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NONNE-MILROY SYNDROME – A CASE REPORT AND REVIEW STUDY WITH CLINICAL ASPECTS

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Background: **Introduction:** *Lymphedema (tissue swelling caused by an accumulation of protein-rich fluid that's usually drained through the body's lymphatic system) in the legs and feet is a result of Milroy disease, which damages the lymphatic system (A network of tissues, veins, and organs known as the lymphatic system collaborates to transport lymph, a colourless, watery fluid, back into your circulatory system). Milroy illness can cause fluid to accumulate in the legs and feet before delivery and occasionally throughout the body (nonimmunehydrops). Lower limb edoema (swelling brought on by an increase in interstitial fluid above the normal lymphatic drainage's capability) after delivery, a fluid accumulation in the scrotum (hydrocele), and skin abnormalities are possible signs. Skin infections and certain cancers are more likely to occur in people with Milroy disease. Milroy illness (Milroy disease is a disorder that interferes with the lymphatic system's typical operation.) develops when the FLT4 gene(The vascular endothelial growth factor receptor 3 protein is made using instructions from the FLT4 gene (VEGFR-3),which regulates the development and maintenance of the lymphatic system) is malfunctioning. It has an autosomal dominant pattern of inheritance. Milroy disease is diagnosed based on the symptoms, a clinical examination, and further tests. Genetic tests could confirm the diagnosis. The goal of treatment is to control the symptoms.*

Key words:FLT4, VEGFR-3, Nonne-Milroy, ICT, ECM, HLTS, VLNT,

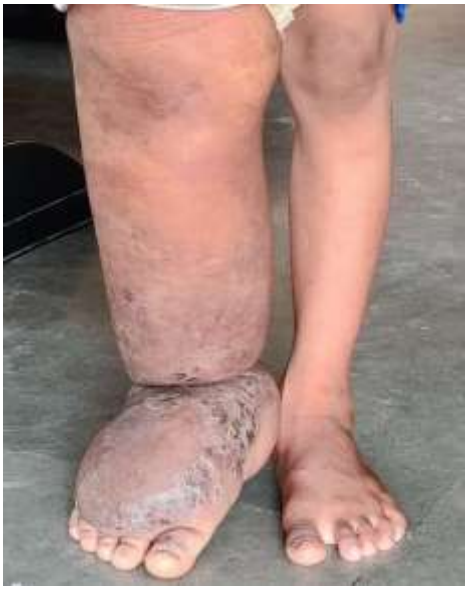
Conditional Description: Since birth or early childhood, Nonne-Milroy syndrome (a lymphatic system condition that affects growth and causes disfiguring swelling in the limbs), a rare primary lymphedema, has been associated with firm, non-pitting edoema of the lower extremities of the complete leg or may just affect the feet or toes. The lower limbs' duplex ultrasonography revealed intact blood vessels. Lymphoscintigraphy (The sentinel lymph node, which is the first node to receive lymph from a tumour, is located by lymphoscintigraphy; it may be removed and analysed for malignant cells.) showed lymphatic aplasia in both lower limbs. After ruling out alternative hereditary causes of primary edoema, the patient was diagnosed with either primary lymphedema or Nonne-Milroy syndrome. His chylous effusion was treated with bilateral pleurodesis (A procedure known as pleurodesis causes a little inflammation of the pleura around the lung and chest cavity) and tetracycline, and after a year of follow-up, there was no sign of recurrence.

Primary (Idiopathic: pertaining to or designating any illness or ailment that appears suddenly or for which there is no established cause) and secondary (acquired), the latter of which has a recognised pathogenic change, are the two main classifications of lymphedema. Lymphatic vessels can be either hypoplastic (a serious congenital cardiac condition where the left side of the heart is underdeveloped) or hyperplastic

(An increase in the number of cells in an organ or tissue) but are nonfunctional in primary lymphedema, which can occur alone, in conjunction with other clinical issues, or as part of a specific illness. Primary lymphedema is a congenital abnormality that results in aberrant interstitial protein-rich fluid buildup (abnormal increases in pressures may result in interstitial edoema or swelling of the extracellular matrix) whereas secondary lymphedema is a consequence of lymphatic blockage or disruption of the lymphatic arteries. The diagnosis of primary lymphedema was made since our patient had congenital lymphedema.

