

MIDDLE EAR MUSCLE DYSFUNCTION AS THE CAUSE OF MENIERE'S DISEASE

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Abstract

The symptoms of Meniere's disease form a distinct cluster: bouts of vertigo, fluctuating hearing loss, low-frequency tinnitus, and a feeling of pressure in the ear. Traditionally, these signature symptoms have pointed to some sort of pathology within the inner ear itself, but here the focus is shifted to the middle ear muscles. These muscles, the tensor tympani and the stapedius, have generally been seen as serving only a secondary protective role in hearing, but in this paper they are identified as vigilant gate-keepers – constantly monitoring acoustic input and dynamically adjusting hearing sensitivity so as to enhance external sounds and suppress internally generated ones. The case is made that this split-second adjustment is accomplished by regulation of inner ear pressure: when the middle ear muscles contract they push the stapes into the oval window and increase the pressure of fluids inside the otic capsule. In turn, hydraulic pressure squeezes hair cells, instantly adjusting their sensitivity. If the middle ear muscles should malfunction – such as from cramp, spasm, or dystonia – the resulting abnormal pressure will disrupt hair cells and produce Meniere's symptoms.

A wide-ranging review of Meniere's disease and the middle ear muscles reinforces the link between the two. Since every striated muscle is prone to dystonia – an involuntary contraction involving derangement of its underlying control loop – middle ear muscle dystonia would lead to elevated pressure and abnormal hair cell function. The hypothesis is based on recognizing that the inner ear is a hydrostat – a cavity filled with fluid whose pressure is controlled by the middle ear muscles. Since the fluid is incompressible, even a slight contraction of the muscles can increase the pressure in the labyrinth to 3 kPa. The effect of such a pressure on the sensing cells within is crucial. Outer hair cells carry an internal turgor pressure of about 1 kPa, behaving physically like inflated balloons, and hence contraction of the middle ear muscles can instantly overcome internal cellular pressure, switch off ion channels, and reduce hearing sensitivity.

This paper brings together supporting evidence and sets out major implications for Meniere's disease, including possible treatments.

Key words: hydrostat • intralabyrinthine pressure • middle ear muscles • Meniere's disease • dystonia • cochlear amplifier

TRASTORNOS DE LOS MÚSCULOS DEL OÍDO MEDIO COMO CAUSA DEL SÍNDROME DE MÉNIÈRE

Resumen

Dentro del grupo de los síntomas del síndrome de Ménière pueden diferenciarse: vértigo, pérdida progresiva de la audición, acúfenos en el rango de frecuencias bajas, sensación de presión en los oídos. Los síntomas antes mencionados, característicos de esta enfermedad, tradicionalmente se han asociado a cierta patología dentro del oído medio, en este caso se pone hincapié sobre los músculos del oído medio.

Dichos músculos – el músculo tensor del tímpano y el músculo tensor del estribo – se percibían hasta ahora como unos que cumplen la función protectora del aparato auditivo de forma meramente secundaria, sin embargo en este artículo se reconocen como controladores que vigilan constantemente los estímulos acústicos y reajustan de forma dinámica la sensibilidad auditiva con el fin de reforzar los sonidos externos y atenuar los generados internamente.

En el caso mencionado, el ajuste inmediato se realiza regulando la presión en el oído interno; cuando los músculos del oído medio se contraen, empujan el estribo hacia la ventana oval y causan el aumento de presión del líquido dentro del laberinto. Por su parte, la presión hidráulica reduce el diámetro de los capilares, ajustando de manera constante su sensibilidad. Si los músculos del oído medio experimentan problemas con un funcionamiento correcto – por ejemplo aparecen contracciones, espasmos o distonía – los capilares se deterioran a consecuencia de esa presión atípica, lo cual conduce a la aparición de los síntomas del síndrome de Ménière. Observando de forma integral el síndrome de Ménière y los músculos de oído medio se puede reafirmar la relación que existe entre ellos. Como cada músculo estriado es susceptible a la distonía – las contracciones involuntarias por trastornos del principal bucle de control – la distonía de los músculos del oído medio causaría una presión elevada y el funcionamiento incorrecto de los capilares.

La hipótesis se basa en el reconocimiento del hecho de que el oído medio es un presostato: una cavidad rellena de líquido cuya presión viene controlada por los músculos del oído medio. Como el líquido es incompresible, incluso una contracción minúscula de los músculos puede aumentar la presión dentro del laberinto óseo hasta de 3 kPa. El impacto de esa presión dentro de los capilares es crítico. Los capilares externos que mantienen la turgencia a nivel de 1 kPa se comportan como unos globos hinchados, por tanto la contracción de los músculos del oído medio puede rápidamente superar la turgencia, desactivar los canales iónicos y reducir la sensibilidad auditiva.

El presente trabajo relaciona las pruebas científicas existentes y presenta las principales causas del síndrome de Ménière, así como las posibilidades de su tratamiento.

Palabras clave: presostato • presión dentro del laberinto óseo • músculos del oído medio • síndrome de Ménière • distonía, amplificador coclear

НАРУШЕНИЯ МЫШЦ СРЕДНЕГО УХА КАК ПРИЧИНА БОЛЕЗНИ МЕНЬЕРА

Изложение

Среди симптомов болезни Меньера можно выделить головокружения, прогрессирующую потерю слуха, низкочастотный шум в ушах, чувство давления в ушах. Традиционно вышеуказанные характерные симптомы указывали на определённую патологию в области среднего уха, в данном случае делается упор на мышцы среднего уха.

Данные мышцы – мышца, напрягающая барабанную перепонку, и стременная мышца – до сих пор считались играющими только второстепенную роль защиты органа слуха, однако в данной статье они будут исследованы как чувствительные контролеры, постоянно контролирующие акустические раздражители и динамично адаптирующие слуховую чувствительность, чтобы усилить внешние звуки и подавить возникающие внутри.

В вышеуказанном случае немедленная адаптация происходит путём регулировки давления во внутреннем ухе – когда мышцы среднего уха сокращаются, выталкивают стремя в овальное окно и увеличивают давление жидкостей внутри лабиринта. Давление жидкостей, в свою очередь, сужает капилляры, неустанно адаптируя их чувствительность. Если мышцы среднего уха имеют проблемы с правильным функционированием, в частности, из-за сокращений, спазмов или дистонии, капилляры повреждаются вследствие нетипичного давления, что приводит к появлению симптомов синдрома Меньера. Комплексное наблюдение за падалексимией и мышцами среднего уха усиливает связь между ними. Поскольку каждая поперечнополосатая мышца восприимчива к дистонии – произвольным сокращениям, включающим нарушения их основной регулировочной петли – дистония мышц среднего уха привела бы к повышенному давлению и неправильному функционированию капилляров.

Гипотеза опирается на определении, что внутреннее ухо является гидростатом – выемкой, заполненной жидкостью, давление которой контролируется мышцами среднего уха. Поскольку жидкость несжимаема, даже небольшое сокращение мышц может увеличить давление в костном лабиринте до 3 кПа. Воздействие такого давления в области капилляров является ключевым. Наружные капилляры, поддерживающие внутриклеточное давление (тургор) на уровне 1 кПа, ведут себя как надутые воздушные шары, таким образом, сокращение мышц среднего уха может мгновенно преодолеть внутриклеточное давление, выключить ионные каналы и редуцировать слуховую чувствительность.

Настоящая работа сочетает существующие доказательства и представляет главные причины болезни Меньера, а также возможное лечение.

Ключевые слова: гидростат • давление внутри костного лабиринта • мышцы среднего уха • болезнь Меньера • дистония • улитковый усилитель

ZABURZENIA MIĘŚNI UCHA ŚRODKOWEGO JAKO PRZYCZYNA CHOROBY MENIERE'A

Streszczenie

W zespole objawów choroby Meniere'a można wyróżnić: zawroty głowy, postępujący ubytek słuchu, szumy uszne o niskich częstotliwościach, uczucie ciśnienia w uchu. Tradycyjnie powyższe charakterystyczne objawy wskazywały na pewną patologię w obrębie ucha środkowego, w tym przypadku kładzie się nacisk na mięśniach ucha środkowego.

Mięśnie te – napinacz błony bębenkowej oraz strzemiączkowy – były do tej pory postrzegane jako pełniące jedynie drugorzędą rolę ochronną narządu słuchu, jednak w tym artykule zostają rozpoznane jako czujni kontrolerzy, stale monitorujący bodźce akustyczne i dynamicznie dostosowujący wrażliwość słuchową w celu wzmocnienia zewnętrznych dźwięków i stłumienia wytwarzanych wewnętrznie.

W powyższym przypadku błyskawiczne dostosowanie następuje poprzez regulację ciśnienia w uchu wewnętrznym – gdy mięśnie ucha środkowego kurczą się, wypychają strzemiączko do okienka owalnego i zwiększają ciśnienie płynów wewnątrz błędnika. Z kolei ciśnienie hydrauliczne zwęża naczynia włosowate, nieustannie dostosowując ich wrażliwość. Jeśli mięśnie ucha środkowego mają problemy z prawidłowym funkcjonowaniem – np. przez skurcze, spazmy czy dystonię, naczynia włosowate zostaną uszkodzone w następstwie nietypowego ciśnienia, co doprowadzi do pojawienia się objawów choroby Maniere'a. Kompleksowa obserwacja choroby Maniere'a oraz mięśni ucha środkowego wzmacnia związek między nimi. Jako, że każdy mięsień prądkowany jest podatny na dystonię – mimowolne skurcze obejmujące zaburzenia ich podstawowej pętli regulacyjnej – dystonia mięśni ucha środkowego prowadziła do podniesionego ciśnienia i nieprawidłowego funkcjonowania naczyń włosowatych.

