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REVIEW

Research progress on the pathogenesis of multiple symmetrical lipomatosis

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ABSTRACT

Multiple symmetric lipomatosis, also known as madelung's disease, is a rare syndrome characterized by the accumulation of multiple symmetric subcutaneous adipose tissues that significantly affect patients' quality of life. Since the aetiology of the disease is still unclear, surgical intervention by doctors based on clinical experience is currently the main treatment. However, the recurrence rate remains high even after surgical intervention. Therefore, studying the pathogenesis of this disease is particularly important for overcoming this challenge. In this paper, we reviewed and summarized recent research results on the pathogenesis of this disease to provide possible research directions and treatment strategies for this disease, but no clear mechanism was identified.

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Multiple symmetric lipomatosis (MSL), also known as Madelung's disease or Launois – Bensaude syndrome, was first described by a British physiologist and surgeon, Benjamin Collins Brodie, in 1848 [1]. In 1888, Otto Wilhelm Madelung provided a comprehensive summary of the disease and named it Madelung's disease. MSL is characterized by symmetrical deposits of adipose tissue between the subcutaneous and deep fascia, resulting in painless symmetrical nodules. However, MSL commonly appears in the neck, shoulder, and proximal upper extremities, forming a 'pseudoathletic' or 'buffalo hump'. MSL is more common in middle-aged men than in middle-aged women and has a male-to-female ratio of approximately 19:1. It is found predominantly in Europe, particularly in the Mediterranean region, while reports from Asia are scant [2–4]. Alcoholism is a common risk factor, although the exact mechanism is still unclear [5].

To date, no systematic review has been conducted on the pathogenesis of MSL. Nevertheless, treatment of MSL relies mainly on surgical intervention, which involves liposuction or fat excision, with interventions limited to symptomatic relief. The surgical approach is determined by the severity of the disease, the site of adipose tissue deposits, and the patient's expectations. Therefore, this article reviews the advancements in MSL research, summarizing current findings concerning its pathogenesis to improve the understanding of the disease aetiology.

I. Epidemiological characteristics of multiple symmetric lipomatosis (MSL)

Multiple symmetric lipomatosis, as a rare syndrome characterized by multiple, symmetric abnormal adipose tissue accumulation under the skin, is crucial for better phenotypic analysis of various manifestations of the disease and the establishment of standardized diagnostic methods.

Based on the distribution of fat deposition, Giuliano Enzi [6] classified it into two phenotypes in 1984: Type I characterized by symmetrical masses concentrated in the neck, shoulders, supraclavicular triangles, and proximal upper limbs, and Type II characterized by symmetrical masses in the abdomen and lower limbs, often overlooked due to its similarity to common obesity. Subsequently, Gerd Donhauser [7] further divided it into four phenotypes in 1991: Type I characterized by neck masses, Type II by pseudoathletic type, Type III by gynaecoid type, particularly in the lower body, especially the thighs and inner knees, and Type IV by abdominal type. To better study the disease, Daniel Schiltz [8] divided it into three phenotypes (with one phenotype further divided into three subtypes) in 2018: Type Ia characterized by the neck, Type Ib by the Neck, shoulder girdle, upper arms, Type Ic by the neck, shoulder straps, upper arms, chest, abdomen, upper and lower back, Type II by the Hips, bottom, and

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upper legs, and Type III by General distribution skipping head, forearms, and lower legs

Multiple symmetrical lipomatosis is a rare disorder of lipid metabolism, with most cases reported sporadically. A systematic summary of the epidemiology and clinical characteristics of this disease is highly important for clinical prevention, diagnosis, treatment, and postoperative care.

Quanzhe Liu [3] et al. analysed 14 studies that met the inclusion and exclusion criteria and summarized the epidemiology and clinical features of the disease. Among the 286 cases, the majority were in Europe (79.7%), particularly in southern regions such as Portugal (37%) and Italy (21.3%). Some cases were also reported in Asia, accounting for 11.2% of the total. The average age of the patients was 51.4 years (range 26–75), with a male to female ratio of 272:14 (19:1). In 7 studies involving 120 patients, 68.3% had a normal BMI, 9.2% were obese, and 22.5% were overweight. According to the Enzi classification, the disease described in 9 studies was predominantly Type I in 175 cases (92.1%) and Type II in 15 cases (7.9%). Lipomas most commonly occur in the neck, accounting for 57% of cases. The most common complications were liver disease (51.2%), followed by hypertension (24.2%), macrocytosis (22.0%), dyslipidaemia (20.7%), and hyperuricaemia (17.4%). Moreover, patients had similar habits, such as a history of long-term alcohol abuse and smoking, which accounted for 89.5% and 53% of the cases, respectively. Among the 443 patients, 69.5% underwent lipectomy, 24.2% underwent suction lipectomy, and 6.1% received a combination of lipectomy and suction lipectomy. The overall recurrence rate was 18.3%, with recurrence rates of 18.8% for lipectomy and 19.4% for suction lipectomy.

