OVERVIEW OF THE ANTENATAL DETECTION OF LYMPHATIC MALFORMATION, ITS ASSOCIATED GENETIC FACTORS, AND THE COMPLICATIONS

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Abstract

Lymphatic malformation (LM) is a dysfunction of the lymphatic system that is associated with genetic diseases. The clinical manifestation is established, but the outcome concerning genetic abnormalities is still not well understood. This review reports the advancement of technology in detecting LM antenatally, its associated genetic factors, and the complications of LM. Articles which were mainly case reports published from 1983 to 2023 were obtained from the search in Ovid MEDLINE and Scopus using the keywords "gene*", OR, "DNA", OR "epigenetic*" AND "lymphatic malformation" OR "cystic hygroma". The advancement of technology over the years has contributed to the various types of genetic investigations conducted on a foetus with LM, including fluorescence in situ hybridization and multiplex ligation-dependent probe amplification. Poor prognosis indicated by the presence of genetic or karyotype abnormality results in opted termination of pregnancy, intrauterine death, or death at early hours of life. The PTPNII, FOXC2, FOXF1, and SRY genes and various chromosome abnormalities are associated with LM. The complications of LM include bone deformity, cardiac and urinary anomalies, and the worst is foetal hydrops. This critical dysfunction warrants future research directions to identify risk factors or biomarkers to prevent future cases of pregnancy with LM.

Keywords: Lymphangioma, Cystic, Genes, SRY, FOX

Introduction

Lymphatic malformation (LM) is a congenital malformation of the lymphatic system characterised anatomically by dilated lymphatic ducts or aberrant growth of lymphatic vessels (1). LM is a developmental anomaly in which the lymphatic fails to connect normally to the venous channel. Abnormalities of the lymphatic system are associated with several diseases such as hypertension, atherosclerosis, obesity, cancer, immunity, autoimmune diseases, metabolic syndrome, and abnormalities of brain, spine, or nerve in later life (2). This malformation is also known as cystic hygroma or lymphangioma.

Histologically, it is referred to as benign proliferation of lymphatic vessels characterised by intervening fibrous tissue of the lymphatics with lymphoid aggregates and a layer of flattened, elongated endothelial cells that line the lymphatic spaces (3). Under naked eyes, LM appears as a soft tissue mass underneath normal skin and is the major cause of soft tissue and skeletal overgrowth problems. Commonly, LM was found in the head and neck.

Serre's classification of LM is linked to complication rate, divided into Stages I to V. Stage I patients had unilateral infrahyoid disease and a 17% incidence of complications overall. Stage II patients had unilateral suprahyoid disease and a 41% incidence of complications. Stage III patients had unilateral suprahyoid and infrahyoid disease, and a complication rate of 67%. Stage IV patients with bilateral suprahyoid disease had a complication rate of 80%, while stage V patients with bilateral suprahyoid and infrahyoid disease had a 100% incidence of complications (4).

In 2018, International Society of Vascular Anomalies Classification (ISSVA) described the malformation as macrocystic (cystic space at least 2 cm), microcystic (cystic space less than 2 cm), and mixed lymphatic malformations (5).

The malformation develops at the end of the sixth week of gestation and is located predominantly in the neck, accounting for 20% to 25% of cervical lymphatic tumours (6). It has an incidence of approximately 1:1000 to 6000 births and 1:750 miscarriages. A diagnosis of LM is usually deduced upon ultrasound in the first trimester of pregnancy or early second trimester. Amniocentesis will be conducted to confirm the diagnosis once nuchal thickness is observed via ultrasonography during pregnancy (7). Foetal echography will also be performed as LM is associated with the cardiac anomaly, to provide more information on the severity of malformation and aids in patient management (8).

Abnormal development of lymphatic vessels leads to LM. One of the reported causes of LM is the somatic mutations identified in the lymphatic endothelial cells (LEC) (9). LECs are found within intranodal lymphatic sinuses, where they are involved in managing the distribution of lymph and antigens. Besides being fluid transporter, LECs have a direct impact on T cells, facilitating peripheral tolerance to self-antigens, and are significant factors in various diseases including cancer metastasis. LECs allow lymph percolation and control the access of soluble molecules and particles in the cortex of lymph nodes (10). As the knowledge of specific markers for vascular or LEC is still lacking, the current classification of LM is based on clinical, radiologic, immunohistochemical, and haemodynamic studies rather than cellular genealogy.

