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Pathophysiological Mechanisms and Multimodal Therapeutic Strategies in Meniere's Disease

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Abstract. Meniere's disease is a long-term inner ear condition that leads to vertigo, hearing loss, and tinnitus. It affects primarily women between the ages of 40 and 60 years. It is hard to treat due to its numerous causes. Research has indicated that issues like fluid buildup in the inner ear, immune system attacks, and reduced blood flow could all play a role. Diagnostic tests like vascular endothelial function testing (VEMP), electrocorticography (ECoG), and 3T magnetic resonance imaging (MRI) can assist, but all have drawbacks and are frequently utilized together. Treatment strategies encompass diuretic therapy, intratympanic injections, vestibular rehabilitation, neuromodulation, and immunomodulatory interventions. However, no single modality has proven universally effective; physicians must therefore implement individualized, combination-based treatment regimens. This review delineates the principal pathogenic mechanisms of Meniere's disease and critically evaluates a range of therapeutic approaches, highlighting the importance of personalized treatment algorithms and multidisciplinary care models to optimize patient outcomes in Meniere's disease management.

Keywords: Meniere's disease, endolymphatic hydrops, immune inflammation, microcirculation, multimodal therapy

1. Introduction

Pathophysiology and comprehensive treatment modalities of Meniere's disease. Meniere's disease is a chronic inner ear condition characterized by spontaneous vertigo, fluctuating sensorineural hearing loss, tinnitus, and the sensation of fullness in the ears. The incidence across the world is predominantly 17 to 46 per 100,000 individuals. In Chinese population studies, the prevalence has been found to be 21 to 31 per 100,000 individuals, with lower awareness and delayed diagnosis in rural populations [1]. Most patients are middle-aged people between 40 and 60 years, with a higher incidence in females. Vertigo is the hallmark symptom of Meniere's disease, often occurring suddenly and recurrently. It can last for 20 minutes to several hours and can occur 1 to 2 times a week to several times a month. In the clinical population, more than 70% of the patients had at least one episode of vertigo per month, and approximately 30% had more than two episodes per week. These vertigo attacks are often accompanied by other symptoms such as nausea, vomiting, sweating, impaired balance, and anxiety [2]. Another clinical symptom is an auditory change, a fluctuating sensorineural hearing loss that starts in the low frequencies and then advances to full-band loss.

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Hearing may be partially recovered during an attack, but after several attacks, it becomes mainly permanent. Longitudinal studies illustrated that more than 60% of MD patients will have permanent hearing loss within five years of onset [3].

The diagnostic tests include audiological examination such as pure tone audiometry, which often reveals characteristic presentation of low-frequency hearing loss, generally between 125 and 5000 Hz. Other diagnostic tests include electrophysiological tests. Vestibular-evoked electromyographic responses can assess otolith function and indicate dysfunction. Electrocochleartesting may indicate an elevation of the SP/AP ratio and an increase in endolymphatic edema. At the same time, endolymphatic edema can be seen with 3T delayed enhanced scanning. The sensitivity of 3T MRI for the detection of endolymphatic hydrops has been reported to be over 80% in clinically definite MD cases. However, diagnosis can be challenging as it overlaps with other conditions. For example, vestibular migraine is an atypical hearing loss with migraine history, where vertigo attacks are shorter in duration and higher in frequency. Sudden deafness Hearing loss is abrupt and not heralded by a protracted attack of vertigo. It may also be an autoimmune inner ear disease. Hearing loss occurs in a brief period and mostly responds to immunosuppressants. Pathophysiological mechanisms of Meniere's disease primarily involve endolymphatic fluid dynamics imbalance, immune-inflammation response, and abnormalities of inner ear microcirculation. Endolymph retention is a key pathological feature, which can result from the failure of ion channels such as aquaporin and TRPV4, leading to fluid retention and pressure increase in the membranous labyrinth of the inner ear. Immunologic abnormalities also play a role since some patients carry anti-inner ear autoantibodies that are capable of activating the complement system and causing local inflammation. The situation may further be worsened by the increase in pro-inflammatory cytokines such as TNF-α and IL-6. Inner ear microcirculatory derangements in the form of impaired blood flow also add to hypoxia, metabolic waste product accumulation, and tissue edema that cumulatively increase inner ear structural damage. Treatment methods for Meniere's disease include traditional drug treatments such as oral diuretics and salt-restricted diets and local injections (e.g., dexamethasone, aminoglycosides), despite their long-term benefits not being so satisfactory. Vestibular rehabilitation training and neuromodulation approaches, i.e., transcranial magnetic stimulation, are also employed to aid in the recovery of balance function. More recently, application of immune modulation combined with neural stimulation has been regarded as a new treatment for patients. This review will systematically synthesize and evaluate the current understanding of the pathophysiological mechanisms of Meniere's disease, including endolymphatic hydrops, immune-inflammation, and microcirculatory disturbances, and explore the efficacy and feasibility of multimodal treatments to establish a theoretical basis for personalized and targeted holistic management strategies in clinical practice [4].

