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Children with Microvillus Inclusion Disease in Oman

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Abstract

Microscopic villus inclusion disease (MVID) is a highly uncommon autosomal recessive disorder that causes severe congenital diarrhea and high morbidity and death rates in infants. Difficulty in diagnosis is compounded by the fact that only a few numbers of genetic panels can detect the most frequent mutations. We describe a series of cases, including three infants with MVID caused by an STX3 mutation. We report the serial case of three Omani children diagnosed with MIVD. Parents were first-degree consanguinity. The first and second cases were sisters. The third case was their cousin. They were Total parenteral nutrition (TPN) dependent, with frequent hospital admissions due to central lines infection and other complications. The second case passed away during our study due to septic shock at ten months of life. On the other hand, her sister (case one) is free from TPN, studying in school with good quality of life, despite her diagnosis of plastic bronchitis due to elevated central pressure secondary to stenotic/chronic thrombosis of the central venous system. The third case was a male, their cousin. He is TPN dependent 22 hours/day, with monthly repeated admissions due to dehydration and electrolyte imbalance due to his condition. Moreover, he has visual impairment due to primary retinopathy with maculopathy. In conclusion, the Sultanate of Oman needs to consider highly specialized pediatric gastroenterology centers to care for the affected cases of MIVD and other disorders. Additionally, genetic counselling is currently limited to only two centers in Oman. It needs to be implemented all over the areas of Oman because observations that the incidence of MVID is higher in families with a pre-existing case of MVID and that there is a high rate of consanguinity in parents of children with MVID indicate a genetic basis for this disorder, which is probably inherited on an autosomal recessive basis.

Subject Areas

Pediatrics

Keywords

Microscopic Villus Inclusion Disease (MVID), Diarrhea, Oman, Consanguinity, Total Parenteral Nutrition (TPN)

1. Introduction

Microvillus inclusion disease (MVID) is a severe congenital enteropathy characterized by uncontrollable watery diarrhea that often begins during the first days but may occur as early as the first months of life [1]. It is also called congenital familial protracted diarrhea, congenital microvillus atrophy, Davidson's disease and familial enteropathy microvillus. In 1978, MVID was first reported in medical literature by Davidson and his colleagues [2] [3]. They described five babies with severe chronic diarrhea of neonatal onset and shared histological results. MVID is autosomal recessive with locus heterogeneity; the majority of patients have biallelic mutations in the myosin 5b gene (MYO5B), while abnormalities in syntaxin 3 (STX3) and syntaxin binding protein 2 (STXBP2) account for other cases of MVID [1].

There were three types of MVID: The early MVID with complete protein loss from microvilli in the villi and crypts; The late-onset MVID, where microvilli proteins are absent at the ends of the villi and on the sides, but typical microvilli are present at the base of the villi and crypts. These patients become symptomatic as early as the second month after birth, with less severe symptoms; Finally, the typical MVID, where microvilli proteins such as vinculin and syntaxin are absent or defective only at the crypts, but where typical microvilli are present on the surface of the villi [4].

Nowadays, it is believed to have a frequency of 1:1000.000, and there are just a few reported occurrences worldwide [3]. There have been less than 200 cases of MVID recorded in the medical literature. The actual extent to which this disease exists is unknown [5]. According to the international registry of (MVID) patients and a database of associated gene mutations, there were about 188 MVID patients and 106 mutations [6]. In the Arab world, the prevalence of MVID is unclear. In 2012, Oman began reporting the first case [7]. It was a healthy-term girl born vaginally. She was healthy and had been breastfed for three days when she started having ten days of watery stools. She was dependent on prenatal nutrition at the local hospital. She expired at four months, secondary to recurrent line infections with deteriorating liver disease [8].

This study aims to report a series of three children with MVID, the most frequent complications of the disease and the quality of their life. The importance of this research paper also comes from the fact that the first child is considered one of the exceptional cases worldwide that were diagnosed with MVID and were able to reach the age of nine by stopping the use of TPN or any other supportive medical or surgical treatment.