Hipoteza opiera się na rozpoznaniu, że ucho wewnętrzne jest hydrostatem – wnęką wypełnioną płynem, którego ciśnienie jest kontrolowane przez mięśnie ucha środkowego. Ponieważ płyn jest nieściśliwy, nawet niewielki skurcz mięśni może zwiększyć ciśnienie w błędniku kostnym do 3 kPa. Wpływ takiego ciśnienia w obrębie naczyń włosowatych jest kluczowy. Zewnętrzne naczynia włosowate utrzymujące wewnątrzkomórkowe ciśnienie (turgor) na wysokości 1 kPa zachowują się jak napompowane balony, zatem skurcz mięśni ucha środkowego może błyskawicznie pokonać ciśnienie wewnątrzkomórkowe, wyłączyć kanały jonowe i zredukować wrażliwość słuchową.

Niniejsza praca łączy istniejące dowody i prezentuje główne przyczyny choroby Meniere'a, w tym możliwe leczenie.

Słowa kluczowe: hydrostat • ciśnienie wewnątrz błędnika kostnego • mięśnie ucha środkowego • choroba Meniere'a • dystonia • wzmacniacz ślimakowy

Introduction

Meniere's disease (MD) is a chronic, incapacitating, and so far incurable inner ear disorder affecting hearing and balance. The four distinctive symptoms of MD – vertigo, fluctuating hearing loss, low-frequency tinnitus, and aural fullness – occur in a unique cluster, strongly suggesting a common origin [1]. Distinctively, the person afflicted with MD experiences sudden, random attacks of unusual severity, often lasting hours at a time, which eventually subside, leaving the sufferer to wait for the next disabling attack, days or weeks or months later. In the long term, hearing and balance progressively deteriorate. Remarkably, ever since Prosper Meniere in 1861 first identified the cluster of symptoms named after him, the cause of MD has proven elusive, despite more than 150 years of medical research [2–4].

Here, a fresh approach to the disorder is taken and, after examining symptoms of the disease and their circumstances, a single largely invisible factor is identified which fits the diverse features of the complaint. That factor is taken to be raised hydrostatic pressure within the fluids of the labyrinth caused by hyperactivity of the tensor tympani, a muscle hidden away within the middle ear. Normally, the tensor tympani operates silently and effectively as a gate-keeper within the middle ear to regulate the sensitivity of the cochlea to sound. However, after recognizing how cochlear sensitivity can be adjusted by regulating hydraulic pressure within the labyrinth, it becomes possible to appreciate that if the control system should malfunction – perhaps by muscle spasm or loss of its set-point – then it could lead to elevated intralabyrinthine pressure and a Meniere's attack. Over time, increased pressure resulting from overactivity of the muscle would lead to damaged hair cells and compromised hearing and balance.

Emphasis is placed here on a functional fit between the organ-scale hydrostat and thousands of other much smaller hydrostats – the outer hair cells (OHCs) contained within it. Specifically, the body of each OHC is itself a hydrostat – a pressure vessel which, like an inflated balloon, carries an internal pressure of 1 kPa [5]. As later calculations show, if the tensor tympani contracts with a force of 0.3 gram weight, it will raise the hydraulic pressure of the cochlear fluids by 1 kPa; this pressure will in turn overcome the OHC's internal turgor pressure, causing the inflated cell to become flaccid and thus switching off the cochlear amplifier. Whereas the middle ear muscles normally act quietly and efficiently to control pressure and hearing sensitivity, any focal dystonia – a muscle cramp or spasm – could lead to abnormally high pressure and a Meniere's attack. Each symptom of MD – vertigo, fluctuating hearing loss, low-frequency tinnitus, a feeling of pressure in the ear – is compatible with this muscular dysfunction theory. A wide range of supporting evidence is put forward, and some promising avenues for treating this debilitating affliction are suggested.

Background to MD: Suspected hydrops

The symptoms of MD are puzzling, in that they are clearly emanating from within the inner ear, and yet, anatomically and pathologically, nothing much appears to be out of place. There are indications of distension of

membranes [6,7], which for many years has been suggestive of an excess of endolymph, which in turn might explain the pressure-related symptoms. For decades “endolymphatic hydrops” was synonymous with MD [8]. In the hydrops model, an attack was typically seen as the effect of rupture of Reissner's membrane, allowing endolymph and perilymph to mix. As will be discussed later, endolymphatic hydrops can no longer be considered the fundamental cause of MD, although it may be a symptom [9,10]. The main problem with the hydrops theory is that not all MD cases show hydrops, and not all hydropic ears (notably those induced in animals) show vertigo [6,11]. Distinctively, MD is a uniquely human disease. Over the years, many theories have been proposed, but none has been generally accepted and the cause of MD remains a medical mystery [12]. However, a range of triggers have been identified, and these provide additional clues: fatigue, stress, viruses, allergic reactions (including foods), migraine, various psychosomatic factors, and maybe excessive salt intake.

As expressed by a number of authors, endolymphatic hydrops may largely be an epiphenomenon [13] for which only weak and often contradictory evidence can be found [8,10,14,15]. A recent evaluation in the Cochrane data base [15] found no evidence that surgical interventions to alleviate endolymphatic hydrops were successful. However, the hydrops idea persists, perhaps because of its long history and because alternative mechanisms are lacking. That is not to say that distensions in the inner ear cannot be seen in MD; there are now high-resolution MRI scans which indicate a correlation between MD and an elevated volume of endolymph [4], but the problem remains that a high proportion of asymptomatic ears also show enlarged endolymphatic spaces [6,16]. It seems that a focus on endolymph is not based on clear-cut evidence (see [10] for evidence against the hydrops hypothesis; see also [17]). There might be a common factor that leads to both elevated pressure and an enlarged volume of endolymph, but the endolymphatic sac itself does not appear to be the primary locus. In this context, what else could give rise to raised pressure inside the inner ear?

The proposal put forward here is that all the symptoms of MD are consistent with dystonia of the middle ear muscles – manifesting as loss of control and elevated pressure in the labyrinth. The explanation relies first on recognising the aptness of the intralabyrinthine pressure (ILP) theory of middle ear muscle function – the theory that the middle ear muscles are constantly at work, adjusting the hydraulic pressure within the cochlea and thereby controlling the gain of the cochlear amplifier [18]. The known relationship between MD and pressure invites a closer look at how pressure affects the labyrinth and the crucial role the middle ear muscles play in controlling it.

No hydrops, but elevated pressure

Elevated pressure in the labyrinth has, from a wide range of circumstantial evidence, long been considered a possible cause of MD attacks. Ever since Hallpike and Cairns reported what they thought was distension of Reissner's membrane in thawed specimens of post-mortem temporal bones [19], the rise in pressure has been attributed to excess production of endolymph, and for this reason MD

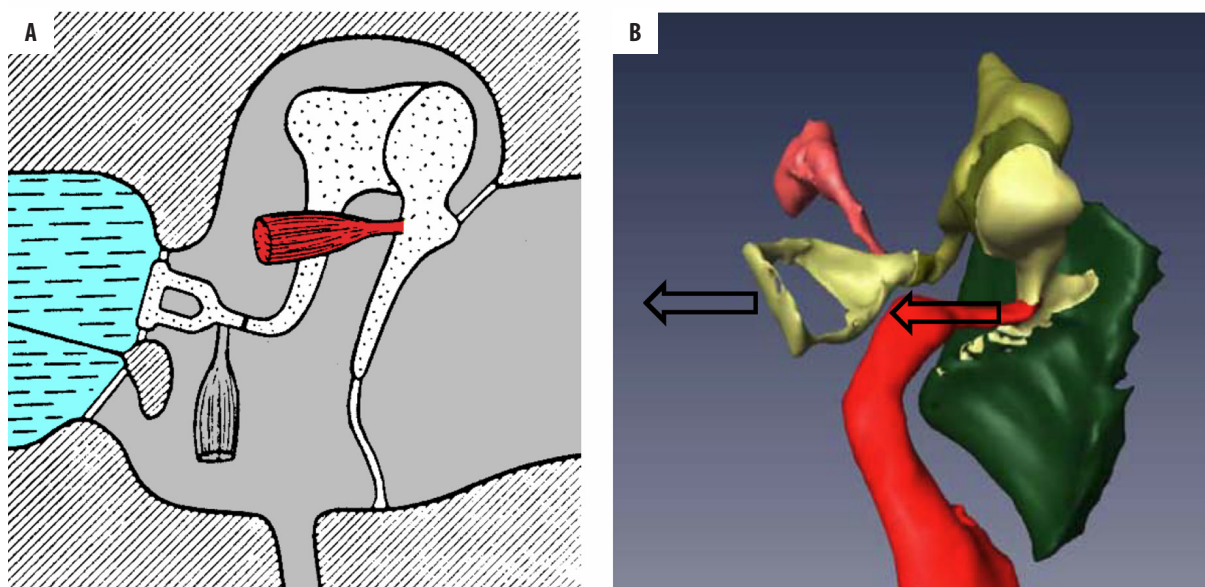


Figure 1. The middle ear muscles. **(A)** Diagram showing the tensor tympani (red) attached to the malleus, and the stapedius (grey) attached to the stapes. When the tensor tympani contracts, the ossicular chain is pulled forward, forcing the stapes into the cochlea and raising the pressure of the fluids within. Adapted from Kirikae [23]. **(B)** 3D reconstruction from histopathology, showing the middle ear muscles in red, ossicles in yellow, and the tympanic membrane in green. Arrows indicate motion resulting from tensor tympani contraction. Image kindly supplied by R. Pennings and M. Bance, Dalhousie University

has become almost synonymous with endolymphatic hydrops, even though hydrops does not now seem to be the cause [9,11,20]. Clinicians have long searched for the cause of the hydrops, blaming it for the pressure which disturbs hearing and balance and seeking ways of overcoming the problem by reducing production of endolymph. These methods, involving either drainage or even surgical removal of the endolymphatic sac, have been tried, but a common view now is that it is mistaken to equate endolymphatic hydrops with MD [8]. The newly proposed definition of MD by an international team [6] does not include endolymphatic hydrops [4]. Nevertheless, there is now a wide literature describing attempts to mimic MD by inducing hydrops in experimental animals through destruction of the endolymphatic sac or other means. Again, the relevance of this work has also been questioned [8].