2. Pathophysiological mechanisms

2.1. Endolymphatic fluid dynamics imbalance

The pathophysiology of Meniere's disease is primarily an endolymphatic hydrodynamic imbalance, endolymphatic fluid overload, and increased inner ear pressure. Endolymphatic edema, i.e., inner ear membranous labyrinth excess fluid, is the pathognomonic pathology of Meniere's disease. Dysfunction of endolymphatic sac absorption or labyrinthine aqueduct stenosis blocks fluid drainage and causes elevated inner ear pressure. Thus, pressure homeostasis and hearing ability of the receptor cells are lost. Ion channel abnormalities Aquaporin 2 and aquaporin 4 regulate fluid permeability through membranes [5]. TRPV4 ion channels manage osmotic pressure and volume

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equilibrium within and outside the cell. Dysfunction in these channels can lead to endolymphatic fluid buildup, aggravation of edema and inner ear pressure imbalance.

2.2. Immune-induced inflammatory response

A subset of patients exhibits evidence of autoimmunity, including anti–inner ear antibodies and complement activation, which together compromise receptor cell integrity and blood–labyrinth barrier function. Activation of the complement system can cause destruction of the receptor structure and trigger a local inflammatory response. The influence of pathologic process of inflammatory cytokines. IL-6 and TNF-α were significantly elevated in the perilymph and blood of patients [6]. These inflammatory factors may obliterate the inner ear barrier, hasten the inflammation, and result in recurrence and exacerbation of disease.

2.3. Inner ear microcirculatory dysfunction

The inner ear relies on a delicate microvascular network for oxygen and nutrient delivery, which is vulnerable to pressure or lesion-induced microcirculation disorders. Reduced blood perfusion can lead to local hypoxia, which decreases the metabolic rate of tissues and affects tissue edema and the generation of metabolic products. The integrity of the blood-labyrinth barrier is lost, and inflammatory mediators penetrate into the inner ear fluid space, aggravating endolymphatic edema. Meanwhile, metabolites are poorly excreted, and tissue edema and toxic damage accumulation occur, further impeding hair cell function. Meniere's disease pathogenesis is characterized by interweaving of multiple factors. The key one is disturbed fluid metabolism, but pathological immune system reactions and disorders of inner ear microcirculation also play a significant role in the development of disease. These mechanisms can also interact with each other and have a combined effect on the development, occurrence and recurrence of the disease.

3. Clinical presentation and diagnostic approaches

3.1. Vertigo and auditory symptoms

Patients typically present with spontaneous, rotational vertigo lasting 20 minutes to several hours, recurrently episodic in frequency. The frequency of attacks varies from person to person and can be episodically worsened. A mild feeling of instability between attacks is experienced by most patients. The associated symptoms are usually accompanied by nausea, vomiting, sweating, anxiety and autonomic nervous system symptoms. Some patients develop vestibular prodroms such as full head or auditory symptoms. The first hearing change is mainly low-frequency fluctuation. Sensorineural hearing loss can develop into permanent hearing loss over the entire frequency range during the course of the disease. Tinnitus and aural fullness commonly co-occur.

3.2. Diagnostic techniques

Diagnostic tests Audiology testing Pure tone audiometry is the basic tool, showing 125–500 The low-frequency auditory threshold of Hz rises. Some patients have noticeable differences between the interval and the attack in hearing. Other tests may include speech recognition rate and acoustic impedance testing for middle ear and cochlear function evaluation. Vestibular Evoked Myogenic Potentials (VEMP) assess otolith organ integrity, and electrocochleography (ECoG) reveals elevated summating potential/action potential ratios indicative of endolymphatic hydrops. Delayed-

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enhancement 3T MRI following intratympanic Gd–DTPA administration visualizes hydrops with > 80 % sensitivity in confirmed cases [7].

3.3. Differential diagnosis

Vestibular migraine is diagnosed with shorter but more frequent attacks of vertigo, accompanied by typical or atypical migraine symptoms, without definite persistent hearing loss. Vestibular migraine is diagnosed with shorter but more frequent attacks of vertigo, accompanied by typical or atypical migraine symptoms, without definite persistent hearing loss. Sudden deafness is mainly unilateral and rapidly progressing hearing loss, not necessarily followed by repeated attacks of vertigo. MRI would typically be used to exclude auditory neuropathy. Autoimmune inner ear disease is of rapid progression and may have bilateral symmetrical hearing loss. It typically responds well to glucocorticoids or immunosuppressants and requires ancillary diagnosis by immunological markers.