LM is associated with a foetal chromosomal abnormality in 93.8% and gene anomalies in 6.15% of the cases (11). Several genes have been implicated, the common ones being Sex-determining Region Y (SRY), Forkhead Box (FOX), and Protein Tyrosine Phosphatase Non-receptor Type 11 (PTPN11) genes. There was also a report that 50% of LM is associated with chromosomal alterations such as trisomy 21, monosomy X (45, X), trisomy 18, and trisomy 13 (12). Specifically, 36% of LM patients with chromosomal alterations are diagnosed with Down Syndrome (13). LM in a foetus with chromosomal abnormalities can occur in other lethal and sublethal aneuploidy syndromes.

LM was also reported in newborn babies with normal karyotypes. The rate of these congenital anomalies in those with normal karyotypes ranged from 25% to 53%. Even in the absence of congenital and karyotype anomalies, newborn with LM has a perinatal death rate of up to 11% and developmental disorders of up to 5.9% (12). The long-term morbidity of LM patients is often related to how LM affects other critical structures such as nerves, blood vessels, lymphatics, and airways (14). Quality of life can be significantly impaired in many cases. Early diagnosis or prevention of LM is crucial for efficient treatment intervention, yet this remains clinically challenging worldwide. Several studies have reported LM-associated mortality rates of up to 2-6%, mainly due to lung infection, bronchiectasis, or airway blockage (14). Recurrent inflammation of the affected area leads to cellulitis, bleeding, swelling, and pain (15). Complications arising from surgery to remove the LM are location-dependent, which include damage to nervous and vascular systems that leads to lymphatic leakage or fistula and excessive haemorrhage.

The purpose of this review is to give an overview of the evolution of technology for LM detection, the associated genetic factors, and the complications of LM.

Methodology

Search strategy

For a thorough search of medical and health sciences journals, this review incorporates databases from Scopus and Ovid MEDLINE. The database was accessed in two rounds: on 19th February 2020 and 20th June 2023 from Ovid Medline and Scopus. The search strategy involved a combination ("AND") of the "gene*", OR, "DNA", OR "epigenetic*" AND "lymphatic malformation" OR "cystic hygroma". Additionally, the references of all retrieved articles were reviewed for related citations. Search and identification of studies for inclusion were performed by the corresponding author.

Inclusion and exclusion criteria

All case studies or clinical studies found within the search were included. These include studies of genetic relation, normal karyotype, and methods of identification of LM. Due to limited resources, only manuscripts written in English were included in this review. Case studies, case series, letters to the editor and short communications were included. Review articles were excluded. This review focused on the patient with LM with or without any other genetic syndromes right after the LM was detected during prenatal follow up.

Screening of articles for eligibility

Retrieved articles were screened in three phases. In the first phase, title of the articles that do not match the inclusion criteria were omitted. In the second phase, abstracts of the articles that did not meet our inclusion criteria were omitted. In the final phase, full texts of the remaining articles were read and assessed thoroughly to exclude articles that did not meet our inclusion criteria or articles that fulfilled the exclusion criteria. Duplicates were removed. All authors were involved in the screening phase. All the articles have been approved by all authors before proceeding to data extraction.

Data extraction and quality assessment

Data extraction and quality assessment were completed by all authors using data extraction form independently to standardise the process. We resolved the discrepancies following independent data extraction and quality assessments until there was 100% agreement. The following data were extracted from the selected studies: author/title/location; study design; objectives; pre- and post-delivery manifestation; technique; result; and conclusion.

All the data was arranged into three main topics including antenatal detection, associated genetic factors related to lymphatic malformation, and complications of LM.

Antenatal detection of lymphatic malformation

Type of prenatal screening samples

The changes in the types of samples used in antenatal screening for chromosome abnormalities to confirm LM were observed for the past five decades. Analysis from the reported studies shows that prenatal screening was conducted in pregnant mothers between 9–23 weeks of gestation (16). In the early 1980s, the samples used were amniotic fluid. During pregnancy, foetal samples that are commonly used for laboratory analysis include amniotic fluid obtained from amniocentesis, placental tissue from chorionic villus sampling, or serum from foetal blood (17). Karyotyping to determine chromosome abnormality in the 1980s and 1990s involved culturing fibroblasts derived from amniotic fluid.