The difficulty facing experimenters is that the inner ear is about the size of a pea and the volume of fluids within it is so small that the fluid contents (endolymph and perilymph, which together occupy just 2 drops or 0.1 mL) are virtually incompressible, making accurate pressure measurement difficult. The fluids are contained within incompressible bone, with the major pressure relief points being the oval window (within which sits the stapes) and the round window. Looked at another way, it only requires a minute displacement of the stapes for the pressure within the labyrinthine fluids to change considerably – a stapes motion of just 0.1 mm will cause the pressure to rise to 3 kPa (based on a round window compliance of 10^{-13} m⁵/N [21]). Taking meaningful long-term measurements on this tiny, inaccessible system is a challenge.

Compounding the problem, the function of the middle ear muscles has long been assigned a secondary role, and

it is only over the last few decades that the cochlea has moved on from being considered a passive linear receiver of sound. Only since Kemp's ground-breaking discovery of otoacoustic emissions nearly 40 years ago [22] has the cochlea emerged as an active, electrically driven device whose action is part of a sophisticated feedback loop. We are learning that the cochlear amplifier, the unidentified device within the cochlea which serves to amplify weak sounds, is a sensitive mechanism with many subtle properties.

A noteworthy feature of the cochlear amplifier is an inbuilt resistance to overload. The cochlea has a dynamic range of 120 dB, meaning it can detect sound over an extraordinary intensity range of a million, million times. Strategically placed at the entrance to the cochlea, the tensor tympani and the stapedius stand guard. These tiny muscles, the smallest skeletal muscles in the human body, can be seen as part of a fast-acting gain control circuit (the acoustic reflex) which prevents damage to the delicate hair cells. Connected to the middle ear bones via tendons (Figure 1), the muscles spring into action whenever sound levels approach damaging levels and, through coordinated contraction, physically attenuate cochlear sensitivity. How they do so is not completely understood, but the case that it involves regulation of inner ear hydraulic pressure is discussed in the next section.

As an indication of the important role that pressure plays in normal cochlear function, there are long-standing observations of what can happen if hydraulic pressure within the inner ear is lost, such as through a labyrinthine fistula. Sometimes encountered as an unwanted outcome of surgery for otosclerosis, leakage of fluid from the otic capsule produces sudden vertigo, tinnitus, and severe sensorineural

hearing loss [24] – the same distinctive symptoms as seen in MD. Goodhill reports that sudden hearing loss occasioned by barotrauma can also sometimes be traced to simple rupture of the oval or round windows, leading to loss of intralabyrinthine pressure.

The following text investigates evidence for a direct structure–function relationship between the middle ear muscles and pressure. The conclusion is that the intralabyrinthine pressure theory provides a unifying account of the role of the middle ear muscles and, significantly, how their dysfunction might lead to MD.

The ILP theory of middle ear muscle function

Knowledge of how the middle ear muscles function remains rudimentary. For many years, it was thought that contraction of the muscles simply stiffened the chain of acoustic transmission through the middle ear bones [25]. However, a fresh perspective on how the middle ear muscles act was put forward in 2011 when the case was made [18] for reviving an alternative theory: that contraction of the middle ear muscles, particularly the tensor tympani, pushes the stapes into the oval window and raises the hydraulic pressure of the fluids in the otic capsule, as shown in Figure 1. The core of the intralabyrinthine pressure (ILP) theory is that the gain of the cochlear amplifier is directly controlled by pressure in the labyrinth and that the role of the middle ear muscles is to regulate this pressure. The ILP theory sees the outer hair cells as directly sensitive to the hydraulic pressure in the fluids surrounding them, so, when the pressure rises, the result is an instant reduction in cochlear amplifier gain – effectively protecting the hair cells against acoustic overload. Explicitly, if it is assumed that the tensor tympani muscle exerts a maximum contractile force of 1 g wt, this will be transmitted via the ossicular chain to the stapes (area of 3.2 mm²), where its piston-like action will generate a pressure of 3 kPa in the labyrinthine fluids. Such a figure for inner ear pressure is consistent with a range of observations on intracochlear pressures [26,27]. According to the ILP theory, such a pressure causes a reduction in cochlear amplifier gain (usually interpreted as sound attenuation when electrode measurements are made in live animals) of up to 30 dB, with most of it occurring at low frequencies (below 1 kHz). In this way, the acoustic reflex exerts a powerful effect, although the standard explanation by which the reflex “stiffens” the acoustic chain produces only minor changes – physical measurements show an acoustic transmission loss of only a few decibels [18]. The acoustic reflex even works with bone-conducted sound, producing the familiar pattern of reduced sensitivity at low frequencies [28,29]; such an observation is consistent with an effect on the cochlea itself, not just the ossicular chain.

The ILP theory, originally formulated by Gellé in the 1880s, carries good explanatory power, although it must be acknowledged it is not the current textbook explanation for how the acoustic reflex works. Silently and swiftly, and with minimum effort, contraction of the muscles immediately increases pressure and reduces the gain of the 30,000 outer hair cells. Because the labyrinthine fluids are virtually incompressible and the stapes works against the compliance (10^{-13} m⁵/N) of the round window membrane [21], the

motion is minute – of the order of a tenth of a millimeter or less (see Helmholtz [30]) – so it is not surprising that the pressure rise, itself difficult to measure, has been overlooked. As will be shown, the middle ear muscles are well adapted to the task of providing sustained and finely graded isometric contraction, with many small-diameter fibres [31].

Normally, the middle ear muscles function as intended and our hearing is constantly protected against overload. The muscles play a vital role, springing into action if a loud external sound reaches the cochlea, or whenever a loud internal sound – speaking, yawning, or chewing – is produced [28,32,33]. In this way, the muscles allow external sounds to be clearly heard even when we are speaking. The system is similar to that which operates in bats, where the animal's middle ear muscles rapidly attenuate self-generated ultrasonic calls (perhaps more than 100 per second) while at the same time allowing intervening faint echoes to be perceived. Even a whisper or a touch to the cheek will trigger the muscle [32]. The surprise is that, subjectively, we do not notice this constant gain-riding. It is rather like our vision filling in the gaps whenever we blink or move our eyes, making the outside world appear stable. The middle ear muscles regulate sound input to the ear not unlike the way in which the iris muscles regulate light input to the eye. Subjectively, the fluttering sound one hears when yawning or tightly closing the eyes is the sound of the tensor tympani at work.

Ordinarily, the muscles sit poised ready to contract in response to a loud sound. Under abnormal conditions, however, it is possible for muscle control to be lost. In particular, like all muscles, the middle ear muscles might suffer from a cramp or spasm, creating a sudden spike in inner ear pressure – a Meniere's attack. Extended over longer time-spans, elevated pressure is likely to produce damage to the pressure-sensitive hair cells responsible for hearing and balance. This prediction, which follows from the ILP theory, provides a unified understanding of MD, and the following text elaborates the hypothesis.

Middle ear muscles, raised pressure, and MD – the evidence

It has been known for many years that elevated pressure in the ear canal of normal subjects can produce vestibular symptoms such as nystagmus and vertigo [34–36]. Indeed, pressure applied this way can also cause other Meniere-like symptoms: subjective tinnitus [37]; hearing loss at low frequencies [18]; pitch anomalies [38], and, of course, a feeling of fullness in the ear [12]. In each case, the applied ear canal pressure leads to the stapes pressing on the oval window and increasing intralabyrinthine pressure, a connection that has been reasonably well documented and acknowledged [39]. However, if similar symptoms to MD occur from simply elevating ear canal pressure, this prompts the question: what other mechanism could exist for driving the tympanic membrane inwards and increasing intralabyrinthine pressure? The answer suggested here is that it is contraction of the middle ear muscles, predominantly the tensor tympani.

This paper makes the case that hyperactivity of the middle ear muscles can lead to a rise in labyrinthine pressure

and, in certain susceptible individuals (perhaps 1 in 1000 of the population), a calamitous Meniere's attack. The case is based on the following observations.

Sudden attacks

It is remarkable how people with MD can go for long periods, sometimes years, without problems, and then suddenly be struck down within minutes by an attack. The simultaneous involvement of balance and hearing disorders during a Meniere's attack – typically explosive in onset and sometimes abrupt in termination – point to a single physical factor rather than a biochemical imbalance. Pressure is put forward as the likely physical factor. House [3] provides an important clue. In the midst of an attack, accompanied by intense vomiting, patients sometimes report hearing a snap, at which point their symptoms are suddenly gone, perhaps for months. This quick resolution again supports some sort of direct physical effect, and the idea that an attack is brought on by dysfunction of the middle ear muscles is consistent with this observation. The explanation is that the inner ear muscle feedback loop is suddenly upset and is gradually restored – just like with most muscle cramps – after which pressure returns to normal and the symptoms disappear.