Runze Li [4] et al. analysed the medical records of 54 Chinese patients with this disease retrospectively and reported the following results: 98.15% of patients with MD were male, with an average age of 56.65 ± 7.93 years. Most patients had a history of long-term smoking and/or alcohol abuse. According to Donhauser's classification, Type 1 accounted for 61.11%. MD patients often present multiple systemic complications, with endocrine system diseases being the most common, accounting for 81.48% of cases. Notably, as many as 20.37% of patients had concurrent cancer, particularly gastrointestinal tumours. Over 70% of patients underwent surgical treatment, but the postoperative recurrence rate was significant, with approximately 40% experiencing recurrent adipose tissue after surgery.

Previous retrospective studies have shown that this disease commonly occurs in individuals aged 40–60 years, with a male-to-female ratio ranging from 15:1 to 30:1. It is usually asymptomatic but is associated with various metabolic disorders, such as hyperuricaemia, hyperlipidaemia, diabetes, hypertension, liver disease, hypothyroidism, and renal tubular acidosis. Alcohol abuse is a highly correlated risk factor for the development of MSL. Additionally, smoking, obesity, sex, and age may be associated factors for Madelung disease, although they are not determining factors. Clinically, effective treatment methods for MSL are lacking, which results in disappointing disease control. Although other preventive measures, such as alcohol cessation and weight loss, may help control the amount of MSL fat, they cannot slow the progression of the disease.

Additionally, some case reports are also worth our attention.

The study by Olimpia Musumeci et al. [9] presented new findings that deserve attention. According to their research results, none of their MSL patients had chronic high alcohol intake, diabetes, or lipid abnormalities. Moreover, compared to previously published data, the presence of MSL in females was greater than that in males, and the onset of the disease was usually associated with muscular involvement.

A further study [10] linked MSL to tissue damage induced by high alcohol intake, suggesting that an enhanced inflammatory response may play a role in the onset of this disease. In addition, the involvement of the liver and its association with lymphatic system collapse are related to the specific locations where fat accumulates, such as the neck and chest, which are areas densely populated with lymphatic vessels. Therefore, alcohol and other mediators of lymphatic leakage may play important roles in MSL.

Rodrigo Gomes da Silva [11] et al. discovered a patient with clinical manifestations of symmetrical lipomatosis in the chest and interscapular regions, accompanied by mild macrocytosis and thrombocytopenia. They first described the rare association of MSL with immune thrombocytopenic purpura.

Hirotsugu Noguchi [12] et al. reported a case of MSL with distinctive histological features. The tumour tissue in this case was composed of mature adipocytes, accompanied by fibrous septa and proliferation of spindle cells. Notably, there are local myxoid changes and aggregations of spindle cells. The histological characteristics of this case resemble those of spindle cell lipoma (SCL) and typical liposarcoma (ALT/WDL) but lack the characteristic abnormal stromal cells and expression of MDM2 and CDK4 present in the latter, providing important evidence for the diagnosis of this disease.

It is commonly believed that the disease is associated with long-term alcohol intake; however, Carlos José de Miguel Sánchez [13] et al. reported a case of a non-alcoholic male patient with a family history. The

patient, a 51-year-old man, presented with gradually worsening fatigue and exertional dyspnoea, with a previous history of MSL. His mother also had MSL and developed myoclonus and myopathy at age 52, eventually leading to respiratory failure. Muscle biopsy revealed ragged red fibres (RRFs) and mitochondrial cytochrome C oxidase-negative (COX-) fibres. These findings indicate that this condition may serve as an early marker of mitochondrial disease, particularly in non-alcoholic patients. Concurrently, these findings validate a potential association between the disease and mitochondrial dysfunction, especially in relation to the m.8344A>G mutation. Mingzi Zhang [14] et al. reported a case of benign symmetric lipomatosis in a female patient. This condition is extremely rare in women, and the patient in this case had no apparent risk factors. The literature mentions that the disease is typically associated with endocrine disorders, metabolic disturbances, and alcoholism; however, no such history was evident in this case. Similarly, Cheng Jiao [15] et al. reported the case of a female patient without a history of alcohol abuse. Hanan El Ouahabi [16] et al. reported a case of a male patient without a history of alcohol abuse and with a genetic predisposition.

There are also reports describing rare complications of the disease, such as the teams of Shayan Soomro [17] and Mingkwan Lumyongsatien [18] reporting cases associated with exophthalmos and orbital involvement and the teams of Masanori Kudoh [19], Miguel Mayo Yáñez [20], and Luz Marina Calvo Hernadez [21] reporting cases associated with macroglossia.

II. Histological characteristics of MSL

As a rare syndrome characterized by the symmetrical accumulation of abnormal adipose tissue, the study of the characteristics and sources of MSL adipose tissue is important for explaining its pathogenesis.