However, as time progressed, other samples such as chorionic villi and foetal tissues obtained from post-mortem were used for genetic analysis. In the early 2000s, faster and more sensitive method – such as quantitative polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) – was used to determine gene mutations. Over the past ten years, cytogenetics techniques have evolved and more specific methods such as multiplex ligation-dependent probe amplification (MLPA) and microarray were used to detect mutations in confirming LM in the foetus (18). The technological advancement in cytogenetics provides valuable diagnostic and prognostic information on congenital and developmental abnormalities in the foetus that allows early diagnosis of congenital diseases such as LM (19). Cytogenetic analysis is a microscopic method used to determine the gain, loss, or rearrangement of genetic material during mitosis and meiosis (20).

Evolution of various cytogenetic techniques in lymphatic malformation patients

In earlier years of diagnosing LM, cytogenetics analysis involved 'solid stained' chromosomes which allow easy quantification of chromosomes. This method is known as conventional karyotyping. This simple method however fails to distinguish chromosome pairs from others that are similar in size and general morphology (20). In the subsequent years, better resolution of chromosome abnormalities was achieved through the banding technique. In this non-fluorescent method, gross chromosomal abnormalities which include structural abnormalities as small as 5–10 Mb and the ability to distinguish every chromosome pair unequivocally were able to be determined (21).

Interestingly, in the years 2000–2016, a cytogenetic technique used to confirm LM showed substantial milestones in identifying the mutations involved. This technique is known as fluorescence in situ hybridization (FISH) and is used as an adjunct to other prenatal tests such as ultrasound and karyotyping (22). FISH offers higher resolution compared to banding technique: FISH involves the use of fluorescent-labelled DNA or RNA probe to bind specifically to a complementary DNA sequence on the chromosome. Then, by using a fluorescence microscope, it is possible to visualize and discern specific genetic markers or abnormalities.

Besides FISH, multiplex ligation-dependent probe amplification (MLPA) is another advanced technique that can determine various mutations in nucleic acid sequence from a small sample. This technique uses synthetic DNA probes that directly bind to the targeted DNA sequences. The ligation of the probes together indicates the presence of the target DNA segment in the correct copy number. Conversely, if there is a deletion or duplication in the target region, complete ligation cannot be established. In a recent publication, the authors used whole genome single nucleotide polymorphism-based copy number microarray analysis to further characterise the mutation identified in foetus diagnosed with LM (23). This method provides a global analysis of the chromosomal alterations and allows precise localization and identification of the gene content that is involved in the mutations (24).

The evolution of the cytogenetic techniques has certainly enabled a better diagnosis of LM based on more specific information on the genetic abnormalities involved; the evolution is summarised in Figure 1.

Evolution of imagine techniques for detection of lymphatic malformation

A review of current research in the field of lymphatic malformation detection includes the ongoing developments in imaging technology and image analysis techniques. Ever since the availability of ultrasound, LM has been diagnosed based on the assessment of nuchal translucency (NT) thickness between the foetal skin and the subcutaneous soft tissue at the neck and cervical spine, during the first or second-trimester routine ultrasonography. However, recent advancements in imaging technology, artificial intelligence, and machine learning for the past 5–10 years have led to the integration of various technologies in the diagnostic process.

During the first trimester, the NT measurement serves as a screening method for most common numerical chromosomal abnormalities before confirmation by cytogenetic and FISH analysis of cultured amniotic fluid (25). Interestingly, it was postulated that the outcome of LM is associated with the timing of onset in LM cases with normal karyotypes. This translates to detection in the first trimester tends to have a worse outcome than later in pregnancy. It was noted 88.6% of all cases diagnosed in the first trimester are associated with chromosomal abnormalities and major congenital anomalies that adversely affect the prognosis. However, a good foetal outcome was noted in 67.9% of all cases with no structural anomalies in the first trimester with normal microarray