The accompanying symptoms of aural fullness, headaches, pain in the occipital muscles, and nystagmus (Ch 2 of [40]) also support the pressure explanation. Indeed, the whole argument linking MD with endolymphatic hydrops tacitly assumes it is pressure itself which is the provoking agent. According to the present hypothesis, however, it is the action of the middle ear muscles which deranges pressure levels, not an excessive rate of fluid production (hydrops).

In overview, the inner ear is an exquisitely sensitive pressure-sensing mechanism [3], and this paper suggests that the middle ear muscles, although not anatomically a part of the inner ear, play a key role in regulating its internal pressure and responsiveness to sound.

It has been well recognised by a range of authors that contraction of the middle ear muscles can affect inner ear pressure (see [18]), and a description of how this affects hearing sensitivity – the intralabyrinthine pressure theory – has already been sketched above. It is important to recognise, however, that the pressure rise can, if sustained, be sufficient to disable and, in the long term, cause permanent damage to hair cells concerned with hearing and balance. The labyrinth is an almost sealed hydraulic vessel (Figure 2), and the cochlear and vestibular aqueducts (discussed later) have insufficient hydraulic conductivity to dissipate a sudden plunger action of the stapes.

Fluctuating hearing experienced by Meniere's sufferers is a day-to-day reminder of how delicately poised the inner ear system is. Usually a Meniere's attack begins unilaterally, but over time it tends to become bilateral [41]. Often a sudden reduction in hearing is a premonition of a Meniere's attack, and tinnitus is another common warning sign [40]. Almost inevitably, MD progresses to involve both ears [1], and interestingly in such cases Kitahara found that fluctuations in hearing sometimes occurred simultaneously in both ears, or sometimes they alternated

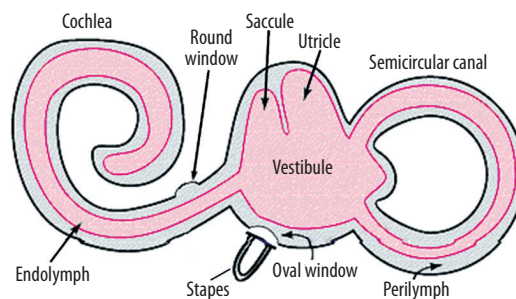


Figure 2. The otic capsule is a cavity within solid bone, and is an almost hydraulically sealed system. When the stapes is pushed in by the tensor tympani, the round window bulges out by an equal amount, as endolymph and perilymph are incompressible. Pressure of the fluids therefore depends almost totally on the force generated by contraction of the tensor tympani. [Modified from <http://www.eneurosurgery.com>]

between the ears [42]. This makes it highly unlikely that membrane rupture is responsible but it does lend support to the idea of tensor tympani malfunction, since the muscles are part of a bilateral system. Cases where Meniere-like symptoms have resulted from acoustic overload [43] also indicate middle ear muscle involvement.

When a muscle spasm begins, there will be a sudden rise of pressure, and the typical MD symptoms will start. It is important to note that, in the early stages, the hearing loss in MD has the same typical pattern of low-frequency hearing loss (upsloping audiogram) as occurs with the acoustic reflex (loss of sensitivity below about 1 kHz: p.142 of [20]; p.20 of [8]; [18]) and with sudden hearing loss [40,44].

In the long term, sustained elevated pressure will damage hearing hair cells. As a later section describes, hair cells are pressure sensors, a property used to detect small oscillating changes in pressure (i.e., sound). The clearest example of such pressure sensing is the dogfish [45], which senses sound pressure directly, without requiring stereocilia deflection. The interplay between pressure detection and particle displacement is a subtle one [46], and the interested reader is referred to earlier work [18] for a fuller discussion.

TTT syndrome and its similarity to MD

It is remarkable how similar the symptoms of MD are to another disorder, tonic tensor tympani (TTT) syndrome, a complaint first described by Klockhoff which characteristically involves spontaneous fluctuation in middle ear impedance but is subjectively associated with vertigo, tinnitus, fullness in the ear, tension headache, and dysacusis [47]. Klockhoff ascribed the syndrome to an elevated tonus of the tensor tympani, which he thought was due to mental stress. Of interest, he notes the difficulty of distinguishing the syndrome from Meniere's disease, although he himself thought they were two separate complaints (because there were no sudden attacks and the prevailing view that MD must somehow be due to "hydrops"). Klockhoff makes clear that contraction of the tensor tympani is more of a startle reflex than an acoustic reflex, and can be

activated by a puff of air to the eye, touch to the outer ear, yawning, chewing, swallowing, speaking, or even anticipation of a loud sound. However, unlike with the stapedius, sound alone does not appear to elicit a tensor reflex [47].

Although Klockhoff's original work on TTT syndrome was based on more than 200 cases, TTT syndrome was subsequently regarded as largely an oddity. It is only in recent years that the wider implications of the syndrome have been recognized and interest has been revived. In 2006, an audiologist specializing in treating tinnitus and hyperacusis [48] recognized the relevance of TTT syndrome to patients who were suffering these complaints, who had temporomandibular problems, or were call-centre workers who had experienced acoustic shock from wearing head-sets. Westcott and her colleagues began a more intensive study of 345 patients [49] which identified TTT syndrome as an involuntary, anxiety-based condition where the threshold for reflex activity of the tensor tympani had been reduced, causing frequent spasm. It was found to affect some 60% of patients in total, and many of the symptoms could be seen in other patient groups as well. The study concluded there was a basic relationship between tinnitus, hyperacusis, and TTT syndrome, and raised a number of clinical implications. According to the hypothesis here, one of these is MD. Both TTT syndrome and MD involve dysfunction of the TT, although in slightly different ways. TTT syndrome can be said to involve a somewhat overactive TT, but it is suggested that a full MD attack is caused by spasm of the muscle, causing an overwhelming rise in intralabyrinthine pressure. With raised pressure, there will be a direct sensation of pressure in the ear (aural fullness), there will be fluctuating hearing loss, and, as pressure affects the semicircular canals as well, there will be vertigo. As for tinnitus, the connection between tinnitus and ear canal pressure has already been mentioned.

Effect of sectioning muscle tendons

What may be regarded as the best evidence that malfunction of the middle ear muscles causes MD comes from studies in which the tendons to the muscles have been cut (tenotomy). In patients with Meniere's disease, the simple result of tenotomy of the stapedius and tensor tympani muscles is that attacks cease almost completely [50,51] and dizziness is markedly reduced [52]. Surprisingly, although these papers have led to new interest in the role of the middle ear muscles, they have not brought about a revolution in treatment of MD, as might be expected. The reasons for the reticence are illuminating, and will be examined below, but first it is worth noting that tenotomy of the middle ear muscles is a procedure with a long history. It was advocated as a treatment for MD back in the 19th century [51,53], but fell out of favour because, without antibiotics, there was risk of serious infection. It was only revived in 2003 by Franz and colleagues, who reported outstanding results when tried on a group of 20 Meniere's patients. In this study, the frequency of vertigo attacks was reduced to zero in 70% of them, hearing improved by an average of 13 dB, tinnitus was markedly reduced, and the sensation of pressure and fullness in the ear was relieved. Tellingly, when scar tissue occasionally caused the stumps of the tendons to reconnect, the symptoms returned. In two follow-up studies [50,52], there were

similarly dramatic results: 26 of 30 subjects had zero vertigo attacks following the procedure and the dizziness handicap inventory fell from 52 to 4.

These powerful demonstrations have been cautiously received, although the potential of tenotomy has been supported by Albu et al. [54]. The main reason for the reticence seems to be a real difficulty in seeing how sectioning a mere tendon could affect the inner ear, where the Meniere's symptoms arise. Franz et al. speculated that perhaps "tenotomy prevents muscle-induced mechanical irritations of the hydropic inner ear." Here the authors appear to be taking the hydrops as the starting point, and that the muscles are only responsible for aggravating what they describe as "primary endolymphatic hydrops". At yet another point, they suggest how pathological cramps of the muscles might "intensify" the symptoms of MD. In a later paper [50], they acknowledge that the tensor tympani has the ability to increase pressure in the labyrinth, but only beyond a certain "trigger point", and that the preexisting hydrops of MD is the primary factor in raising cochlear pressure. In Loader et al. [52], the idea is expressed somewhat differently: it is said that tenotomy prevents the elevated pressure, due to hydrops, from displacing the ossicles and causing reflex action of the tensor, which would then add to the pressure and trigger symptoms.

To contrast this position with that taken by the present paper, the model being put forward here is that *the muscles themselves are fully and directly responsible for MD*. In accordance with the ILP theory, their role is, via contraction, to precisely control intralabyrinthine pressure at all times – when speaking, chewing, swallowing, in response to loud sound – and if control is lost, such as through muscle spasm or general dystonia, MD is the immediate result. As expressed earlier, endolymphatic hydrops could basically be a roundabout way of ascribing a cause to the raised pressure whose damaging effects are widely evident throughout the labyrinth. The raised pressure, however, is not the sign of a metabolic imbalance but of the aberrant functioning – dystonia – of the middle ear muscles.