Case study: I discuss the case of a 7-year-old kid in India who had swollen lower limbs and his scrotum, with flare-ups and remissions of the symptoms.A congenital defect in lymphatic drainage may have been the cause of the vaginal edoema that appeared at 6 months of age. Milroy's illness and other potential causes of paediatric lymphedema are examined.

Since birth in India, a child male patient with age 7, In the mammary, axillary, infra-axillary, lower inter-scapular, and infra-scapular regions on the left side of his chest, as well as the infra-axillary and infra-scapular regions on the right, there was stony dullness with reduced vesicular breath sound. His ESR was not elevated, and his Mantoux and immunochromatographic card tests (ICTImmunochromatography (or lateral flow tests) Combining migration-based capillary flow separation of the sample molecules and reagents on a solid substrate. The identification and detection procedures are based on the antigen–antibody immune reaction) for filaria were also negative.The equilibrium of interstitial fluid is maintained in large part by lymphatics. In the sixth to seventh weeks of an embryo's life, the human lymphatic system begins to develop.



Growth factors, intercellular, and cell extra cellular matrix (ECM) (The body's cells and tissues are surrounded by a dense network of proteins and other molecules that provides structure and support) communication systems all work together to strictly regulate lymphangiogenesis(Lymphangiogenesis is the process through which new lymphatic vessels are created from already-existing ones). Due to inadequate lymphatic transit and drainage, interstitial protein-rich fluid builds up, which results in lymphedema. The vast majority of lymphedema patients may be identified with a careful history gathering, physical examination, and ultrasound. Due to its minimally invasive nature and safety for the

lymphatic endothelium (The endothelium, a monolayer of endothelial cells, constitutes the inner cellular lining of the blood vessels (arteries, veins, and capillaries), as well as the lymphatic system, making it in close proximity to the blood, lymph, and moving cells), isotopic lymphoscintigraphy (A potent diagnostic imaging technique, lymphoscintigraphy may be performed with low chance of unfavourable side effects. This exercise discusses the uses of lymphoscintigraphy in modern medicine and emphasises the function of the multidisciplinary team in the treatment of cancer patients who show concern for nodal involvement and lymphatic system flow pathology) is typically regarded as the gold standard for the diagnosis of lymphedema.Alternatives include direct lymphography, computed tomography, and magnetic resonance imaging. Primary (idiopathic) and secondary (acquired) lymphedema are the two main forms, with the latter having a recognised pathologic modification such blockage or injury to the lymphatics. Primary lymphedema can occur alone or in conjunction with other disorders. The diagnosis of primary lymphedema was made since our patient had congenital lymphedema. Primary lymphedema can have a variety of hereditary origins, including Turner's syndrome, Noonan syndrome, Yellow nail syndrome, Lymphedema-distichiasis syndrome, Hypotrichosis-lymphedema-telangiectasia syndrome (Hypotrichosis-lymphedema-telangiectasia syndrome (HLTS) is an uncommon disorder linked to scant hair, as the name implies (hypotrichosis), lymphedema, and telangiectasia, particularly on the palms of the hands symptoms, and many more.Milroy disease is a very uncommon kind of primary lymphedema that is often brought on by a FLT4/VEGRF3 gene mutation. In Milroy disease patients, the superficial lymphatics of the afflicted edematous regions are believed to be aplastic or hypoplastic. Chylothorax (Chylothorax is an uncommon but deadly illness when lymph from the gastrointestinal tract (chyle) builds up in the chest cavity) can appear in Milroy disease sufferers between the second and fourth decade of life. Patients with hereditary lymphedema may develop pleural effusions for unclear reasons.It is thought to be caused by a fundamental flaw in the growth of lymphatic vessels. However, it is unknown why thoracic involvement manifests later in life. Atypical Nonne-Milroy syndrome is the medical term for Nonne-Milroy illness with chylothorax, as in our case. Over time, the thoracic involvement and leg edoema often get worse. Long-term limb edoema is treated with non-operative methods include compression therapy, massages, specific exercise, and manual lymphedema drainage.