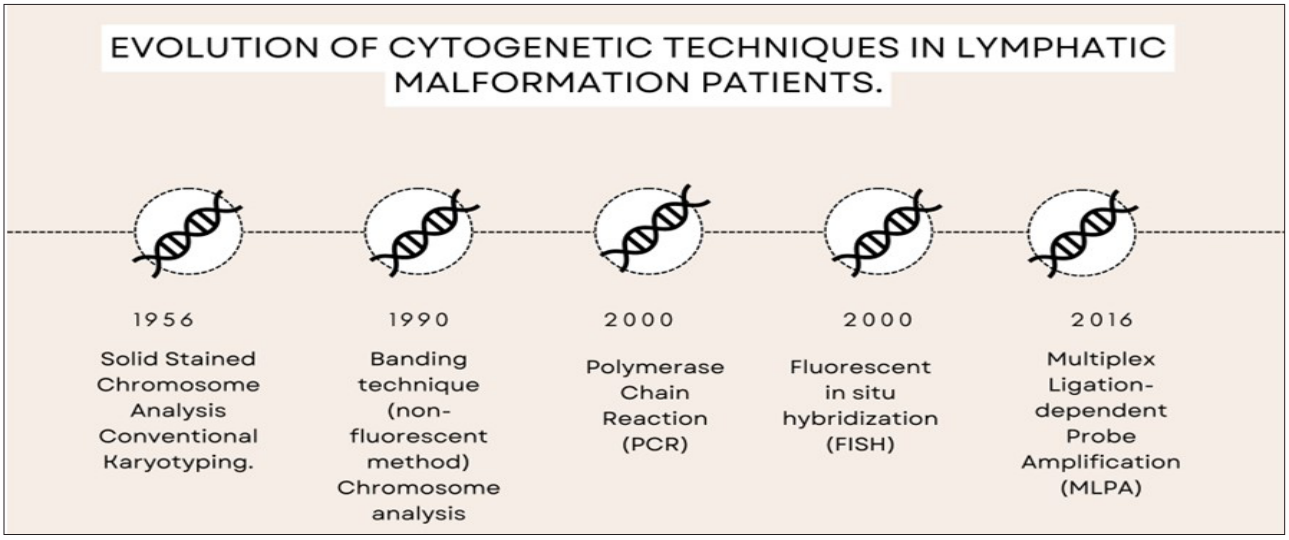

Figure 1: Summary of evolution of cytogenetic techniques in lymphatic malformation patients (16-24)

analysis (26). A study conducted in Turkey between 2014 and 2018 on 106 confirmed cases of LM reported a correlation between increased NT during first-trimester screening and chromosomal abnormalities, structural malformations, and foetal death (27).

The recent advancements in machine learning on image analysis techniques also gave had an impact on LM detection. In one recent study, it was demonstrated how deep learning has the potential to support the early and accurate identification of LM from first-trimester ultrasound scans (28). The study used an image dataset comprised of 289 distinct ultrasound images, which included 160 control images with normal NT measurements and 129 cases with lymphatic malformation. With a sensitivity of 92% and specificity of 94%, the model demonstrated excellent prediction of LM. However, frequent misclassifications were observed when the foetus was close to the placental membrane. In future research, this model will be applied to a larger, multi-centre dataset with greater image parameter variability and a greater variety of lymphatic malformation-specific features (28, 29).

LM is also known as part of the clinical presentation of numerous congenital disorders. Studies on the use of exome sequencing for single-gene disorders in unexplained nonimmune hydrops fetalis (NIHF) could indirectly diagnose LM. NIHF is defined as the presence of one or more pathologic foetal fluid collections, such as LM, pleural effusion, pericardial effusion, ascites, skin oedema, and an increased NT thickness (3.5 mm), or a combination of these conditions. In this study, exome sequencing successfully diagnosed 29% of the cases as NIHF (29).

This review demonstrates that the identification of LM presentation in ultrasound examination during the late first trimester or early second trimester, along with the detection of chromosomal abnormalities using cytogenetic analyses, is associated with worsened survival rates in the foetus. The combination of the ability to observe LM accurately with magnetic resonance imaging (MRI) and advanced genetic analysis is expected to improve LM detection and management. The complications related to LM can be prevented and the life quality will be improved.