As in all things, preconceptions are hard to shift, and this is especially the case with the hydrops basis of MD, probably because no other theory has emerged to take its place. A similar example is the ILP theory itself, which has long been put aside because auditory science could not see a way by which pressure surrounding the basilar membrane could affect a mechanical travelling wave [18]. The travelling wave rose to become the core causal entity, and it required the emergence of the cochlear amplifier before it became possible to see that static pressure could indeed have an effect on such an active device without necessarily involving a mechanical travelling wave. Likewise, without entertaining the possible validity of the ILP theory, it is not possible to appreciate how small muscles, via their mechanical and fluid connections, can have major effects on hearing and balance. The end result has been that, in response to Franz's findings, clinicians have found it difficult to conceive that small cryptic muscles, buried in bone some distance from the inner ear, could possibly produce the catastrophic symptoms of MD. If a single example of the potent effect of pressure is needed, the reports cited

earlier of what a small perilymphatic fistula can lead to are salutary.

Tenotomy has also shown its value in curing related inner ear afflictions, such as myoclonus of the middle ear muscles [55,56]. The symptoms, often involving a clicking, buzzing, or thumping sound, involve repetitive contractions of the middle ear muscles. In this case, the myoclonus is usually triggered by facial muscles. When the tendons to the middle ear muscles are cut, problems are almost invariably overcome, and the tinnitus (usually objective in these cases) disappears.

Of course, there are side-effects of cutting the tendons, and people who have had the procedure done often complain of hyperacusis, with sound becoming louder, distorted, and tinny [57]. However, given the terrors of a Meniere's attack, that appears to be a lesser complaint.

Voluntary contraction of TT

The clearest connection between the middle ear muscles and intralabyrinthine pressure can be seen in subjects who can voluntarily contract their tensor tympani muscles [29,58–60]. In general, the effect of voluntary contraction is to move the tympanometric peak – the position of maximum mobility of the entire ossicular chain – to negative ear canal pressures (for example, Aron et al. (2015)). Aron et al. found that the baseline middle ear pressure averaged –38 daPa, whereas after contraction it measured –54 daPa. Effectively, that increased negative pressure is needed in order to balance the force generated by the tensor tympani. Such a perspective leads to the suggestion that the baseline pressure should best be interpreted as the resting force exerted by the tensor tympani, meaning there is a constant (tonic) tensor contraction. The muscle is always ready to spring into action (isometrically) should it be required – most commonly to protect the cochlea from overload whenever a person speaks.

The dynamic implications of a contracted tensor tympani merit closer examination. The tensor tympani is exerting a contractile force which requires a pressure of about 50 daPa across the ear drum to counteract. However, when the trans-tympanic pressure is no longer active, what then counteracts the muscle's force? Given that the pressure in the middle ear must for most of the time be virtually zero (because of the regular ventilating effect of the Eustachian tube), the countervailing force must reside in the pressure of the fluids inside the labyrinth. That is, the contraction of the tensor tympani muscle pushes the ossicular chain forward, causing the stapes to be pushed into the oval window. This displacement of the stapes, acting on an incompressible fluid sealed within a bony capsule, raises the intralabyrinthine pressure. The relief point is the round window membrane (Figure 1). In humans, the cochlear aqueduct is filled with tissue and incorporates a one-way valve [61,62], so a positive pressure difference between the cochlea and cerebrospinal fluid has a long time constant. These hydraulic factors are discussed in Bell [18], but the outcome is that a 50 daPa pressure at the tympanum is in equilibrium with a 1,250 daPa pressure (12.5 kPa) at the stapes. The pressure amplification is provided by the lever ratio of the middle ear (about 25), and means

the labyrinthine fluids are normally under pressure. Since the stapes has an area of 3.2 mm², a force of 1 gram on it will generate a pressure of 3 kPa in the cochlear fluids. In normal circumstances, therefore, there appears to be a pressure inside the cochlea of about 1 kPa, and the gain of the cochlear amplifier is suitable for conversational levels. However, to hear more acutely, we need to relax our middle ear muscles; conversely, if there is a need for additional protection, our muscles exert an even stronger force, perhaps a gram or two. All this normally happens quickly and silently, so that the functioning of the middle ear muscles has tended to be overlooked. It is only malfunction of the system – as in MD – that brings this vital control circuit to light. Spasm of the tensor tympani could create many grams of force, and the result would be kilopascals of pressure inside the labyrinth, leading to the maladies that have been described.

Another case of voluntary contraction was studied by Angeli et al. [59], and this work shows how a small change in tensor tympani force can be effective in regulating hearing. These workers studied a single subject who could contract muscles on both sides, and they found that it caused a shift in the tympanometric peaks from zero to –50 and –100 daPa (their Figure 2). Most distinctively, however, the subject noted a marked reduction in hearing, and the audiogram (their Figure 1) corroborates this. It shows a low-frequency loss, reaching 35 dB at 0.25 kHz – the same pattern as usually ascribed to “the acoustic reflex”. This observation directly supports the ILP theory. An attenuation of –35 dB is a 56-fold reduction, an amount which needs to be set against direct physical measurements of sound transmission from ear canal to cochlea, where figures of only several decibels, at most, are seen. This paradox was the initial motivation for reviving the ILP theory [18].

Voluntary contractions also led to clear changes in thresholds – air and bone – in a recent study by Wickens et al. [29] of 5 subjects. The average change at 0.25 kHz was 10 dB for bone conduction and 22 dB for air conduction. The deterioration in bone conduction thresholds is of particular interest, for it suggests that in this case pressure is having a direct effect on the cochlea itself, not on sound transmission along the ossicular chain.

It is known that the tensor tympani can be stimulated by forceful closure of the eyes, when a fluttering sensation will be heard. Because of this, it is of interest to consider the results of a study by Rock [60a] of “forceful eyelid closure syndrome” or FECS. The audiogram shows the characteristic low frequency loss when the eyes were shut, and again the attenuation at low frequencies amounted to 30–35 dB. Rock notes (p.34) that tensor tympani contraction will lead to an increase in intralabyrinthine pressure and that the effects of FECS are similar to Klockhoff's TTT syndrome. He reports that tensor tympani contraction was always elicited before (or simultaneously with) talking or humming.

Aural fullness

Clinicians have had difficulty explaining the sensation of pressure or fullness in the ear associated with a Meniere's attack [8,12]. Fullness is an almost universal report, and

is often a warning sign of an impending attack and goes away again when the attack ends [63]. And yet, as Mattox points out, there is no recognised mechanism for sensing hydraulic pressure in the inner ear, so where does the sensation come from? If one assumes that the middle ear muscles are responsible for the excess pressure, then sensing by primary spindles within the muscles could explain the effect. Relevant here are the experiments of Densert and colleagues, who were able to decrease the sensation of fullness in Meniere's patients by applying static pressure of about 15 daPa to the ear canal [64].

Hennebert's sign and the Tullio phenomenon

When pressure is applied to the ear canal and vestibular symptoms such as vertigo and nystagmus occur, the reaction is called a positive Hennebert's sign and is rare in normal subjects. In Meniere's patients, however, a positive reaction is frequent, and in terms of the present hypothesis this is significant. Nadol [65] found that 29 of 81 ears suffering from MD exhibited Hennebert's sign, compared to zero of 100 normal ears. Nadol ascribed the reaction to fibrous connections between the stapes and the labyrinth (vestibulofibrosis), but a more plausible connection is hydraulic: inward motion of the stapes causes fluid pressure to rise, and this directly affects the vestibular hair cells. This hydraulic mechanism can also explain why even just inserting vents in the tympanic membrane (grommets) can reduce symptoms in a proportion of Meniere's patients [66,67]: a grommet will equalize pressure between the middle ear and the atmosphere, avoiding the possibility that inadvertent underpressure in the middle ear will, through inward deflection of the ear drum, cause a corresponding overpressure in the inner ear.

Another curious phenomenon is sometimes seen when the ear is subjected to high-intensity, low-frequency sound. In normal subjects, there is an acoustic reflex but there are no vestibular effects. However, among Meniere's patients, it is notable that an enhanced vestibular reaction is frequently seen. Stephens and Ballam [68] found that 7 of 25 Meniere's patients had an enhanced vestibular reaction (Tullio phenomenon or sono-ocular reaction), an effect which was absent in the controls. Given that the sound stimuli used are likely to produce a reflex contraction of the middle ear muscles, this provides an indication that MD patients have poor control of the middle ear muscles (or have impaired flow through the channels conducting fluid in and out of the labyrinth, a possibility discussed later).

Tinnitus

Tinnitus is a symptom of many hearing disorders. Given the size of the subject matter it will not be discussed in detail here. It is sufficient for our purposes to simply note that one of the effects of raising pressure in the ear canal is subjective tinnitus [37], and the simplest and clearest explanation must be that the increased pressure has, like tensor tympani contraction, forced the stapes into the otic capsule and increased fluid pressure. It has been noted [69] that tinnitus can result from voluntary contraction of the middle ear muscles. It is of interest that the tinnitus associated with MD is of the low-frequency type (below about 2 kHz [70,71]), and so it is supposed that the

hair cells at the apex are the most sensitive to pressure, an idea which in turn connects to observations that raised ILP (as in the acoustic reflex) reduces hearing sensitivity below about 2 kHz [18].

It is significant that low-frequency OHCs are much longer than high-frequency ones [72], so that the former are expected to be more susceptible to changes in static pressure than the latter; consequently it is understandable why the acoustic reflex mostly affects low frequencies, and why MD first impairs these same frequencies.

