrophy, periorbital extremity, suborbital atrophy. clefts, ptosis and colobomas. Although rare, acute angle-closure glaucoma has also been reported. Progressive retinal dystrophic alterations may eventually reduce vision to the ability to count fingers and see light. Attenuated or extinguished responses are frequently visible on electroretinograms. Early repair of vision issues, such as the use of corrective lenses for strabismus or refractive problems, benefits development. To stop the evolution of pigmentary retinopathy, there is, however, no effective medication currently available. Patients should get thorough ophthalmologic examinations on a regular basis to check for refractive problems or retinal dystrophy.

Hematologic

Cohen syndrome frequently has leukopenia, notably neutropenia. When present from birth, severe congenital neutropenia (SCN) is usually mild to moderate, noncyclic, and not deadly. Neutrophil leukocytosis is a common side effect of bacterial infections in patients. SCN could not have serious bacterial infections, but other patients might have chronic or recurring gingivitis, recurrent infections, or aphthous ulcers. Cellularity in bone marrow is often normal or elevated. De Ravel et al. identified one patient who had asymptomatic chronic thrombocytopenia and what they believed to be Cohen syndrome; however, this result has not been reported elsewhere in the literature. Two sibling cases of hypercoagulability with deficiencies in protein C, protein S, and anti-thrombin III complicated by severe thrombosis have been reported; however, molecular testing in this report did not definitively rule out Cohen syndrome as the cause. Neutropenia may be treated with recombinant human granulocyte colony stimulating factor (rHG-CSF). Patients with SCN and recurring infections and/or aphthous ulcers would benefit from using rHG-CSF. To check for neutropenia in these people, serial absolute neutrophil count (ANC) measurements are also necessary.

Gastrointestinal

As many as 75% of patients have reported having trouble feeding as newborns.

Musculoskeletal

Cohen syndrome sufferers typically have thin hands and feet. While hypotonia is frequently first noted during the newborn period, it becomes clear by the age of one. Later on, spasticity might appear. Cubitus valgus, genu valgum, pes planovalgus, kyphosis, scoliosis, ligamentous laxity, and articular hypermobility are just a few more musculoskeletal abnormalities that may be present, many of which are attributable to underlying muscular hypotonia. One transverse palmar crease, thenar and hypothenar hypoplasia, slight syndactyly, a significant space between the first and second toes, and lumbar lordosis may also be present in some people. Cohen syndrome has also been linked to reports of juvenile rheumatoid arthritis.

Neurologic

Brisk tendon reflexes, muscle hypotonia, and motor incoordination or "clumsiness" are characteristics that are rather common among patients. Additionally, cerebellar hypoplasia has been documented. An enlarged corpus callosum may be discovered during a magnetic resonance imaging (MRI) study to rule out other potential reasons of mental impairment, supporting the diagnosis. Although they have been mentioned in certain cases, seizures and electroencephalographic (EEG) abnormalities are not typical characteristics of Cohen syndrome. Patients may receive low-voltage, painless EEGs.

Cardiac

Cohen syndrome has been associated with a number of cardiac defects, including aging-related decreased left ventricular function, valvular defects (such as a floppy mitral valve and mitral regurgitation), vascular defects, such as a dilated descending aorta, cardiac systolic murmurs, ST segment abnormalities (ST-segment depression, T-wave inversion), essential hypertension, and pulmonary hypertension. Along with frequently meeting numerous criteria for metabolic syndrome, patients frequently exhibit lower levels of high-density lipoprotein (HDL).

Endocrine

Delayed onset of puberty is typical. North et al. described identical twin girls with Cohen syndrome with precocious puberty, although this is not typical. Gonadotropin deficiency, growth hormone deficiency, insulin resistance, non-insulin-dependent diabetes mellitus, and cryptorchidism have been described. After elevated fat accumulation in VPS13B-deficient cells, insulin resistance is observed through a reduction in phosphorylation of AKT (a protein kinase), which may explain the impaired glucose tolerance in some Cohen syndrome patients. Thus, it may be important to monitor blood pressure, lipid metabolism parameters, fasting blood glucose levels, and glycated hemoglobin (A1C) annually. Furthermore, older patients may have an abnormal glucose tolerance despite relatively normal fasting blood glucose levels. It may, therefore, be prudent to perform oral glucose tolerance tests in adolescence, and every five years thereon.

