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A review on yunis-varon syndrome

Ch. Bhagya Sri[1*], R. Harshavardhini[2], V. Syam Kumar[2], K. Ramakrishna[2], A. Venkata Shiva[2], Kadari Sowjanya[3]

[*1, 2]-Pharm.D, Department of Pharmacy Practice, Avanthi Institute of Pharmaceutical Sciences, Vizianagaram

[3] DMO - nephrology department, Sri hostolic hospitals, Hyderabad

Abstract

Yunis Varon Syndrome was first discovered by Emilio Yunis and Humberto Varon in the year 1980. It affects both genders in equal number. Most of the infants are with Cleidocranial dysplasia, ectodermal anomalities, distal aphalangia. By the characteristic features which including deformity of the pelvis, dislocation of hips , bone fracture, urinary tract abnormalities, central nervous system abnormalities by this they have reported the condition as Yunis Varon Syndrome. This is an autosomal recessive inherited multisystem disorder due to FIG4 gene mutations, consanguineous marriages, Lysosomal defects, which may leads to improper in the functioning of organs in the infants. Metabolic disorders in which abnormal growth due to some toxic substances in the body. Affected people with this syndrome may experience breathing problems, abnormalities in the skeletal system, congenital heart defects. Genetic testing for mutation can be detected through diagnosis. In some conditions they may also be detected before birth of the baby that is prenatally by ultrasonography. Many of the infants did not survive beyond on year. Genetic counselling will be of benefit for affected individuals and their families.

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*Corresponding Author
Ch. Bhagya Sri

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Introduction

Yunis varon syndrome is a rare condition which may leads to the abnormal formation of body parts. Yunis – Varon in the year 1980 first described the syndrome based on three Colombian families (4). They reported five infants who had cleidocranial dysplasia, ectodermal anomalities, distal aphalangia, severe micrognathia [1].

It is an extremely rare autosomal recessive inherited multisystem disorder. Mutations in FIG4 have been identified in several consanguineous families. This syndrome undergoes phenotypic and molecular delination. The phenotypic changes involves the clavicles and head mandible , and distal limbs. Craniocerebral anomalities which may include poor growth of cranial bones, large fontanels and some malformations [1].

In some children, urinary tract abnormalities may also occurs which may include abnormal placement of urinary opening.

In the year 1983, Hughes and Partington reported a case with same pattern of malformations, mental retardation which they have also referred the condition as Yunis- Varon syndrome [1].

Affected people with this syndrome may experience breathing problem, brain malformations, heart defects, skeletal abnormalities and some difficulty in body functioning. Yunis-Varon syndrome has been been reported less than 15 cases in 1980s of which the infants did not survive beyond one year of age.

This syndrome is inherited in an autosomal ressive manner. AS it may be due to FIG4 encoding gene mutations which results in complete loss of protein function. Yunis Varon syndrome affects less than 2,00000 people in United States. This syndrome is passed due to hereditary, imbalance of FIG4 mutations, a history of consanguinity.

High risk involves when both parents are carriers and defective gene passes which may results nearly 25% chance of having an affected child, who could be the carrier like parents. Some affected infants include abnormalities in the skeletal region, dislocation of both hips, abnormalities of the heart such as cardiomyopathy.

Epidemiology

Yunis- Varon syndrome has been described relatively in the year 1980s. In the US it is estimated to be fewer than 1000.

Yunis- Varon syndrome is an extremely rare disorder that affects males and females in equal numbers.

Many of the infants who are affected with this condition did not survive beyond one year.

Etiology

Yunis- Varon syndrome is an autosomal recessive genetic condition which may be caused due to the FIG4 gene mutation.

FIG4 mutations can also cause Charcot- Marie- Tooth disease, which is a condition with improper functioning of peripheral nerves, brain malformations.

Yunis- Varon syndrome may be due to defects in lysosomal storage. Lysosomal storage diseases are a group of metabolic

disorders in which there is abnormal growth of toxic substances in our body cells.

Mutations in VAC14 gene also causes this syndrome.

Yunis- Varon syndrome may also be due to history of consanguinity.

Pathophysiology

Yunis- varon Syndrome was 1st discovered by Emilio Yunis and Humberto Varon from the national university of Colombia. Yunis and Varón 1st described the syndrome that bears their name in 1980, based on 3 Colombian families with a total of 5 affected children. Several mutations in the FIG-4 and VAC14 encoding gene results to Yunis-Varon Syndrome [4].

Some mutations lead to complete loss of protein function, some involve amino acid substitution at highly preserved residue. Not all mutations result in YVS, some mutations result in various forms of charcot- marie- tooth diseases, amytrophic lateral sclerosis II. YVS has been described relatively recently in the 1980's and since then roughly around 25 cases have been reported around the world.

FIG4 encodes a lipid phosphatase that is part of a multiprotein complex regulating the abundance of the signaling phosphoinositide PI [3, 5] P. The protein complex, which is localized on the membranes of late endosomes and lysosomes, also contains the kinase PIKfyve/FAB1 that converts PI [3] P to $PI(3,5)P_2$ and the scaffold protein VAC14. The transient production of $PI(3,5)P_2$ at the cytoplasmic surface of intracellular vesicles is thought to mediate vesicle fusion and trafficking via interaction with effector proteins such as WIPI1. Deficiency of FIG4 results in instability of the biosynthetic complex, reduced PI (3, 5) P_2 concentration, and accumulation of enlarged intracellular vacuoles containing the lysosomal membrane proteins LAMP1 and LAMP2. Lack of FIG4 also results in faulty myelination of the central and peripheral nervous systems and hypoplasia of the corpus callosum.