Voluntary control of the tensor tympani and psychosomatic aspects of MD

The middle ear muscles are striated, or skeletal, muscles. This means that, like all such muscles, they are not just triggered by reflexes but are also, to varying degrees, under voluntary control. It is therefore significant that the symptoms of TTT syndrome include psychological factors such as anxiety, fear, and fright, and even anticipation can cause contraction of the tensor tympani. The sight of a toy gun has been cited as a stimulus [48].

A number of authors have pointed out that MD attacks are often triggered by stress, and that emotional components play a strong part [9,73]. Indeed, some have even suggested that MD is a purely psychosomatic ailment, explaining why many treatments, through a placebo effect, have produced favourable outcomes [17,74]. It is difficult to gauge the strength of these suggestions, but the fact that Meniere's attacks are episodic, and that the middle ear muscles are capable of being contracted voluntarily, provides a framework which supports the hypothesis that MD is due to dystonia of the middle ear muscles. Making the case that there is a real, physical basis for MD opens up a promising avenue for understanding and perhaps curing the condition.

Two linked hydrostats: The labyrinth and the outer hair cell

The text to this point has emphasized that the labyrinth is a hydrostat in which the middle ear muscles control the hydraulic pressure of fluids within. However, so far only a general statement has been made that pressure controls the sensitivity of the outer hair cells. This section presents a specific physical model of how pressure could control that sensitivity: that is, outer hair cells normally carry an internal pressure of about 1 kPa, so when the labyrinthine pressure is increased beyond that point, the cells can no longer counteract the pressure and they momentarily deflate. At that point, electromotility, and cochlear amplifier gain, drops to zero. The middle ear muscles can therefore be powerful controllers of hearing sensitivity.

According to Brownell, the test-tube shaped OHC is a hydrostat [75]. At the same time, it is, according to another view [46], an exquisitely sensitive detector of minute pressure variations – that is, sound. In this case the body of the cell can be taken to be the sensing element rather than the stereocilia, although stereocilia are necessary to complete the feedback loop between neighbouring cells to create a surface acoustic wave (SAW) resonator [76].

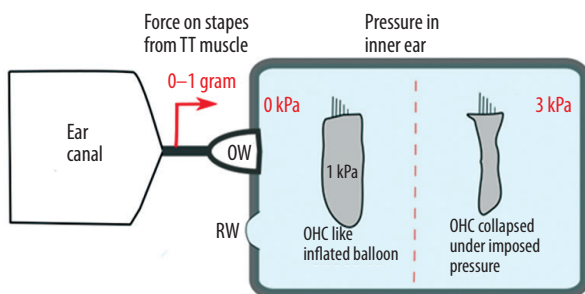


Figure 3. Muscle forces and fluid pressures in the otic capsule, and their effects on outer hair cells. The otic capsule is filled with incompressible fluid, so when the stapes is pushed into the oval window (OW) by contraction of the tensor tympani (TT), the pressure increases. A force of 1 gram wt on the area of the OW (3.2 mm^2) creates a pressure of 3 kPa. This pressure exceeds the internal pressure of the outer hair cells (1 kPa) and causes them to temporarily collapse. This turns down their sensitivity and the cochlear amplifier is switched off

The SAW resonator involves a standing wave between the three rows of OHCs, and the standing wave establishes the cochlear amplifier in a physical form. Acting as both detectors and motors, and cooperating in triplets, 12,000 OHCs can create 4,000 highly tuned cochlear amplifiers, boosting hearing levels a thousand-fold (60 dB). The OHCs do not signal the brain directly; instead they are pre-amplifiers which pass their output to the adjoining inner hair cells (IHCs), where signaling to higher centres begins. If a person should lose their delicate OHCs, perhaps from age or loud noise, leaving only the more robust IHCs, then hearing levels decline by about 60 dB.

Although there have been several suggestions, the physical basis of the cochlear amplifier is still not settled [76,77]. The SAW model, and its dependence on OHC electromotility, provides a direct account of how hydraulic pressure is able to control cochlear amplifier gain. However, there may be other models which can provide a similar outcome, and more research is needed. Irrespective of which model of cochlear mechanics is favoured, all depend on strong OHC electromotility.

There are various efferent connections to the OHCs, and these provide another way of adjusting the cochlea's sensitivity [78]. However, the drawback of neural mechanisms is that they involve considerable delay. There is a way to short-circuit this delay, and this is where the middle ear muscles play a crucial role. Any force exerted by the middle ear muscles is conveyed immediately to the fluids of the inner ear, increasing hydraulic pressure. As the calculations above have shown, the tensor tympani, exerting a force of 1 gram, can cause a corresponding pressure of 3 kPa in the inner ear. According to the ILP theory, this will cause a reduction of hearing sensitivity of up to 30 dB, and this raises the question of how a mild hydraulic pressure can have such a large effect.

Let us look closer at what happens if a sudden increase in pressure is applied to a hydrostat. The following experimental findings were derived from the outer hair cells of

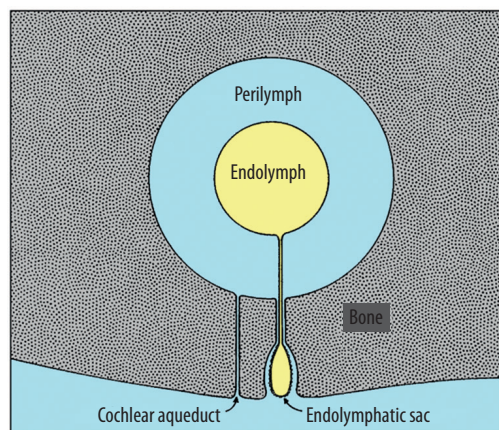


Figure 4. There are two small channels supplying fluid to the inner ear. The cochlear aqueduct supplies perilymph, and the endolymphatic duct supplies endolymph. Although the diameters of the channels are small, and they appear filled with tissue, the hydraulic conductivity of these channels *in vivo* has not been accurately determined. Recent research suggests that the time-constant of pressure decay is long but variable, and there appears to be a one-way valve. However, the question remains unsettled, and more research is needed. [Figure adapted from Harrison and Naftalin [40] and Juhn [89]]

guinea pigs rather than humans, but it is assumed the results are generally applicable.

In a unique arrangement, the body of the OHC is surrounded on all sides by fluid, meaning that the OHC is in direct hydraulic communication with the stapes – that is, we have a hydrostat or pressure vessel surrounded on all sides by cochlear fluid. The OHC is piezoelectric and able to change length cycle by cycle, elongating and contracting in time with oscillating sound pressure [75]. Its outer walls are corrugated and are reinforced by helical fibres which encircle the cylindrical body in both clockwise and anti-clockwise directions. The fibres are oriented at the familiar winding angle of 55° which means that length changes are accompanied by minimal volume changes (that is, it has a Poisson ratio close to 0.5), making length changes possible at up to 100 kHz (as in bats).

Crucially, OHCs need rigidity in order to move the partition at high frequencies, so they carry an internal hydraulic pressure of about 1–2 kPa [75], maintained by some form of osmotic regulation. This turgor pressure causes them to inflate, like a balloon (Figure 3). In brief, the OHC is a hydrostat with a hydraulic skeleton. There is an important consequence of this arrangement: if the pressure surrounding the cells suddenly increases, they will start to collapse, and so, as Figure 4 illustrates, at 1 kPa there will be no pressure difference across its walls and the cell will become flaccid like a deflated balloon [79,80]. The pressure can be applied osmotically [79] or, equivalently, by use of a pipette to adjust intracellular pressure [81]. When collapsed, the transduction efficiency of the OHC goes down [81,82], and so altering the pressure across the cell wall is an effective way of controlling the gain of the

cochlear amplifier [81]. The same experiments also imply that, as well as reacting to static pressure variations in its environment, the body of the hair cell might react directly to oscillating hydraulic pressure in the cochlear fluids – that is, to sound – providing a complementary sensing mechanism to that provided by the stereocilia [46].

In overview, the output of the cell, and the gain of the cochlear amplifier, are tightly controlled by the force exerted by the middle ear muscles. This mechanism is the core of the ILP theory of middle ear muscle action, and it means there is delicate interplay between these extraordinarily sensitive cells and the tiny middle ear muscles. The muscles are constantly on-guard against overload, and if triggered by a loud sound all 12,000 detectors are instantly switched off by an all-enveloping 3 kPa pressure. A physical analogy might be the Cartesian diver, where a change of force on the flexible membrane covering a water-filled container alters the hydraulic pressure on the compressible “diver” within, altering its buoyancy. So although the middle ear muscles might be small, they comprise a fast-acting system which can immediately adjust the gain of all the sensory transducers – cochlear and vestibular hair cells – immersed in the inner ear fluids.

It is now possible to appreciate why the middle ear muscles contain such fine muscle fibres and why they are of the fast and non-fatiguing type [31]. The middle ear muscles are in fact very similar in composition to those of the larynx, which also needs very fine tension control to accurately modulate the human voice. Interestingly, in humans the laryngeal muscles are a frequent locus of dystonia, an aspect explored in more detail in a later section. In echolocating bats, the same fast, high-energy laryngeal muscles are used to produce precise ultrasonic calls [83]. The calls are rapid and intense, and the middle ear muscles are called on to work in a complementary way, instantly turning down hearing sensitivity during a call (to prevent overload, as humans do when they speak) and then immediately relaxing so as to provide full sensitivity for detecting the returning echo. Call rates of more than 160 per second have been recorded [83], a performance requiring so-called superfast muscles [84] which have similar morphology to the tensor tympani. There is an analogous superfast muscle in sound-producing fish which is located between the sound-producing swim-bladder and the fish's ear, again presumably to prevent overload during vocalization [85].