Associated genetic factors related to lymphatic malformation

Paternal and maternal factors

Upon detection of LM using ultrasonography in first trimester or early in second trimester, both parents' blood would be tested for any chromosomal and gene abnormalities. Several studies have reported the presence of three structure chromosomal abnormalities detected through genetic analysis from parental blood screening, and intriguingly, all of these abnormalities originated from the paternal side. The structural chromosomal abnormalities include isochromosome (13q,13q) with karyotype 46, XY pericentric inversion 11(p11q25) with karyotype 46,XY and balanced reciprocal translocation t(10;18)(q25.3;q23) with karyotype 46,XY (30-32). All maternal chromosomes and genes were normal. Hence, it is highly likely that LM presentation in foetal is affected more by paternal rather than maternal structural chromosomal abnormalities.

Foetal chromosomal factor

The foetal genetic analysis from reports showed LM was associated with both chromosome and gene abnormalities. The common aneuploidy documented in LM is trisomy which includes trisomy 21, 13, 18, 3 and trisomy 22 (31, 33). Interestingly, a foetus with multiple chromosome abnormalities (trisomy 21, 18, and 3) was reported to exhibit nuchal oedema without any other abnormalities.

LM is associated with a foetal chromosomal abnormality in 93.8% and gene anomalies in 6.15% of the cases. Syndromic features of chromosomal abnormality such as trisomy or monosomy are common manifestations in LM patients.

The incidence rate of trisomy in LM patients agrees with the literature which reports trisomy 21 is the highest viable autosomal trisomy syndrome followed by trisomy 18 and 13 (34). In the case of sex chromosomal abnormality, monosomy X is the most common pathological karyotype in LM patients (33). A study in 434 cases of nuchal oedema presentation detected in the first trimester reported an 18% risk of developing LM was observed in cases with monosomy X (33). Most of the cases reviewed in this study opted for the termination in the late second trimester or the foetus succumbed to intrauterine death before termination resulting in no survival of LM foetus with trisomy chromosome. Abortion or pregnancy termination in a foetus with LM is reported in 1: 875 cases (35). In the 1980s, cases of LM with an abnormal karyotype and concurrent ascites, pleural fluid, and bilateral pleural effusions were reported to have a poor prognosis (36). Despite this, current medical practises are restricted to providing genetic counselling and reassurance to parents of LM-affected foetuses. Moreover, in cases of recurrent miscarriage, genetic analysis is necessary to further elucidate potential underlying factors.

Several sex chromosome aneuploidies were also reported in a foetus with LM including 47XXY, 47XYY, 46XY/47XYY, 46XY/47XXY, 47XYYl45X, and 46XY/ 45X (37). Loss of the SRY gene (Sex-determining Region Y) at chromosome Y in 46 XY was manifested as a female foetus with LM, foetal hydrops, and anasarca (38). It was postulated that LM is developed as a result of the loss of the SRY gene at the short arm of the Y chromosome (38). Similar manifestations were observed in a foetus with monosomy X without any Y chromosome. Hence, another hypothesis of LM development is due to the loss of Y function in patients with monosomy X.

Figure 2 shows the summaries of the chromosomal abnormalities associated with LM. Almost half of the chromosome (10 pair) abnormalities contain LM. This demonstrated how significant the LM presentation is.