1. Adipose tissue characteristics and sources of MSL

Previous studies have shown that MSL patients have a greater abundance of multichambered, smaller adipocytes, whereas normal subcutaneous adipose tissue (SAT) has less fibre and vascular tissue. However, Ke Chen [22] et al.'s experimental series showed that, compared with normal adipose tissue, adipose tissue lipoma-like masses (ATLLM) from MSL patients had an abundance of fibres, but no difference in the size of multichambered adipocytes or adipocyte-like substances was found. Additionally, Daniel Schiltz [23] et al.'s study revealed that there were no macroscopic or microscopic differences in HE staining between affected adipose tissue and normal tissue from MSL patients. Single vacuole (white) adipose tissue was observed in both the affected and unaffected adipose tissue. No beige or brown adipose tissue was histologically observed, and protein or elastic fibres were not increased. Therefore, they suggested that MSL tumour formation is due to adipose tissue proliferation rather than hypertrophy.

Federica Caponnetto [10] et al. compared the surface phenotype, growth kinetics, adipogenic differentiation potential, and molecular changes in isolated adipose-derived stem cells (MSL-ASCs) from MSL patients with those of healthy ASCs. The experimental results showed that MD-ASCs had smaller cell volumes and faster growth rates than healthy ASCs. Reaching steady state at significantly higher cell density in their growth kinetics. From a histological perspective, all patient adipose tissue was characterized by smaller adipocytes, fibrosis, and vascular reinforcement but not the heterotypic characteristics of adipose tumours. Both MSL-ASCs and ASCs were characterized by an adipose-derived stem cell phenotype, and there was no significant difference in adipogenic differentiation between MSL-ASCs and ASCs. The secreted protein profile of MSL-ASCs may lead to changes in the growth potential and surface phenotype of ASCs, thereby indicating a possible pathological mechanism for the spread of the disease from affected tissue to healthy tissue.

2. MSL and UCP-1

Uncoupling protein-1 (UCP-1), an important marker of brown adipocytes, has also attracted the attention of MSL researchers. Previous studies indicated [9] that the pathogenesis of MSL lipomas appears to be related to alterations in the regulation of brown adipose tissue growth. This hypothesis is supported by the typical anatomical distribution and morphological findings in the affected tissue. Lipoma tumours are located along the body midline and follow the distribution of brown adipose tissue (BAT) in newborns. In contrast to white adipose tissue, BAT produces heat due to the overexpression of UCP1, which is responsible for the uncoupling of oxidative phosphorylation during ATP generation. UCP1 is overexpressed in MSL tissue, confirming its potential origin from BAT.

Daniel Schiltz [23] and colleagues identified 45 patients diagnosed with MSL between 2011 and 2017 from a database of the Regensburg University Hospital. Among them, 10 patients were selected for inclusion in the study. The majority of the samples exhibited overexpression of UCP-1 (9/10 in the affected tissue and 7/

10 in the adjacent tissue), and UCP-1 levels were significantly greater in almost all MSL patients (in both affected and unaffected adipose tissue) than in healthy individuals. These findings suggested that the affected adipose tissue may originate from brown or beige adipose tissue rather than from white adipose tissue.

However, recent contrasting research indicates that the adipose tissue in MSL lipomas is white adipose tissue. Ke Chen [22] and colleagues did not detect UCP-1 overexpression in their study's findings and even observed a decrease in UCP-1 expression. Furthermore, UCP-1 was not overexpressed in mature adipocytes from MSLs upon stimulation with isoproterenol. Rocha [24] and Moonen [25] demonstrated through positron emission tomography-computed tomography (PET-CT) imaging after cold stimulation that the adipose tissue in MSL lipomas did not express UCP-1 or take up 18F-fluorodeoxyglucose (18F-FDG). Marta Sanna [26] and colleagues showed that the adipose tissue in MSL lipomas differed from that in positive brown adipose tissue controls and displayed the typical morphology of white adipose tissue, containing mature and single mismatched adipocytes. Additionally, the adipose tissue did not stain for UCP1 protein and exhibited very low levels of UCP1 mRNA.

3. MSL, CD200, Myf5, p107, and the cell death activator

Cluster of differentiation 200 (CD200), an OX-2 membrane glycoprotein, is a type I membrane glycoprotein that belongs to the immunoglobulin superfamily. CD200 is expressed in various types of cells and plays a critical role in immune suppression and the regulation of antitumour activity [27].

Myf5 belongs to the family of 'myogenic regulatory factors' (MRFs) and is a type of ' basic helix-loop-helix (bHLH) transcription factor'. [28] The Myf5 protein plays a key role in muscle differentiation (skeletal muscle myogenesis) and brown adipose tissue development. This transcription factor is only expressed in embryonic tissues for a few days. During embryonic development, white and brown adipocytes are derived from different progenitor cells. Brown adipose tissue comes from cells expressing myf5 and can also differentiate into skeletal muscle. White adipose tissue is derived from myf5-negative stem cells in the mesoderm.

p107 (retinoblastoma-like protein 1, RBL1) is a tumour suppressor protein that appears to be involved in cell cycle regulation. It is similar to the product of the retinoblastoma 1 gene (RB1), which is phosphorylated in the S and M phases of the cell cycle and dephosphorylated in the G1 phase of the cell cycle. Studies have shown that it plays a role in adipocyte differentiation and is necessary for white adipose tissue differentiation [29].