Direct pressure effects: Theory and experiment

A number of experimental findings involving the effect of pressure on the auditory system support the hypothesis that intralabyrinthine pressure is a likely factor affecting a person with MD. Most directly, there are observations that when a surgeon places even slight pressure on the semicircular canal there are strong vestibular effects [3], and how loss of fluid pressure from a perilymphatic fistula causes Meniere-like effects [24,86]. These augment the earlier findings of Henneberg's sign in which raising pressure in the ear canal can produce symptoms similar to MD. There are three additional areas, listed below, where findings indicate that pressure is the underlying factor in MD.

However, it is first useful to appreciate that two fine channels exist to supply the inner ear with perilymph and endolymph. As Figure 4 shows, the cochlear aqueduct supplies perilymph from cerebrospinal fluid in the cranium, and the endolymphatic duct connects the labyrinth with the endolymphatic sac, which, through absorption, is in fact an outflow point. However, the patency (openness) of these channels for fluid flow has long been a matter of contention [26,87]. Some studies suggest the channels have high hydraulic resistance, but this needs to be confirmed. A number of others have shown that variations in cerebrospinal fluid pressure produce effects on hearing (e.g. [88]), suggesting a direct hydraulic connection.

An important observation due to Rask-Andersen et al. [87] is that in humans, as a consequence of erect body posture, the cochlear aqueduct has developed into a narrow bony canal filled with connective tissue which is sometimes completely obliterated. If the canal were open, there would be large variations in inner ear pressure due to changes in posture, and so the channel is designed to have a long time-constant (seconds to minutes). However, a direct side-effect of hydraulically isolating the inner ear is its sensitivity to middle ear muscle tonus, and, most tellingly, it makes humans the only animals prone to MD (although it raises a suspicion that giraffes may also be susceptible).

All this work reinforces the need to better understand the patency of the hydraulic channels which connect to the labyrinth and which allow pressure to dissipate. Meniere's patients may not only have dysfunction of the middle ear muscles, but the situation may be aggravated by blocked aqueducts.

Let us now examine findings indicating that direct pressure effects are at work in MD.

Pressure chambers

There have been a range of experiments on how people's hearing is immediately affected when they are placed in a pressure chamber. In fact, placing MD patients in a sealed chamber and lowering the pressure has been advocated as an effective treatment for the disease [90,91]. The condition in which changes in pressure lead to dizziness has been called alternobaric vertigo [92]. Both situations show how static pressure is an effective stimulus for hair cells in the labyrinth.

Pitch effects

Remarkably and distinctively, there are variations in pitch which can be connected to changes in pressure. Most relevant here are reports of Meniere's sufferers, who, particularly in the early stages of the disease and before an attack, complain of diaplacusis dysharmonica, meaning that the pitch of sounds heard in the affected ear differs from the pitch heard in the unaffected ear [40]. Interestingly, the pitch on the affected side tends to move upwards if the deafness affects low frequencies (below 3 kHz) and downwards if there is a high frequency loss (above 5 kHz) (*ibid.*, p. 22), and this separation at about 3 kHz is consistent with middle ear muscle reflex measurements which tend to show that while the reflex consistently causes attenuations

below about 2 kHz, it sometimes produces apparent gains at higher frequencies (see discussion in [18]). The pattern is consistent with hydraulic pressure increasing during both middle ear muscle reflexes and Meniere's attacks.

Tying these results together and pointing to intralabyrinthine pressure as the common feature, there are reports which indicate that the pitch of a tone rises when the jaw is tightly clenched [93]; that voluntary contraction of the middle ear muscles caused pitch to rise by a quarter tone [60a]; and Bekesy's observation that pitch rose by 2% when veins in the neck were compressed.

Otoacoustic emissions

Finally, there are measurements of otoacoustic emissions (OAEs), faint signals emitted from the cochlea. Mom et al. measured OAEs in Meniere's patients [94] and found that the effects of body tilt and taking glycerol were similar to a rise in intracochlear pressure. OAE changes in MD patients were three times higher than in controls, pointing to impaired pressure regulation in the condition.

An advantage of spontaneous otoacoustic emissions (SOAEs) is that they are able to connect the subjective pitch experience with objective frequency measurement. It is found that SOAE frequency changes when static pressure in the cochlea changes, either due to natural variations in intracranial pressure [95] or due to voluntary contractions of middle ear muscles [58]. Bell calculates a figure of 20 Hz/kPa for the effect, on which basis a 2% change in frequency at 1 kHz corresponds to a pressure change of 1 kPa. This figure is within the range of pressures calculated above.

The time-constant for a rise in SOAE frequency, taken to be a reflection of an increase in pressure, is several seconds, but a fall takes several minutes [96]. This strengthens the suggestion that there is a one-way valve which quickly allows pressure to rise (and hearing sensitivity to fall), but hearing recovery requires several minutes as the pressure slowly leaks away. Normally, we do not notice these drifts in hearing sensitivity, but during a Meniere's attack, the changes in pressure become noticeable as severe fluctuations in hearing. It is significant that Meniere's sufferers often complain they have difficulty picking up words in a conversation [1,97], an observation suggesting there is a problem with the gain-riding function and its ability to follow speech [32].

Studies on the effect of raised intracranial pressure on distortion product otoacoustic emissions (DPOAEs) have been made by Buki et al. [98], work looking at both experimental and theoretical aspects. In their experiments on gerbils, they found (their Figure 2) that the amplitude of DPOAEs could be reduced by 20 dB or more at frequencies of 1–1.5 kHz when intracranial pressure was raised to 4 kPa. This low-frequency reduction resembles the pattern resulting from voluntary contraction of the middle ear muscles, which is presumed to increase ILP [18]. The modelling of Buki et al. sought to ascribe the decrease to changes in stiffness of the annular ligament – a view also taken by other workers [99] – but such a result could also be due to the direct effect of pressure on the outer hair cells. Relevant to MD, the authors note that when they imposed

a pressure of 5 kPa, DPOAE amplitudes collapsed, and the effect was irreversible if the pressure was maintained. The authors suggest that excessive pressure could permanently damage the cochlea.

Of further interest, Buki et al. cut the tendons of the middle ear muscles and found immediate changes in DPOAE phases of more than 45° at several frequencies (their figure 5), indicating that the muscles exert direct and major effects on cochlear function. A final observation was that the time-constants for pressure rises were shorter than for pressure falls, suggesting once again there appears to be a one-way valve in the system [61,62].

Unique properties of the middle ear muscles

The tiny middle ear muscles have been generally neglected. In a discussion of MD on the web site of the American Hearing Research Foundation, for example, the middle ear muscles are not mentioned and do not even appear on any of the explanatory diagrams. The tensor tympani and the stapedius are the smallest skeletal muscles in the human body [100], and are hidden away inside bone adjacent to the middle ear cavity so that only their tendons are visible. How could their hydraulic effects on the labyrinth have been overlooked for so long?

The tonus of the middle ear muscles is constantly changing [101], a reflection of their state of alertness. Salt and DeMott [102] observed continual spontaneous contractions of the middle ear muscles and associated fluid movements. An impedance trace recorded by Shearer [32] shows ear canal impedance fluctuating up and down in time with speech, an observation supporting the idea that the muscles play a key role in speech production and perception [103]. Tympanometry often shows a constant tremor of the ear drum [104]. As is well known, the stapedius acts in response to acoustic input, but the tensor tympani is different, responding to non-acoustic stimulation – even the anticipation of sound [100]. Although tiny, the middle ear muscles are subject to all the properties, and maladies, to which striated muscles are prone.

Distinctively, the middle ear muscles show the following features. First, the muscle fibres have a high oxidative capacity, allowing them to exert force for long periods without fatigue. Second, the muscles possess a unique mix of muscle fibre types [31], including many short fibres (1–2 mm), which allow them to exert tension with minimal displacement [105]. Effectively, the muscles work isometrically as they press on the stapes – which in turn is restrained by the annular ligament, the incompressible fluid behind it, and the round window. The range of movement is probably no more than 50 to 150 μm, and displacements of 1 nm are considered to have functional significance [106]. The third property necessary to make such a system perform satisfactorily is a dense concentration of motor endplates and proprioceptive elements (spindles) which, working together, allow fine regulation of activity [100,107]. At the same time, of course, such a tightly arranged feedback system opens the possibility for serious malfunction.

The crucial element in this feedback loop is the muscle spindle, a displacement sensor which sets the lower limit

of what can be sensed. The most unusual aspect of the middle ear muscles is that they have a dense concentration of spindles and slow tonic fibres, but few motor end plates [31]. Han et al. [105] make a comparison between the middle ear muscles, the extraocular muscles, and muscles in the vocal folds, all of which contain many short muscle fibres suitable for fine control and prolonged contraction. Instead of contraction coming about with a twitch, as in most skeletal muscles, short muscle fibres undergo slow and prolonged shortening.

In terms of MD, the important point is that the middle ear muscles are part of multiple tight feedback loops involving proprioceptors (muscle spindles) and motor end plates [108], and the fineness and complexity of these loops provides a starting point for understanding what might be going wrong in Meniere's disease.

Dystonia: Loss of muscle control

The text so far has assembled evidence that MD is a case of loss of fine motor control – dystonia – of the middle ear muscles, which leads to high intralabyrinthine pressure and a Meniere's attack. This section provides background on what dystonia is and how it could initiate MD.