2. Causes, Diagnosis, Pathophysiology of MVID

2.1. Causes of MVID

MVID is caused by loss of function changes (mutations) in the myosin Vb (Myo5b) gene, a molecular motor gene responsible for the traffic of proteins into the brush border of epithelial cells. Mutations cause most cases of MVID in Myo5b. However, some patients with MVID with late presentation and milder disease have been reported to have mutations in syntaxin 3, a gene for a SNARE protein that is responsible for vesicle fusion with the membrane.

MVID follows an autosomal recessive pattern of inheritance. Recessive genetic disorders occur when an individual inherits a non-working gene from each parent. If an individual receives one working gene and one non-working gene for the disease, the person will be a carrier for the disease but usually will not show symptoms. The risk for two carrier parents to pass the non-working gene and have an affected child is 25% with each pregnancy. The risk of having a carrier child, like the parents, is 50% with each pregnancy. The chance for a child to receive working genes from both parents is 25%. The risk is the same for males and females.

All individuals carry a few abnormal genes. Parents who are close relatives (consanguineous) have a higher chance than unrelated parents to both carry the same abnormal gene, which increases the risk of having children with a recessive genetic disorder. MVID has been reported in consanguineous families [5].

2.2. Diagnosis of MVID

MVID is diagnosed by evaluating symptoms, excluding other causes of diarrhea, and examining intestinal biopsies. Intestinal biopsies from MVID patients show villus hypoplasia without infection or inflammation. In villus enterocytes, PAS-positive material and the brush border enzyme CD10 accumulate intracellularly. An electron microscope shows microvillus brush boundary atrophy and pathognomonic microvillus inclusions in the villus enterocyte cytoplasm. An MVID diagnosis requires biallelic mutations in MYO5B or STX3. Familial hemophagocytic lymph histiocytosis, an immunological illness caused by STXBP2 gene mutations, has many MVID characteristics [5] [9].

2.3. Pathophysiology of MVID

Vesicular bodies (*i.e.*, secretory granules) within enterocytes. Loss of microvilli on the surface of enterocytes, which can be reduced or absent. Pathognomonic internal microvillus inclusions are found in the apical cytoplasm of enterocytes. These abnormalities can appear in patches throughout the small intestine, with various degrees of intestinal involvement in affected patients. Pathologic abnormalities have also been detected in the epithelium of the large intestine, rectum, stomach, renal tubules, and the biliary tree of some affected patients, in addition to the small intestine.

Mutations in the MYO5B or STX3 genes, which code for proteins involved in

intracellular trafficking and signaling pathways, cause MVID, as previously stated. STXBP2 mutations cause the MVID phenotype as well. Most individuals with MVID have a loss-of-function mutation in the MYO5B gene; however, in milder forms of MVID, mutations in the STX3 gene are frequent [10].

2.4. MVID Management

2.4.1. Medical Management

Although several medicines have been tested in an attempt to treat severe diarrhea experienced by those with microvillus atrophy, none have proved successful. TPN is currently the sole treatment option (TPN). Some agents (e.g., epithelial growth factor, colostrum) that are thought to stimulate better intestinal mucosa development are ineffective. Stool production may be decreased by anti-secretagogue medicines (e.g. somatostatin, octreotide, loperamide, chlorpromazine). However, this effect is of low clinical relevance.

2.4.2. Surgical Management

If the small intestine transplant is successful, the patient may no longer need TPN. Patients who do not respond well to long-term TPN seem to have no other treatment options save transplantation (e.g., because of sepsis, liver damage, or lack of vascular access). Despite the lack of large-scale reports, data shows that early small-bowel transplantation is necessary [11].