The cell death activator CIDEA is an important transcriptional coactivator that regulates lipid secretion in the mammary gland [30]. It has also been shown to activate apoptosis. Mice lacking functional CIDEA have higher metabolic rates, increased lipolysis in brown adipose tissue, and higher core body temperatures when exposed to cold. These mice are also resistant to diet-induced obesity and diabetes.

A study by Daniel Schiltz et al. [23] showed that the subcutaneous adipose tissue of MSL patients was weakly positive. In the control group, adipose tissue was negative for CD200 staining. CD200 was expressed in poorly differentiated white adipose tissue; all tested patient samples were negative for myf5, all samples were negative for p107, and no samples were positive for CIDEA. Immunohistochemical markers (CD200, Myf5, p107, and the cell death activator CIDEA) indicate that pathological adipose tissue may originate from brown or beige adipose tissue rather than from white adipose tissue.

III. Genomic changes in MSL

1. MSL and the mtDNA mutation (m.8344A>G)in tRnalys

Previous studies have suggested that lipomas are often associated with mitochondrial DNA mutations, and mtDNA mutation in tRNALys is the most common mutation associated with myoclonic epilepsy with ragged-red fibres (MERRF) syndrome. Olimpia Musumeci [9] and colleagues conducted a retrospective study of 1,300 mitochondrial disease patients registered in an Italian database and confirmed that MSL is a rare symptom of mitochondrial disease, with a strong correlation between MSL and mtDNA mutation in tRNALys.

Their experimental results showed that of 1,300 patients with mitochondrial disease, 22 had lipoma. Nineteen of these patients had an mtDNA mutation in tRNALys, and 17 of them had the mtDNA (m.8344A>G) mutation in tRNALys. Notably, among the 12 patients who exhibited typical MERRF syndrome, only 4 patients had independent MSL, while the remaining patients had other muscle diseases. Finally, they proposed that MSL is a rare sign of mitochondrial disease. However, identifying MSL is important because it can be considered a warning sign of mitochondrial disease and guide diagnosis. The authors also warned that mitochondrial DNA analysis should

be considered even in isolated cases of MSL, as it can be the only expression of pathogenic mtDNA mutations.

However, Federica Caponnetto [4] and colleagues analysed the adipose tissue of 8 MSL patients for the mtDNA (m.8344A>G) mutation in tRNALys and found no evidence of this mutation. Regarding the 8344A>G mutation, none of the patients were carriers of this mutation.

2. MSL and mtDNA (m.8357T>C) mutation in tRnalys

López-Gallardo, Esther et al. [6] discovered a new mtDNA mutation (m.8357T>C) in tRNALys in a patient with MSL and other skin symptoms.

They constructed three different hybrids through cell hybridization: one with the patient's m.8357T>C mutation (O8357), one positive control carrying the confirmed tRNALys pathological mutation m.8344A>G (O8344), and a negative control group (Owt) without pathological mutations. The research showed that the O8357 hybrids grew more slowly in glucose and lactose culture media than the Owt hybrids. In addition, similar to the O8344 hybrid cells, the O8357 cells exhibited significantly reduced endogenous oxygen consumption, leaked respiration and noncoupled respiration. The specific activity and quantity of respiratory complex IV (CIV) and the level of the p.MT-CO1 subunit were also significantly lower in the CIV group than in the control group. It was also found that the oxidative phosphorylation defect was transmitted in a similar manner to other confirmed tRNALys pathological mutations when the patient's mtDNA was transferred to a rho0 cell line. Finally, the lipomas were separated into lineages as the mutation occurred. As not all patients carrying tRNALys mutations develop lipomas, there must be another factor involved in this process.

Therefore, they proposed that this mtDNA mutation (m.8357T>C) has pathological effects on oxidative phosphorylation and respiratory complex IV and may be associated with MSL syndrome. The 8357T>C mutation is a pathogenic factor of MSL. It has been suggested that MSL cannot be attributed to OXPHOS dysfunction caused by mitochondrial translation defects but rather to changes in additional functions associated with these specific tRNAs.

3. MSL and CBLB (c.197A>T) mutations

The Cbl proto-oncogene B gene (CBLB) is a highly conserved protein that encodes an E3 ubiquitin-protein ligase. It is a crucial factor in promoting protein degradation mediated by proteasomes and is involved in immune responses, insulin resistance, inflammation, allergies, and cancer development. CBLB also regulates the functions of macrophages and T cells, including cell maturation and activity, and is involved in insulin resistance following macrophage infiltration into adipose tissue. CBLB can specifically degrade the insulin receptor substrate 1 (IRS1) protein and negatively regulate PI3K-IRS1-AKT activity. However, CBLB overexpression significantly downregulated the levels of phosphoinositide 3-kinase (PI3K), IRS1, and protein kinase B (AKT) in T cells, acute lymphoblastic leukaemia cells, and osteoblasts.