Clinical Manifestations

Yunis-Varon syndrome is a rare genetic multisystem disorder characterized by:

- Massive fontanelles, clavicular hypoplasia attribute facial features or abnormalities of fingers and toes.
- Aplasia [8] of the distal phalanges of the hand, the distal phalanx of the hallux.
- Abnormal parietal bone morphology, pelvis bone morphology.
- Abnormality of dental structure, the occipital bone.
- Absent sternal ossification, Agenesis of corpus callosum [23].
- Characteristic features may include microcephaly, ear abnormalities, anteverted nares, mid-facial hypoplasia, tented upper lip and small jaw (micrognathia), sparse or absent eyebrows and/or eyelashes [1].
- As infants with Yunis-Varon syndrome grow-up, they may also exhibit failure to gain weight or grow at the expected rate (failure to thrive), severe developmental delays, and/or intellectual disability.
- Infants with Yunis-Varon syndrome show absence or severe underdevelopment (hypoplasia) of one or both of the collarbones (clavicles) and delayed closure of the two soft membraned-covered openings (fontanels) on an infant's head, with abnormal partition of the fibrous joints (sutures) that connect certain bones of the skull [23].
- Children without collarbones or with underdeveloped collarbones may have "droopy" shoulders or, in severe cases, may be able to bring their shoulders together in front of their bodies [23].
- Infants with Yunis-Varon syndrome also have abnormalities of the fingers and toes (digits). The thumbs and the bones at the ends of the fingers and the great toes (distal phalanges) may be absent (aplastic) or underdeveloped (hypoplastic).
- In some cases, other bones may be underdeveloped including the bones between the wrists and the fingers (metacarpals), the bones between the knuckles of the fingers (middle phalanges), the bones of the great toes nearest to the feet (proximal phalanges) or other toes, and/or the bones between the ankles and the toes (metatarsals).
- As a result of these abnormalities, the fingers and toes may be unusually short. In addition, some affected infants may exhibit absence or underdevelopment of the fingernails and/or toenails and/or webbing between the fingers and/or toes (syndactyly).
- Some affected infants may exhibit additional skeletal abnormalities including deformity of the pelvis (pelvic dysplasia), dislocation of both (bilateral) hips, lack of sternal ossification, slender ribs or bone fractures.
- Additional findings that may be associated with Yunis-Varon syndrome include abnormalities of the heart such as cardiomyopathy or congenital heart defects [12].
- In some children, urinary tract abnormalities may occur, including abnormal placement of the urinary opening (meatus) on the underside of the penis (hypospadias), failure of the testes to descend into the scrotum (cryptorchidism) and micropenis.
- Additional findings have been reported in individuals with Yunis-Varon syndrome including central nervous system abnormalities and hypodontia [23].

Diagnosis:

- Certain findings that may suggest a diagnosis of Yunis Varon syndrome may be identified before birth (prenatally) using ultrasonography. In fetal ultrasonography, reflected sound waves are used to create an image of the developing fetus.
- Yunis Varon syndrome may be diagnosed or confirmed after birth based on a thorough clinical evaluation, which is the identification of signs and symptoms [5].
- Genetic testing for mutations in FIG4 can also confirm a diagnosis [5].

Treatment:

- The syndrome is usually fatal in infancy.

- For infants, breathing and feeding difficulties are monitored. Therapies used are symptomatic and supportive.
- Symptomatic measures, such as corrective dental, facial, and orthopedic surgery, depending on the extent of accompanying abnormalities.
- Medical and surgical therapy for treating respiratory distress and the need for adequate and early treatment in newborn infants [5].
- Specific therapies for individuals with Yunis Varon syndrome are symptomatic and supportive. Treatment may require the coordinated efforts of a team of specialists. Pediatricians and specialists, who diagnose and treat skeletal abnormalities (orthopedists), physical therapists, physicians who specialize in diagnosing and treating disorders of the heart (cardiologists), and other health care professionals may need to systematically and comprehensively plan an effective treatment.
- Physicians should closely monitor infants with Yunis Varon syndrome to promptly detect any feeding or breathing difficulties associated with the disorder [5].
- Physicians may recommend preventive measures and/or institute immediate appropriate therapy [5].
- Treatment for feeding difficulties may include artificial feeding methods, such as tube feeding that administers food through a tube directly into the infant's stomach or intravenous feeding in which essential nutrients are administered into a vein using a tube.
- Breathing difficulties, when severe and life-threatening, may require special measures, such as the use of a special machine (ventilator) that supports breathing (artificial respiration).
- Special services that may be helpful to affected children may include special remedial education, special social support, physical therapy, and other medical, social, and/or vocational services.
- Genetic counselling will be of assistance for affected persons and their families [5].

Non pharmacological treatment

As YVS is a genetic disorder the child may not survive survive till a time period of not more than 10 weeks. So one can only manage to make the life of the patient easy by providing them an easy way for feeding and breathing without any difficulties. Counselling to the family members of the patient about the infants condition is very necessary. Social and moral support to the patient as well as the family members is also important.

Quality of life

The life span of the patient with Yunis varon syndrome was very less. As mostly it is seen in infants the life span was between weeks to months.

The life span decreases due to improper functioning of cells in the body which may impact on the quality of life of the infant by abnormal development of organs.

Many of the infants who are affected with this, they did not survive beyond one year.

Future Aspects:

The infant's life time is not more than 10 weeks so we should ensure that the life of infant can be managed with fewer difficulties. As the infant sometimes has hard time breathing appropriate tools can be invented for easy breathing of infants.

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