3. Serial Case Report

3.1. Case 1#

A nine years old female Omani child was born on 06/11/2012. The parents were first-degree consanguinity. She was the third-born child to a 27-year-old mother with no significant history. The antenatal period was uneventful. The baby was born vaginally through the clear amniotic fluid and cried soon at birth. The birth weight was 2.5 kg. She was well and breastfed for four weeks of life when she started to have frequent large watery stools. She had been hospitalized for one month in a local hospital for severe dehydration and then transferred to a specialized tertiary care hospital. She was admitted there to PICU for another month. They started her on TPN. Her condition started to be more stable. She began to gain weight. Her case has been continuously investigated by GI and genetics teams. In 2013, they gave her their first diagnosis of Tufting enteropathy. She was TPN-dependent. At home, TPN was 48 ml/hr for 18 hrs with intra-lipid 7 ml and tolerating orally. But she failed to gain weight due to multiple admissions with central line-associated sepsis and electrolyte imbalances. Then she developed later pigmentary retinopathy with obvious horizontal nystagmus and bilateral proptosis.

In 2016, her intestinal biopsy was reviewed in Austria to have a clear understanding of her condition. Her confirmed diagnosis is (MVID), and her features are characteristic of STX3 mutation-MVID.

Since then, she has had recurrent admissions due to central line-associated

sepsis.

In December 2020, she developed (Retinitis pigmentosa). She is followed for plastic bronchitis due to elevated central pressure secondary to stenotic/chronic thrombosis of the central venous system.

After that, her medical team, with the parents' agreement, changed her goals of care to do-not-resuscitate (DNR). Currently, she is on nocturnal BIPAP with mode; S/T, P = 12/6, R = 25, humidity.

On 13/01/2021 mother decided to stop the TNP against the doctor's plan. The mother reported weight remained stable. The child on Pedi -sure formula and mashed soft solid food

She would be with regular bowel movements if she had diarrhea only 2 - 3 times daily.

Her current weight is 15.4 with Hight of 108.9 cm. She is going to school.

3.2. Case 2#

A term female born via spontaneous vaginal delivery with no complication. She is the second sister of the case (1). She was born on 08/03/2021. Parents are 1st degree consanguineous. She was well and breastfed for four weeks of life when she started to have frequent large watery stools. According to the mother, she has had 2 - 3 times watery diarrhea on and off since birth. There was no blood or mucous. She lost weight from a birth weight of 2.83 kg to a weight of 2.34 kg. At that time, the child was found to have severe dehydration with impaired renal function (prerenal) and severe metabolic acidosis (pH 6.88). She was admitted to PICU. TPN correction started. A Genetics workup confirmed her diagnosis of MVID (STX 3 gene mutation). Then she was TPN dependent. The child was at High risk of thrombosis. She began on Enoxaparin 1.7 mg, and warfarin 1mg once daily. She was on the Hickman line, inserted on 29/4/2021. Then she developed septic behaviors and severe dehydration again. The blood culture showed pseudomonas growth and CLABSI from the peripheral and central lines. After that, the Hickman line was reinserted through the left internal jugular vein under general anesthesia on 9/5/2021.

Admitted again on 12/9/2021 with a history of fever and vomiting under the impression of sepsis/Hickman related. Hickman was reinserted again on 23/9, has persistent positive blood cultures of *Enterococcus faecalis* from the central and peripheral lines. She was admitted again on 06/11/2021 with a mild cough and upper respiratory tract infection and developed compensated septic shock. The blood culture showed a central line bloodstream infection (CLABSI). On 18/11/2021, Hickman was reinserted again. The infection diseases team started her on ampicillin and ceftriaxone. The Current weight is 5.2 kg. She is on TPN 22 hr per day.

On 03/01/2022, the child presented with this problem list:

1) Gram-negative bacteremia and septic shock.

2) Pneumonia with Enterovirus infection.

3) Thrombocytopenia and anemia required platelet and PRBC transfusion.

4) Deranged coagulation.

5) Hepatomegaly with hyperbilirubinemia.

The child was critically ill and admitted to the pediatric intensive care unit for two days, than she passed away on 06/01/2022, child's blood pressure was dropping with bradycardia. She received CPR for 20 minutes with epinephrine doses—seven doses. She received a bicarbonate dose along with a calcium gluconate dose. She had ET bleeding during the CPR, with blood oozing from her nostrils. Pupils—fixed dilated, asystole.

Despite all resuscitative effort's child rapidly deteriorated.