Diagnosis: Only conservative measures can be taken. Certain treatments for lymphedema disorders may possibly alleviate specific symptoms; no cure and it is usually congenital. Genetic counseling can be done. May have similar health conditions, delays, disorders, and physical traits associated with other lymphatic genetic diseases and chromosome #5 abnormalities.

Prognosis: A rare complication is the appearance of lymphangiosarcoma (Within a median of 10 years after mastectomy, lymphphangiosarcoma is characterised by skin alterations in the form of purple-colored elevated cutaneous lesions that proceed to ulceration in a lymphedematous arm.) or angiosarcoma (Angiosarcoma is a kind of cancer that develops in the lining of lymphatic and blood vessels. It frequently affects the skin and can take the form of an ever-expanding lesion that resembles a bruise. A uncommon kind of cancer called angiosarcoma develops in the lining of the blood vessels and lymph vessels) in patients with persistent lymphedema. Some patients may develop protein-losing enteropathy(The small intestine is continually being harmed, irritated, or swollen in enteropathy) and visceral involvement. Chylous ascites and chylothorax rarely occur. Milorydisease does not normally affect life expectancy.

Clinical characteristic in observation : Lower-limb lymphedema, which manifests as pedal edoema before (or before) delivery or develops quickly after, is a hallmark of Milroy disease. Sometimes it shows up later in life. Usually bilateral, swelling can sometimes be asymmetrical. Edema severity can worsen

but sometimes occasionally get better, especially in the early years. Other symptoms of Milroy disease include hydrocele (37% of men), large veins below the knees (23%), upslanting toenails-A significant gene deficiency has recently been identified as the predominant cause of the uncommon autosomal dominant disorder known as primary congenital lymphoedema (Milroy disease). (14%) and papillomatosis- The term "papillomatosis" describes the condition in which dermal papillae protrude beyond the skin's surface, causing the epidermis to be irregularly undulating. (10%), and anomalies of the urethra in males (4 %). About 20% of those who are infected develop cellulitis, which can harm lymphatic vessels; males are substantially more likely to get the illness than females.

Diagnosis/Testing: A proband with congenital or infantile-onset lower-limb lymphedema and a lack of radioactive colloid uptake in the ilioinguinal (The sentinel lymph node (the first node to receive lymph from a tumour), which may be removed and examined for tumour cells, is found using lymphoscintigraphy. The ilioinguinal nerve is a mixed nerve that originates from the anterior rami of the T12 and L1 nerve roots), as well as by the discovery of a heterozygous pathogenic variant in FLT4 by molecular genetic testing, are considered to have Milroy disease.

Management: Treatment of manifestations- To enhance the limb's aesthetics, reduce its size, and lower the risk of problems, a lymphedema therapist may apply tailored stockings and massage. With the use of appropriately fitted compression hosiery, bandaging, and supportive shoes, edoema is frequently treatable. The use of toe gloves and proper skin care are also recommended. Standard therapy for urethral anomalies, hydroceles, and cellulitis.

Prevention of secondary complications- Good skin care, timely antibiotic treatment of infections, and preventive antibiotic use for recurring bouts can all minimise the frequency of cellulitis.

Surveillance- It is appropriate to follow up regularly at a clinic that specialises in treating lymphedema.

Agents/circumstances to avoid-Drugs that may induce leg edoema; prolonged periods of inactivity with the legs in a dependent posture.

Wounds to limbs Evaluation of relatives at risk- In order to determine whether relatives of an afflicted person may benefit from receiving appropriately fitting compression hosiery and counselling on how to lower their risk of developing cellulitis of the legs and feet, evaluation of the apparent asymptomatic at-risk relatives is necessary.

Establishing the Diagnosis:A proband with congenital or infantile-onset lower-limb lymphedema, a lack of radioactive colloid uptake in the ilioinguinal lymph nodes on lymphoscintigraphy, and/or identification of a heterozygous pathogenic variant in FLT4 (VEGFR3) by molecular genetic testing is considered to have Milroy disease. Depending on the phenotype, molecular genetic testing methods can combine gene-targeted testing (single-gene testing, multigene panel) and complete genomic testing (exome sequencing, genome sequencing). Genomic testing does not need the doctor to identify the gene(s) that are most likely implicated, whereas gene-targeted testing does. Individuals with the characteristic findings listed in Suggestive Findings are likely to be identified with Milroy utilising gene-targeted testing due to the disorder's wide phenotypic, as opposed to those whose phenotype(the observable physical properties of an organism) is similar to many other hereditary disorders.