Ke Chen et al. [22] proposed that CBLB may inhibit insulin-induced activity of the IRS1-PI3K-AKT pathway in adipocytes. Whole-genome sequencing of adipose tissue samples from 13 MSL patients identified a mutation (i.e. CBLB c.197A>T) in four MSL patients. The impact of the CBLB c.197A>T mutation on the IRS1-PI3K-AKT pathway in mesenchymal stromal cells (hADSCs) derived from MSL patients was also validated.

Bioinformatics analysis revealed that this mutation is highly conserved among 98 vertebrate species and has a very low mutation frequency. If it occurs at the CBLB p.Q66L site, it is likely to be deleterious. The phenotypes of the CBLB-/- mice resembled the clinical characteristics of human MSL [31] [32], such as the development of MSL in middle-aged males, the accumulation of ATLLM over a long and slow process, and similar lipid-related results in blood biochemistry. No significant changes were observed in the liver after disease onset. Therefore, there is reason to believe that CBLB mutation may be an important risk factor for the development of MSL [22].

4. MSL and FMN2 mutations

MFN2 (mitofusin 2) is a gene encoding a mitochondrial outer membrane protein that plays a critical role in regulating mitochondrial fusion processes, which are essential for maintaining the integrity and function of the mitochondrial network. MFN2 promotes interactions and fusion between mitochondria through its GTPase activity, influencing various biological processes, such as cellular metabolism, energy supply, and apoptosis. Additionally, MFN2 is involved in the formation of contact sites between mitochondria and the endoplasmic reticulum, which are important for calcium signalling and lipid metabolism.

Sarah L. Sawyer [33] et al. identified a homozygous mutation in the MFN2 gene (c.2119C>T; p.R707W) through whole-exome sequencing in two brothers and

an unrelated patient, which is considered a novel causative mutation for MSL. In their study, all three patients developed neuropathic symptoms after presenting with lipomas, but no mutations in the MERFF gene were detected. Additionally, the patients' lipid metabolism markers, such as leptin and adiponectin, were below normal levels, further supporting the hypothesis of mitochondrial dysfunction. Functional experiments revealed that the R707W mutation significantly affects the homopolymerization ability of MFN2, leading to mitochondrial aggregation and impaired mitochondrial fusion capacity.

Anna Braszak-Cymerman [34] et al. reported a case in which a patient presented with a Cushingoid appearance, yet Cushing's syndrome was ruled out through laboratory and imaging examinations. Whole-exome sequencing revealed two pathogenic variants in the MFN2 gene of the patient, specifically c.2119C>T and c.1496-2A>G.

Emilie Capel [35] et al. performed Sanger sequencing of the MFN2 gene in 66 patients referred for abnormal fat distribution, confirming that six patients carried the p.Arg707Trp mutation. Additionally, through detailed clinical, metabolic, and histological analyses, the study suggests that low levels of leptin and adiponectin, along with high FGF21 levels, may serve as biomarkers for MSL.

Establishing an effective cell model to study the specific effects and mechanisms of this mutation presents a challenge owing to the association of MFN2 gene mutations with mitochondrial dysfunction, resulting in abnormal fat distribution in patients. Nidaa A. Ababneh [36] et al. employed Sendai virus reprogramming technology to create a novel induced pluripotent stem cell (iPSC) line named JUCTCi012-A from a 39-year-old woman with multiple symmetric lipomatosis (MSL) carrying a point mutation in the MFN2 gene. This iPSC line exhibits robust proliferation capabilities and multilineage differentiation potential. This cell line provides new tools for studying the disease mechanisms associated with multiple symmetrical lipomatosis (MSL). The iPSC line exhibits robust pluripotency and can differentiate into all three germ layers, offering potential for further drug development and disease modelling.

5. MSL and LIPE mutations

Camille Sollier [37] et al. identified three female patients with biallelic variants in the LIPE gene, specifically c.2828del, p.(Glu943Glyfs *22), c.1890_1891del, p.(Leu631Glyfs *57), c.2077del, p.(Arg693Valfs *76), and c.1261C>T, p.(Gln421*). Dual allelic variants in the LIPE gene lead to the absence of HSL (hormone-sensitive lipase) expression, which subsequently affects adipocyte differentiation and function, resulting in conditions including lipodystrophy, metabolic abnormalities, and neuromuscular damage. This study is the first to elucidate the clinical characteristics of multiple symmetric lipomatosis (MSL) associated with LIPE and explore its pathogenesis through the use of adipose-derived stem cell models.