3.3. Case 3#

The twenty-eight-month male child was born on 08/06/2020. There is 1st-degree consanguinity between mother and father. Birth weight was appropriate for gestational age at 2.7 kg. He had two siblings both were not having any health issues. The history of his illness started at seven months of age, with profuse liquid diarrhea at the rate of 10 to 12 stools per day associated with abdominal bloating and weight stagnation. The child was diagnosed with MVID at that time, confirmed genetically STX3. He was the cousin of the case (1) and (3). He became TPN dependent 22 hours/day through the Hickman line attached to the internal jugular vein inserted on 18/1/2021. He also had primary retinopathy with maculopathy follow-up with ophthalmology.

He is with monthly repeated admissions due to dehydration and electrolyte imbalance due to his condition. Additionally, he is at risk of thrombosis due to his underlying disease. He is on warfarin 2.5 mg OD (not compliant and currently withheld).

Moreover, currently, he has a visual impairment.

4. Discussion

Serial case reports were done to children in the same family with (MVID), STX3 mutation gene. Up to this point, five cases of STX3 problems have led to MVID around the world [12] [13].

MVID is an extremely rare inherited intestinal disorder that takes time to diagnose in affected children. Our case 1# was the second case in the sultanate of Oman. Her final diagnosis takes four yours due to a lack of information about the disease and the similarity of symptoms of some other disorders with MVID, for example: Lactose intolerance and Familial chloride diarrhea or congenital chloride diarrhea (CCD) [14].

Moreover, the sultanate of Oman had only two tertiaries hospitals (Sultan Qaboos university hospital and Royal hospital) where patients with suspected metabolic-related genetic disorders are evaluated and managed. It may explain the long process of diagnosis.

The Consanguineous marriage was the cause of MVID in our cases. It is a typical habit in the Arab world to marry someone who is a second or third cousin. This is known as a consanguineous marriage in the field of clinical genetics.

A linguistic definition of consanguinity is a connection between two people who have a common ancestor. Marriages between people who are more distantly related than second cousins are occasionally included in studies on consanguinity rates because of this. Endogamy, the practice of marrying only within one's tribe or group according to tradition or law, is also widespread in the Arab world [15].

Usually, the MVID has different kinds of symptoms and affects more than just the intestinal tract, like the liver, kidneys [6] and visual apparatus. We can see this clearly at case 3#.

Despite the fact that MVID has no known cure and existing treatments have risks that may reduce the patient's quality of life. Our first case demonstrates the converse to be true. We are unaware of any other incidence of MVID in which the affected individual lived to be nine years old with good quality of life and weaned themselves off of TPN.

5. Conclusions

To provide treatment for the afflicted cases of MIVD and other illnesses, the Sultanate of Oman should consider highly specialized pediatric gastroenterology clinics. Additionally, Oman now only has two clinics that provide genetic counselling. It must be put into practice across Oman because there is a genetic base for this condition, which is likely inherited on an autosomal recessive basis. Observations are that the incidence of MVID is more significant in families with a pre-existing case of MVID and that there is a high prevalence of consanguinity in parents of children with MVID.

Our first child is considered to be one of the exceptional cases that have been diagnosed with MVID around the world who have been able to reach the age of nine without the use of TPN or any other supportive medical or surgical treatment. These cases are considered to be among the rarest of all cases. Because our child was able to reach this age without the assistance of any supporting medical therapy or surgical treatment, the situation of our child is regarded as being remarkable. In contrast, the other examples often ended in early mortality owing to various illnesses, such as our second case, or they lived with a diminished quality of life, such as our third case.

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Ethics Approval

The article describes a case repot. Therefore, no additional permission from our ethics committee was required.

Consent for Publication & Participate

Verbal informed consent was obtained from our case report family to publish

this report in accordance with the journal consent policy.

Availability of Data and Materials

All data generated during this study are included in this paper.

Conflicts of Interest

The author declares no conflict of interest.

Author's Contributions

All work done by Safiya Al-Yaqoubi, she involved in conception, design of the paper, and data collection.

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List of Abbreviations

Microscopic Villus Inclusion Disease (MVID)
Total Parenteral Nutrition (TPN)