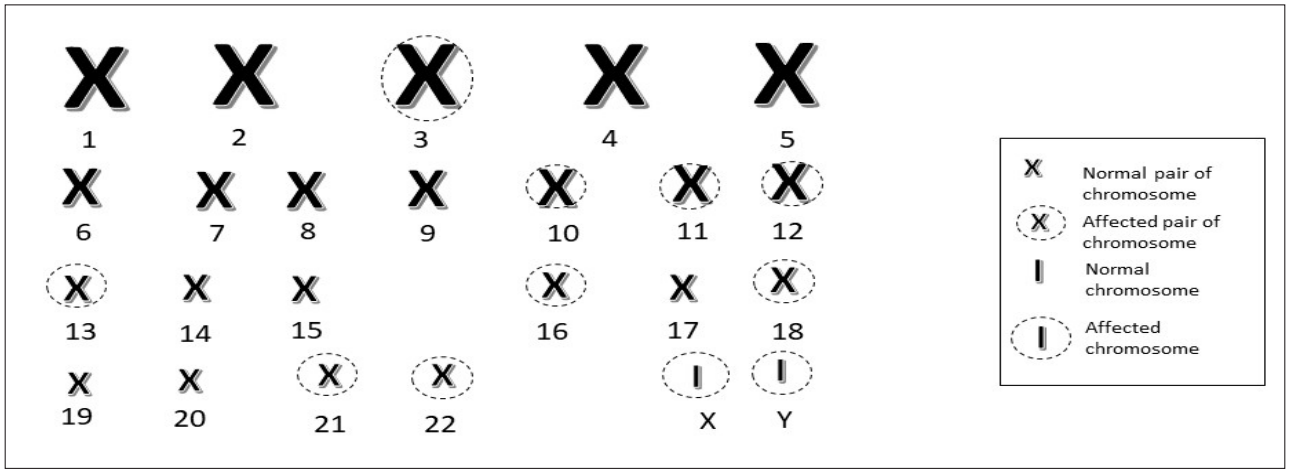

Figure 2: Summary of chromosome abnormalities associated with lymphatic malformation (31, 33-38)

Gene factors

Loss of the SRY gene at chromosome Y in 46 XY was manifested as a female foetus with LM, foetal hydrops and anasarca (38). In the LM case study, it was postulated that LM is also caused by the deletion of the SRY gene on the Y chromosome's short arm (38). The gene SRY (Sex-determining Region Y) is a gene located on the Y chromosome in humans. During embryonic development, it holds a significant role in determining the development of male characteristics (39). In an absent or non-functional SRY gene, the individual develops along the female pathway, fails to achieve normal puberty, and has dysgenic gonads and a high incidence of gonadoblastoma. In mutation of the SRY gene such as translocation into an X chromosome or an autosome, it will lead to disorders of sexual development (DSD). In a series of case studies, XX men had testicular atrophy and their histopathology showed Sertoli cell-only syndrome and Leydig cell hyperplasia (40).

Approximately 50% of Noonan Syndrome cases are caused by mutations in the PTPN11 (protein tyrosine phosphatase non-receptor type 11) gene (41). Noonan Syndrome is one of the leading causes of LM. Studies suggest that Noonan syndrome can be suspected prenatally in cases with large NT in addition to one or more of the following characteristics: LM, pleural effusion, hydrops fetalis, cardiac anomalies, or specific facial features. PTPN11 is one of the mutation hotspots gene detected using Sanger sequencing in Noonan Syndrome foetuses (42). The gene PTPN11 is a gene located on chromosome 12 in humans. This gene encodes a protein tyrosine phosphatase called Src homology 2 domain-containing protein tyrosine phosphatase 2 (SHP-2). SHP-2 plays a critical role in the regulation of cell growth, differentiation, and development. It functions as a signalling molecule that regulates the activity of other proteins through the selective removal of phosphate groups from specific tyrosine residues (43). This dephosphorylation process is essential for fine-tuning and balancing cellular signalling pathways. These mutations

in PTPN11 can lead to abnormal activation of signalling pathways involved in cell growth and development, such as the reticular activating system- mitogen-activated protein kinase (RAS-MAPK) pathway (44).

Several genetic mutations were reported such as deletions of region encoding for FOX (Forkhead Box) gene in 16q24.1 as well as de novo translocation t(5;9)(q11.2;p22) which are associated with hydrops fetalis and LM in the foetus (23, 45). Deletions in 16q24.1 in the region encoding for the FOX gene cluster also have been associated with multiple structural anomalies including heart abnormality, and pulmonary complications such as alveolar deformity, capillary dysplasia, and misalignment of the pulmonary veins. FOXF1 (Forkhead Box F1) and FOXC2 (Forkhead Box C2) are two members of the FOX gene family that is located at chromosome 16 in humans. They are transcription factors that are involved in various developmental processes, including cardiovascular development, lymphatic vessel formation, and adipogenesis (46). They also had been identified as a molecular cascade which regulates extracellular-signal-regulated kinase (ERK) signalling in lymphatic vessel growth (47).

Genetic abnormalities related to nuchal translucency finding

After receiving genetic counselling regarding an elevated risk of foetal genetic disorders, the patient is now faced with the decision of whether to undergo diagnostic prenatal testing. Patients are more likely to choose invasive testing as the number of risk factors, such as advanced age, family history, and ultrasound findings, increases (48). Sanger sequencing, targeting mutation hotspots in frequently implicated genes of Noonan Syndrome, was employed in foetuses presenting with increased nuchal translucency (NT). The study revealed that a germline PTPN11 variant associated with cancer manifested prenatally, resulting in a severe phenotype of Noonan Syndrome (42).