IV. Other possible mechanisms of MSL

Research by Marta Sanna et al. [26] suggested that aberrant activation of CK2, AKT, and ERK1/2 in lipomatous tissue (LT) indicates that downregulating these kinases could be a promising pharmacological tool for preventing the expansion and recurrence of MSL lipomas. Currently, the CK2 inhibitor CX-4945 (NCT02128282) and the ERK1/2 inhibitors ulixertinib (BVD-523) and LTT462 (NCT01781429 and NCT02711345, respectively), which have been used in clinical trials for treating cancer, can be considered potential drugs for targeting LT and preventing the need for reoperation. M2 macrophages play a crucial role in inducing white fat browning and are a potential therapeutic target; relevant studies have been conducted in animal models of obesity [7]. In MSL, functional defects in the adrenal beta 3 adrenergic receptor or decreased inducible nitric oxide synthase (iNOS) are present, as decreased iNOS results in reduced nitric oxide and promotes adipogenesis [8]. The four- transmembrane protein CD9 is involved in cell movement, adhesion, and differentiation. High CD9 levels have been directly linked to enhanced proliferation, adhesion, and in vivo implantation. Moreover, CD9 has been shown to work through the PI3K-AKT-mTOR-p53 signalling pathway, which could be an interesting avenue for future studies of MD-ASCs [10].

V. Conclusion

In conclusion, this article summarizes the current research on the pathogenesis of multiple symmetric lipomatosis (MSL). However, the exact aetiology and pathogenesis of MSL are still unclear. The main controversies are as follows: 1. Whether MSL is related to metabolic disorders and whether there are associated complications. 2. It is unclear whether MSL originates from white adipose tissue or brown/beige adipose tissue. 3. Various omics studies of MSL still lack a unified conclusion.

In summary, in the field of epidemiology, considering the relatively rare incidence of MSL, the limited number of cases and samples in various studies primarily confined to series reports and case sharing, and the failure to cover the majority of patients, only simple summaries of the epidemiological characteristics of the disease can be made, which may affect its generalizability and statistical significance. Additionally, while alcoholism is widely recognized as a risk factor for this disease, case reports have disputed this view. Therefore, it is reasonable to speculate that since not all alcoholics develop lipomas, there must be deeper underlying causes for the development of the disease.

In omics research, the study sample size is small, with most studies involving fewer than 10 patients, which may affect the generality and representativeness of the results. Additionally, there is still a lack of in-depth exploration of disease aetiology and mechanisms, particularly regarding the direct association with chronic alcoholism, which remains poorly understood. The specific physiological mechanisms of pathogenesis have not been thoroughly investigated by various research groups, and detailed mechanistic analyses of how mutations affect disease development are lacking.

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Author contributions

Substantial contributions to the conception or design of the work; Bo Hu(Mr.)or the acquisition, analysis, or interpretation of data for the work.Ze Wang(Mr.)Pengfei Fan(Mr.)

Drafting the work or reviewing it critically for important intellectual content.Bo Hu(Mr.)

Final approval of the version to be published.LeiLi (MD) Tengxiao Ma(MD)

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.LeiLi (MD)

All authors agree to be accountable for all aspects of the work.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Ethics approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

For this type of study informed consent is not required.

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References

[1] Lockwood CB. Clinical lectures on anatomy and morbid anatomy in clinical surgery: delivered at St. Bartholomew's hospital. Br Med J. 1911 Feb 4;1 (2614):239–242. doi: 10.1136/bmj.1.2614.239 PMID: 20765434; PMCID: PMC2333093.

[2] Nerlich AG, Perciaccante A, Donell ST, et al. Madelung's disease in a rare 14th century Franco-Flemish woolen tapestry. Lancet Diabetes Endocrinol. 2022 Sep;10(9):619–620. doi: 10.1016/S2213-8587(22)00213-3 Epub 2022 Jul 15. PMID: 35850131.

[3] Liu Q, Lyu H, Xu B, et al. Madelung disease epidemiology and clinical characteristics: a systemic review. Aesthetic Plast Surg. 2021 Jun;45(3):977–986. doi: 10.1007/s00266-020-02083-5 Epub 2021 Jan 25. PMID: 33492475.

[4] Li R, Wang C, Bu Q, et al. Madelung's disease: analysis of clinical characteristics, fatty mass distribution, comorbidities and treatment of 54 patients in China. Diabetes Metab Syndr Obes. 2022 Aug 6;15:2365–2375. doi: 10.2147/DMSO.S363836 PMID: 35966829; PMCID: PMC9364939.

[5] Vassallo GA, Mirijello A, Tarli C, et al. Madelung's disease and acute alcoholic hepatitis: case report and review of literature. Eur Rev Med Pharmacol Sci. 2019 Jul;23(14):6272–6276. doi: 10.26355/eurrev_201907_18448 PMID: 31364130.

[6] López-Gallardo E, Cammarata-Scalisi F, Emperador S, et al. Mitochondrial DNA pathogenic mutations in multiple symmetric lipomatosis. Clin Genet. 2020 May;97(5):731–735. doi: 10.1111/cge.13701 Epub 2020 Jan 9. PMID: 31912494.

[7] Dong X, Zhang M, Jin X. Adipose tissue in multiple symmetric lipomatosis shows features of brown: beige fat. Aesthetic Plast Surg. 2022 Apr;46 (Suppl 1):22–23. doi: 10.1007/s00266-021-02474-2 Epub 2021 Jul 23. PMID: 34297172.