4. Therapeutic strategies

4.1. Pharmacological interventions

Oral diuretics such as hydrochlorothiazide and ethazolamide help to reduce fluid buildup in the endolymph by reducing fluid retention in the body and thus relieving vertigo [8]. In parallel, dietary therapy to limit sodium consumption is also widely recommended to help in the conservation of inner ear fluid balance stability. Local drug injections are drug injections in the middle ear. Intratympanic administration of dexamethasone targets local inflammation and modulates the immune response within the vestibular apparatus. Aminoglycoside antibiotics such as gentamicin reduce the incidence of incapacitating episodes of vertigo by selectively inhibiting vestibular activity [9]. It is used in patients who are refractory to conventional therapy, but risk of ototoxicity should be considered.

4.2. Physical and neuromodulation therapies

Vestibular rehabilitation training includes head-eye coordination, balance control and gait training, to improve the vestibular adaptation capacity of the patient by employing central compensatory mechanisms. For patients at the chronic stage to reduce long-term residual symptoms of vertigo. Transcranial magnetic stimulation (TMS) offers a non-invasive neuromodulatory approach by altering cortical excitability within vestibular networks, with early studies reporting symptomatic improvement in chronic vertigo and associated hyperacusis. However, optimal stimulation parameters and long-term efficacy remain to be established through randomized controlled trials.

4.3. Combined immunomodulatory and neurostimulatory therapies

With the better comprehension of immune mechanisms of Meniere's disease, new interventional technologies have increasingly investigated multimodal approaches to therapy that integrate immune and neural control. In cases suspected of autoimmune mediation, immunomodulatory treatment such as intravenous immunoglobulin and low-dose immunosuppressants such as methotrexate and azathioprine can be utilized. Neuromodulation procedures such as vagus nerve stimulation and transcutaneous electrical stimulation can improve inner ear perfusion and central nervous system control. Studies have demonstrated that combined treatment models are more effective than single treatments for reducing frequent vertigo attacks and stabilizing hearing. It is likely to be a candidate

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drug for resistant cases in the near future. Further clinical trials are warranted to optimize treatment protocols and confirm long-term benefits, particularly in patient's refractory to conventional interventions [10].

5. Conclusion

Meniere's disease is a chronic inner ear disease with multi-factorial driving forces. Its basic pathological processes are mainly composed of imbalance of endolymphatic volume regulation, immune system-mediated inflammatory process, and inner ear microcirculation structure and function disorders. These three mechanisms may be dominant in different patients, but among them, there is interaction and positive feedback, building a network of complicated pathology, finally leading to clinical presentation of recurrent vertigo, hearing fluctuation, and tinnitus. Traditional treatments such as oral diuretics, low-salt diet, and intratympanic injections still play a role in symptom control, but problems such as enormous individual differences in efficacy and unpredictable side effects cannot be neglected; new technologies such as 3T magnetic resonance imaging, transcranial magnetic stimulation, and immune intervention have showed more promise in mechanism targeting and individualized treatment.

The pathogenesis of Meniere's disease is complicated, and one therapeutic approach is usually hard to fully control symptoms or stop the progress of the disease. Thus, the idea of "comprehensive management" is especially crucial. Medication can alleviate the symptoms in the acute attack stage, neuromodulation technology can improve the balance ability in the long term, rehabilitation training can improve the patient's adaptability ability, and immune intervention can regulate the underlying cause of lesion formation. Individualized diagnosis and treatment plans should be determined under multidisciplinary collaboration based on patient-specific features, such as symptom type, speed of disease progression, concomitant diseases, pathological type, etc., in clinical practice to optimize treatment effect and quality of life for patients.

While numerous treatments exist, they have not yet been sufficiently tested with large-scale, long-duration trials in the clinical environment, making their basis in clinical practice guidelines invalid. Clarity on interactions among inner ear fluid pathology, immune response, and blood circulation disease is lacking, and more research is needed in the lab and biological models. Furthermore, numerous studies were carried out in a single hospital with limited patients. They seldom compare findings in various age or gender groups, which slows the development of precision treatment.

Directions Future research must focus on finding more specific markers in blood or ear fluid and using newer scanning methods for disease detection early. Scientists must study drugs that block specific troublesome pathways, such as aquaporins, TRPV4, or immune molecules. Gene or cell therapy may be supplemented to help patients who are not helped by available treatments. Large multi-hospital studies with large numbers of patients are required to validate the safety and efficacy of combination therapy. Laboratory science, imaging, immunology, and otolaryngology teams must join together to create better mechanisms to move study results to patient care.

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