While increased NT is associated with many genetic abnormalities, some genetic anomalies may not have a direct relationship with LM. For example, there is only one case of LM related to Neu–Laxova Syndrome (NLS) caused by a novel variant in the PHGDH (phosphoglycerate dehydrogenase) gene (49). Exome sequencing in foetus with increased NT has also identified heterozygous likely pathogenic mutation in the ACTB (actin beta) gene which confirms the diagnosis of Baraitser-Winter Syndrome (50). This indicates that an increase in NT is not necessarily correlated with LM in all cases.

Ostensibly, initial karyotype analysis conducted upon observing increased NT or LM in ultrasonography may report normal chromosomes. However, further genetic investigations noted structure abnormality of a single chromosome, including deletion and translocation (30, 33, 37, 51-52). Karyotype analysis alone will not be able to provide detailed information regarding gene abnormality in patients with LM. The presence of aneuploidy suggests a fatal prognosis of the foetus with less than 12 hours of viable time. Hence, LM in ultrasonography findings warrants further genetic evaluation.

Complications of Lymphatic Malformation

A review of LM from 1983 to 2022 describes the effect of this illness on the foetus. LM is a benign growth which arises from inborn obstruction of lymphatic drainage (53). Since the year 1983, LM has been noted in foetus with generalized hydrops detected early and during the second trimester (31, 33, 38). Besides generalized hydrops, LM patients were also noted to have cleft palate, bilateral hexadactyly, undescended testes, and internal autolytic changes (52). Aortic coarctation in foetuses with LM has been documented to cause narrowing in the main blood supply of the body, leading to reduced viability and ultimately resulting in intrauterine death (31). LM also can present with omphalocele which is detected in the womb via ultrasound (26). Omphalocele is described as when the infant's intestines, spleen, or other organs are located outside of the abdomen of the foetus through the belly button (26).

LM most commonly co-exist with Turner Syndrome followed by Noonan Syndrome and Down Syndrome (54). The features found in syndromic babies with LM involving most of the organs—e.g., congenital myopathy, muscular ventricular septal defect, microcephaly, mental retardation, pulmonary atresia, coronary artery fistula, heterotaxy syndrome—leads to intrauterine death and neonatal death due to prematurity (55).

Panigrahi et al. (56), reported that the effect of the foetus with LM and chromosomal abnormalities includes complicated cardiac anomalies such as transposition of great arteries, hypoplastic left heart, double outlet ventricle, tetralogy of Fallot, and ectopia cordis. Bone deformities such as pectus excavatum, hypoplastic thorax, shortened long bones, syndactyly, cleidocranial dysostosis, absent radius, campomelic dysplasia, micrognathia, brachycephaly, and broad metopic suture might also present in the LM foetus with a chromosomal abnormality. Other systems that are also involved include urinary tract anomalies, such as renal aplasia, multicystic kidneys, and pyelectasis (56).

The massive swelling of LM causes compression, infection, and haemorrhage (57). Patients usually present with bronchiolitis. This complication was preventable and manageable if fast treatment was taken. Otherwise, a late or missed diagnosis could have sinister effects on the patients. Treatment options such as OK-432, sirolimus, propranolol, and sclerotherapy (employing agents like bleomycin, doxycycline, and ethanol) would be prioritised to decrease the size of lymphatic malformations. Sclerotherapy is currently the gold standard of treatment for macrocystic or mixed lymphatic malformations (5). Surgical treatment is needed to remove the swelling, except in premature babies or the involvement of

neurovascular structure adjunction to the LM. The risk of morbidities and mortality rate of 2–10% if damage to the neurovascular structure during surgery (58).

Conclusion

Increased LM cases have been reported annually for the past five years despite its rare incidence rate. The increased detection rate may be due to the implementation of aneuploidy screening in a foetus with nuchal translucency (NT) detected in the first trimester. The presence of aneuploidy in LM results in a poor prognosis. To date, there are no known associations of risk factors (which include age, race, and parity) with LM prognosis. This review concludes that the technology advancement aids early antenatal detection and genetics related to LM despite the poor prognosis. Early detection aids prenatal diagnosis and grants valuable information for appropriate counselling. Future research in identifying LM-associated risk factors and biomarkers that can be detected in either the parents or the foetus will provide enormous benefits to both parents and the foetus.

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Competing interests

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