Genetic Counselling: The hereditary form of Milroy disease is autosomal dominant. The majority of people with Milroy illness have a parent who is afflicted. There is a 50% chance that siblings will inherit a FLT4 pathogenic variation if one of the proband's parents (A *proband* is an individual who

is affected by a genetic condition or who is concerned they are at risk.) is afflicted and/or carries it. A heterozygous sibling may be more or less severely afflicted than the proband in Milroy illness due to intrafamilial variability and lower penetrance. Prenatal testing for a pregnancy at greater risk and preimplantation genetic testing are both options if the FLT4 pathogenic mutation has been found in an afflicted family member. The dorsum of the foot may enlarge during pregnancy, along with moderate pleural effusions that often go away and (very rarely) more severe edoema (foetal hydrops) in an afflicted foetus.

Diagnosis-Suggestive Findings

Milroy disease should be suspected in individuals with the following clinical features, radiographic findings, and family history.

Clinical features:

Lower-limb swelling that is:Usually (not always) bilateralPresent at birth or develops soon after

Note: In neonates the swelling predominantly affects the dorsum of the feet; with age, the swelling may improve or progress to affect the below-knee region (rarely extending above the knees).

Large-caliber veins below the kneesUpslanting and small, dysplastic toenailsDeepinterphalangeal creases of the feetHydroceles in males

No internal clinically significant lymphatic issues (e.g., intestinal lymphangiectasia, pleural or pericardial effusions)

Radiographic findings: Typically, lymphoscintigraphy shows that there is little tracer absorption into the peripheral lymphatics. As a result, neither drainage channels nor absorption in the ilio-inguinal nodes are seen. This is a sign of Milroy disease and is referred to as "functional aplasia". Although the lymphoscintigraphic findings are distinctive and helpful for diagnosis, the test is not always necessary.

Lymphedema Medication: Retinoid-like Agents (Tretinoin, retinylpalmitate, retinaldehyde, isotretinoin, and tazarotene)**.** Anthelmintics (Anthelmintic is the term used to describe a drug used to treat infections of animals with parasitic worms)Topical Skin Products9+Antibiotics

Lymphoscintigraphy: About 20% of those who are affected develop cellulitis, with males significantly more likely to contract the infection than females [Brice et al 2005]. Milroy disease is frequently distinguished from other lymphatic conditions by the presence of cellulitis, which can harm the body's natural lymphatic vessels and increase the degree of swelling. In the toe web spaces, a radioactive colloid is injected, and the ilioinguinal nodes' uptake is periodically evaluated. To ascertain if there is a deficiency in radioactive tracer uptake, lymphoscintigraphy is done. Different patterns on lymphoscintigraphy can be seen in Milroy illness and other types of lymphedema [Connell et al 2013,

Sarica et al 2019]. Lymphoscintigraphy can identify whether there is a problem with lymphatic drainage in the limb that is "unaffected" in situations of unilateral edoema.

Surgical Intervention: VLNT together with therapeutic lipectomy proved to be a reliable technique in moderate cases of Milroy disease, providing an alternative path for lymph drainage, and reducing the lymph load and the excess of subcutaneous adipose tissues, thus improving patients' quality of life.

Observation in summary: As untreated lymphedema prolongs, it can develop into lymphangiosarcoma – a lymph-related cancer that limits a patient's life expectancy from a few months to two years. Untreated or mismanaged lymphedema can also lead to sepsis(Sepsis is the body's extreme response to an infection), a scary, potentially terminable infection that rapidly spreads throughout the entire body.

Patient Consent Statement: The author attests that they have all necessary patient permission form preparing manuscript. The patient has granted permission to use his photo. Thepatient is aware that his initials and name willnot be published.

Contribution of the Authors: All authors actively participated in all stages of preparing manuscript.**Financial Support and Sponsorship:** No

Conflict of Interest: No

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