Genetics

Cohen syndrome is an autosomal recessive condition that Tahvanainen et al. initially identified on chromosome 8 at the Chediak-Higashi syndrome gene (CHS1) locus in 1994. The vacuolar protein sorting 13 homolog B (VPS13B, COH1) gene on chromosome 8q22.2 encodes a transmembrane protein and is transcribed from 62 exons that cover an 864 kb genomic area in Saccharomyces cerevisiae. A total of 4,022 amino acids make up the 44.8 kilodaltons (kDa) molecular weight of the translated protein VPS13B. VPS13B is a transmembrane protein that is involved in the development and operation of the eye, haematological system, and central nervous system. It is hypothesised to work in the vesicle-mediated transport and sorting of proteins within the cell. VPS13B co-localizes with the cis-Golgi matrix protein GM130 at the Golgi complex where it forms a physical and functional complex with the small GTPase RAB6. This complex is essential for preserving the structural and functional integrity of the Golgi complex. Additionally, it has been demonstrated that VPS13B is essential for both endosome-lysosome trafficking and the glycosylation of Golgi proteins. It is still unknown what alterations in this protein do to cause Cohen syndrome's phenotype.

DIAGNOSIS [7-9]

Suggestive Findings

- Retinal dystrophy appearing by mid-childhood
- Progressive high myopia
- Acquired microcephaly
- Non-progressive intellectual disability and global developmental delay
- Hypotonia
- Joint hypermobility
- Typical Cohen syndrome facial gestalt: thick hair and eyebrows, long eyelashes, wave-shaped palpebral fissures, broad nasal tip, smooth or short philtrum, and hypotonic appearance
- Short stature
- Small or narrow hands and feet
- Truncal obesity appearing in or after mid-childhood
- Friendly disposition
- Neutropenia

Establishing the Diagnosis

Cardinal features

- Retinal dystrophy and high myopia
- Microcephaly
- Developmental delay
- Joint hypermobility
- Typical Cohen syndrome facial gestalt
- Truncal obesity with slender extremities

- Overly sociable behavior
- Neutropenia

Molecular testing approaches can include the following:

- Single-gene testing
- Targeted analysis
- A multigene panel

TREATMENT [10-11]

Cohen syndrome is treated according to the distinct symptoms that are present in each patient. The coordinated efforts of a group of professionals may be necessary throughout treatment. The treatment of an affected child may require the coordinated efforts of paediatricians, paediatric neurologists, orthopedists, ophthalmologists, psychiatrists, speech pathologists, and other medical specialists. It is advised that afflicted individuals and their families get genetic counselling.

There are many different and difficult treatment approaches that can be employed to treat Cohen syndrome patients. The particular treatment strategy must be highly individualised. Depending on the specifics of the patient's case, a thorough discussion of the potential benefits and risks, including possible side effects and long-term effects, the patient's preference, and other pertinent factors, doctors and other members of the health care team should decide whether to use a particular treatment. This includes consulting with the parents of an affected child or an adult patient.

It's crucial to intervene in children's development at an early age to make sure they can develop to their full potential. Therapy in the areas of occupational, physical, and speech will help the majority of affected youngsters. Different forms of behavioral and rehabilitative therapy may be helpful. There may be a need for additional medical, social, and/or vocational services, as well as specific remedial schooling. It's also crucial to provide psychosocial assistance for the entire family.

Spectacles and eyeglasses to aid vision are among the specific therapies for Cohen syndrome. Low vision training may be required in later years for those with visual impairments. Standard medicines, such as antibiotics, can be used to treat recurrent infections. Granulocyte-colony stimulating factors (G-CSF) may occasionally be administered as a treatment for neutropenia. The hormones that naturally cause the bone marrow to produce neutrophils are re-created in G-CSF. The bone marrow produces more neutrophils and they are more effective in killing bacteria thanks to G-CSF.

CONCLUSION

The early indications and symptoms of the patient can be improved, but there is no actual cure for this illness. When a child exhibits microcephaly, neutropenia, or developmental abnormalities, it is imperative to consider an early diagnosis. To avoid such issues, the various professionals should carefully consider the characteristics and work. This is crucial for the patient, who will benefit from a suitable intervention, as well as the relatives, who can receive proper counselling regarding the underlying cause, prognosis, and associated hazards. Additionally, doctors need to be aware of concerns related to neutropenia, inadequate teeth and problematic airway during anaesthesia, and feeding issues as they may call for extra care and attention.

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