Dystonia is an incurable posture and movement disorder characterized by involuntary muscle contractions in which a muscle or pair of muscles contorts into abnormal postures or movements, sometimes painfully [109,110]. Dystonia can affect any muscle, but it is usually focal, affecting only a single area of the body, such as writer's cramp in the hand or dysphonia of the larynx. Instead of two muscles working together smoothly, there is loss of control and the muscles undergo sustained, unwanted co-contractions. Although the fundamental cause of dystonia is unknown, it is thought that the condition is caused by loss of inhibition involving the basal ganglia and processing of muscle spindle input, and is often associated with reflex pathways [109]. In a patient with writer's cramp, for example, vibration can often induce the dystonia. The malady is the third most common movement disorder (after Parkinson's and tremor).

In primary dystonia there is no other underlying disorder, and the affliction tends to be confined to a particular muscle or set of muscles. Once it begins, the condition becomes chronic with irregular recurrence, just like MD. Typically, in adult-onset dystonia the condition first makes an appearance when an individual is in their forties; in MD the typical age of onset is 40–60 [9,16]. The core hypothesis of this paper is that a Meniere's attack is caused by dystonia of the tensor tympani and the stapedius, which normally work harmoniously together. Over time, recurrent overpressure from frequent attacks leads to hair cell damage, permanently impairing hearing and balance.

The tensor tympani is taken to be the prime agent for causing overpressure because when it contracts it forces the stapes footplate directly into the oval window (Figure 1). On the other hand, when the stapedius contracts, it pulls the stapes sideways, causing a hinge-like rotation, an action which might enable fine adjustment of pressure. The details need elucidating, but it does appear to be a

delicate, finely tuned arrangement which has the potential for misalignment. If there is a runaway rise in muscle force, as in dystonia, a sudden rise in intralabyrinthine pressure could result.

General discussion

For many years auditory science has tried to accurately measure intracochlear pressure, an important parameter whose noninvasive measurement *in vivo* has proven elusive [26,98]. A general lack of success has meant that the crucial role that pressure plays in cochlear mechanics has been largely unrecognized, obscuring our understanding of the middle ear reflex and the role that intracochlear pressure plays. A suggestion made by Bell [18] is that measurement of the shift in SOAE frequency could be a proxy for intracochlear pressure, although calibration may not be easy.

After recognising hydraulic pressure as an important factor, the focus naturally turns to the role of OHCs as hydrostats, an apt description of their pressure vessel construction which we owe to Brownell [111]. Seeing the OHC as a hydrostat has major implications for hearing, and allows the delicate interplay between these highly sensitive cells and the middle ear muscles to be understood.

For a long time, pressure has been seen as a prime factor in precipitating MD, although it has been viewed in the context, possibly erroneous, of endolymphatic hydrops, which is now regarded more as an accompanying symptom [6,11,13]. However, by appreciating that regulation of inner ear pressure is the middle ear muscles' principal role, a direct link between these muscles and MD can be established.

A review of temporomandibular disorders (TMDs) by Ramirez et al. [112] also drew parallels between symptoms of this disorder and those seen in TTT syndrome and MD. TMD symptoms are related to TTT syndrome, and both involve overactivity of the tensor tympani. Once again, symptoms include tinnitus, vertigo, hearing loss, and otic fullness, and it is suggested that TMDs also lead to elevated pressure in the labyrinth via the middle ear muscles. One of the models considered by Ramirez et al. as an underlying cause of TMD is involvement of the tensor tympani muscle, which they suggest might produce rises in perilymphatic and endolymphatic pressures.

If endolymphatic hydrops is an epiphenomenon, as the findings of Merchant et al. imply [11], a complete re-examination of the mechanisms causing MD is called for [13]. The proposal here – that the disorder involves the middle ear muscles – provides a new avenue for exploration, one which will require new assessments of how these muscles function [18]. From a historical perspective, vertigo and tinnitus were part of the cluster of MD symptoms from the beginning, but fluctuations in hearing and aural fullness were only recognised later, at about the time when the term “endolymphatic hydrops” first gained currency [113]. From what has been learnt since, endolymphatic hydrops was a hypothesis which was grasped eagerly because other unifying theories were lacking, although the theory seems to have been based on scant and perhaps

faulty evidence. The possibilities opened up by high-resolution MRI are exciting, but so far only correlations have been found [16] and no biological marker for MD has yet been identified [6].

The other thing that history can teach us is that many of the original insights did have some validity. Tenotomy was a valuable early insight [53], and until about the middle of last century, activity of the middle ear muscles was considered a cause of elevated intralabyrinthine pressure which could underlie hearing and balance problems in otosclerosis and MD [103,114]. Kobrak was of the opinion that “stapedial hyperpressure” was due to “spastic muscular activities”, especially of the tensor tympani (*ibid*, p.434), while Tomatis thought that MD was an anomaly or twitch in “the tension of the stirrup muscle... which regulates the pressures of the fluid in the labyrinth” (*ibid*, p.187). More recently, Pennings et al. speculated that spasm of the tensor tympani might be a trigger for Meniere’s disease [99], but their efforts were focused on conductive losses in cadavers rather than on sensorineural effects, and the idea does not appear to have been pursued.

It is significant that MD patients frequently complain of poor speech discrimination, hyperacusis, and binaural diplacusis [8,14], observations consistent with the fast pressure-regulating and gain-riding model. The present paper supports such interpretations, and proposes a more detailed and concrete account in terms of dystonia and its effects on hair cells.

The history of MD over the last century and a half has been summarized by Eisen [113], who says that because understanding MD has proven elusive, the literature has been rife with conjecture, experimental treatments, and anecdotal evidence. It has been, he says, a recipe for a creative and colourful history, if nothing else. Performing experiments on animals in order to cure a uniquely human malady has been misleading [8] and can be taken as an argument against the practice. The difficulty has been compounded by an inability to see how one overarching mechanism could simultaneously exert its effects over both the semicircular canals and the cochlea. The ILP theory provides a framework by which one invisible factor – hydraulic pressure – could do so, and at the same time it gives a ready explanation for feelings of aural fullness. Governed by muscle dynamics, pressure can suddenly appear and disappear without leaving a trace. Surprisingly then, MD does appear to have a mechanical cause [8,115], and yet its origins are outside the inner ear.

Indeed, a reason the tensor tympani has been overlooked as a potential cause of MD is probably because investigators have focused exclusively on the inner ear, where the symptoms appear to derive, without realizing that the middle ear muscles have functional effects on the whole hearing system. Even Meniere himself considered that the tympanic membrane and the middle ear were not involved in the disease [113]. Putting the middle ear muscles back into the picture provides a consistent and testable theory.

Within this long history, it is discouraging to observe how many treatments have been proposed and abandoned. According to Thomsen and Bretlau [74], dozens of treatments

have been proposed to cure, control, or alleviate MD, and none has withstood the test of time. One of the most popular treatments has been endolymphatic shunt surgery [97], which is supposed to relieve a build-up of fluid (hydrops) in the endolymphatic sac [116]; however, a recent Cochrane review comes to the conclusion that there is no significant difference between the treatment and a control group [15].

The study by Franz et al. [51] provides compelling evidence that MD is intimately connected with the middle ear muscles. However, the authors had difficulty understanding the connection, suggesting that somehow hydrops might trigger the middle ear muscles (rather than the reverse). Nevertheless, the paper opens up a fresh approach to the condition, and the perspectives offered in the present paper suggest that tenotomy deserves a reappraisal.

One possible argument may be raised against the thesis of this paper. Although the success rate of tenotomy was high, MD patients were not always completely cured by the operation. If MD were caused by dystonia of the middle ear muscles, then tenotomy should give a 100% cure. However, such an inference does not take into account the fact that MD usually starts out being unilateral but then develops into being bilateral [41]. On this basis, tenotomy on one side could still allow MD to develop in the contralateral ear.

Similarly, not all patients suffering myoclonus of the middle ear muscles suffer MD. In this case, the explanation might be that MD also requires additional conditions – perhaps high hydraulic resistance in the cochlear aqueduct, for example – and there could well be other special conditions relating to the middle ear muscle control loop.

Gathering diverse evidence from the literature, this paper has assembled a circumstantial case that aberrant behavior of the middle ear muscles can cause MD. If the hypothesis is correct, then treatment of MD may lie in preventing overactivity of these small and cryptic muscles. It would be unwise to claim that a cure simply entails section of muscle tendons, although the work of Franz et al. does point in this direction. Surgery is not always appropriate, but certain drugs, notably botulinum toxin [109], have been used to successfully treat dystonia, and perhaps a trial of such drugs in Meniere’s patients could have a positive outcome.

Conclusions

An explanation for the origin of MD has been proposed based on consideration of the ILP theory of middle ear muscle function. It considers the labyrinth to be a muscular hydrostat – a sealed volume filled with fluid whose pressure is controlled by a muscle – so that abnormal contraction of the tensor tympani leads to overpressure of the labyrinthine fluids. In turn, this leads to a reduction in hearing sensitivity, a sense of pressure and fullness in the ear, disturbance to balance, pitch anomalies between the ears, and tinnitus – the key symptoms of MD.

The fresh interpretations raised here might be useful in diagnosing and treating MD. As Alford acknowledges [2], MD has been a diagnostic dilemma for generations. “The

panoply of symptoms, signs, and clinical features has served to bewilder ... and has resulted in a variety of conjectural theories," he says. Thirty years later, the pathophysiology of MD continues to remain obscure, and it is hoped that the new perspectives offered here might contribute to more effective treatment of this distressing complaint.

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