[8] Chen K, Wang L, Yang W, et al. Profiling of differentially expressed genes in adipose tissues of multiple symmetric lipomatosis. Mol Med Rep. 2017 Nov;16(5):6570–6579. doi: 10.3892/mmr.2017.7437 Epub 2017 Sep 7. PMID: 28901441; PMCID: PMC5865826.

[9] Musumeci O, Barca E, Lamperti C, et al. Lipomatosis incidence and characteristics in an Italian cohort of mitochondrial patients. Front Neurol. 2019 Feb 27;10:160. doi: 10.3389/fneur.2019.00160 PMID: 30873109; PMCID: PMC6402385.

[10] Caponnetto F, Manini I, Bulfoni M, et al. Human adipose-derived stem cells in madelung's disease: morphological and functional characterization. Cells. 2020 Dec 30;10(1):44. doi: 10.3390/cells10010044 PMID: 33396896; PMCID: PMC7824042.

[11] Gomes da Silva R, Detoffol Bragança R, Ribeiro Costa C, et al. Multiple symmetric lipomatosis. J Cutan Med Surg. 2011 Jul-Aug;15(4):230–235. doi: 10.2310/7750.2011.10026 PMID: 21781630.

[12] Noguchi H, Masuda R, Hisaoka M. Multiple symmetric lipomatosis with spindle cell proliferation. Pathol Int. 2016 May;66(5):311–312. doi: 10.1111/pin.12397 Epub 2016 Feb 27. PMID: 26922721.

[13] de Miguel-Sánchez CJ, Gómez GL, Hidalgo RL, et al. Multiple symmetric lipomatosis as a marker of mitochondrial disease. Case report and review of the literature. Neurol Sci. 2024 Jul 26. doi: 10.1007/s10072-024-07710-6 Epub ahead of print. PMID: 39060540.

[14] Zhang M, Xiao Y, Chang G, et al. Perineal benign symmetric lipomatosis in a female patient: a case report. Am J Case Rep. 2024 Apr 30;25:e943803. doi: 10.12659/AJCR.943803 PMID: 38685699; PMCID: PMC11068072.

[15] Jiao C, Liu W, Qiao Y, et al. A case report on madelung's disease and comprehensive review of the literature. Orphanet J Rare Dis. 2024 Aug 17;19(1):302. doi: 10.1186/s13023-024-03303-w PMID: 39154182; PMCID: PMC11330121.

[16] El Ouahabi H, Doubi S, Lahlou K, et al. Launois-bensaude syndrome: a benign symmetric lipomatosis without alcohol association. Ann Afr Med. 2017 Jan-Mar;16(1):33–34. doi: 10.4103/aam.aam_26_16 PMID: 28300050; PMCID: PMC5452705.

[17] Soomro S, Ziahosseini K, Sharma P. Proptosis of the eye: a potential form of madelung's disease. BMJ Case Rep. 2021 Sep 12;14(9):e243669. doi: 10.1136/bcr-2021-243669 PMID: 34511421; PMCID: PMC8438748.

[18] Lumyongsatien M, Selva D. Bilateral symmetric lipomatosis of the orbit in madelung's disease. Orbit. 2022 Apr;41(2):268–270. doi: 10.1080/01676830.2020.1852261 Epub 2020 Nov 26. PMID: 33243058.

[19] Kudoh M, Omura K, Satsukawa A, et al. Symmetric lipomatosis arising in the tongue presenting as macroglossia and articulatory disorder. Case Rep Otolaryngol. 2016;2016:2061649. doi: 10.1155/2016/2061649 Epub 2016 Jun 19. PMID: 27413566; PMCID: PMC4930821.

[20] Mayo Yáñez M, González Poggioli N, Álvarez-Buylla Blanco M, et al. Benign symmetric lipomatosis with lingual involvement: case report and literature review. Journal Of Stomatology, Oral And Maxillofacial Surgery. 2018 Apr;119(2):148–150. doi: 10.1016/j.jormas.2017.11.006 Epub 2017 Nov 10. PMID: 29129710.

[21] Calvo Hernadez LM, Riol López E, Peña Ferrera L, et al. Macroglosia secundaria a enfermedad de Madelung [Macroglossia in Madelung's disease]. Med Clin (Barc). 2016 Nov 18;147(10):e59. Spanish. doi: 10.1016/j.medcli.2016.03.045 Epub 2016 May 30. PMID: 27255987.

[22] Chen K, Wan X, Zhao L, et al. Cbl proto-oncogene B (CBLB) c.197A>T mutation induces mild metabolic dysfunction in partial type I multiple symmetric lipomatosis (MSL). Diabetes Metab Syndr Obes. 2020 Oct 6;13:3535–3549. doi: 10.2147/DMSO.S273780 PMID: 33116705; PMCID: PMC7547790.

[23] Schiltz D, Tschernitz S, Ortner C, et al. Adipose tissue in multiple symmetric lipomatosis shows features of Brown/Beige fat. Aesthetic Plast Surg. 2020 Jun;44(3):855–861. doi: 10.1007/s00266-020-01666-6 Epub 2020 Mar 10. PMID: 32157376; PMCID: PMC7280331.

[24] Rocha N, Bulger DA, Frontini A, et al. Human biallelic MFN2 mutations induce mitochondrial dysfunction, upper body adipose hyperplasia, and suppression of leptin expression. Elife. 2017 Apr 19;6:e23813. doi: 10.7554/eLife.23813 PMID: 28414270; PMCID: PMC5422073.

[25] Moonen MPB, Nascimento EBM, van Kroonenburgh MJPG, et al. Absence of 18 F-fluorodeoxyglucose uptake using positron emission tomography/computed tomography in madelung's disease: a case report. Clin Obes. 2019 Jun;9(3):e12302. doi: 10.1111/cob.12302 Epub 2019 Feb 27. PMID: 30815996; PMCID: PMC6593737.

[26] Sanna M, Borgo C, Compagnin C, et al. White adipose tissue expansion in multiple symmetric lipomatosis is associated with upregulation of CK2, AKT and ERK1/2. Int J Mol Sci. 2020 Oct 26;21(21):7933. doi: 10.3390/ijms21217933 PMID: 33114687; PMCID: PMC7662313.

[27] Ong WK, Tan CS, Chan KL, et al. Identification of specific cell-surface markers of adipose-derived stem cells from subcutaneous and visceral fat depots. Stem Cell Reports. 2014 Feb 6;2(2):171–179. doi: 10.1016/j.stemcr.2014.01.002 PMID: 24527391; PMCID: PMC3923222.

[28] Tapscott SJ, Weintraub H. MyoD and the regulation of myogenesis by helix-loop-helix proteins. J Clin Invest. 1991 Apr;87(4):1133–1138. doi: 10.1172/JCI115109 PMID: 1849142; PMCID: PMC295115.

[29] Porras DP, Abbaszadeh M, Bhattacharya D, et al. p107 determines a metabolic checkpoint required for adipocyte lineage fates. Stem Cells. 2017 May;35(5):1378–1391. doi: 10.1002/stem.2576 Epub 2017 Feb 23. PMID: 28233396.

[30] Li P. Cidea, brown fat and obesity. Mech Ageing Dev. 2004 Apr;125(4):337–338. doi: 10.1016/j.mad.2004.01.002 PMID: 15063110.

[31] Chen K, Xie Y, Hu P, et al. Multiple symmetric lipomatosis: substantial subcutaneous adipose tissue accumulation did not induce glucose and lipid metabolism dysfunction. Ann Nutr Metab. 2010;57(1):68–73. doi: 10.1159/000317641 Epub 2010 Aug 17. PMID: 20714139.

[32] Chen K, He H, Xie Y, et al. miR-125a-3p and miR-483-5p promote adipogenesis via suppressing the RhoA/ROCK1/ERK1/2 pathway in multiple symmetric lipomatosis. Sci Rep. 2015 Jul 7;5:11909. doi: 10.1038/srep11909 PMID: 26148871; PMCID: PMC4493643.

[33] Sawyer SL, Cheuk-Him Ng A, Innes AM, et al. Homozygous mutations in MFN2 cause multiple symmetric lipomatosis associated with neuropathy. Hum. Mol. Genet. 2015 Sep 15;24(18):5109–5114. doi: 10.1093/hmg/ddv229 Epub 2015 Jun 17. PMID: 26085578.

[34] Braszak-Cymerman A, Walczak MK, Skorczyk-Werner A, et al. From cushing syndrome to lipodystrophy: an ultra-rare case of MFN2-associated lipomatosis. Pol Arch Intern Med. 2023 Jun 23;133(6):16495. doi: 10.20452/pamw.16495 Epub 2023 May 10. PMID: 37162328.

[35] Capel E, Vatier C, Cervera P, et al. MFN2-associated lipomatosis: clinical spectrum and impact on adipose tissue. J Clin Lipidol. 2018 Nov-Dec;12(6):1420–1435. doi: 10.1016/j.jacl.2018.07.009 Epub 2018 Jul 25. PMID: 30158064.

[36] Ababneh NA, Ali D, Barham R, et al. Establishment of a human induced pluripotent stem cell line, JUCTCi012-a, from multiple symmetric lipomatosis (MSL) patient carrying a homozygous Arg707Trp (c.2119C > T) mutation in the MFN2 gene. Stem Cell Res. 2020 Oct;48:101967. doi: 10.1016/j.scr.2020.101967 Epub 2020 Aug 31. PMID: 32916636.

[37] Sollier C, Capel E, Aguilhon C, et al. Lipe-related lipodystrophic syndrome: clinical features and disease modeling using adipose stem cells. Eur J Endocrinol. 2021 Jan;184(1):155–168. doi: 10.1530/EJE-20-1013 PMID: 33112291.