Chapter

Menière's Disease: Etiopathogenesis

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Abstract

This chapter will discuss idiopathic Menière's syndrome. That is to say—Menière's disease. We will start with a brief recall on the History of Menière's disease beginning with the description of the syndrome by Prosper Menière in 1861, the description of endolymphatic hydrops in temporal bone studies by Hallpike and Cairns in 1938 and by Yamakaua in the same year. Endolymphatic hydrops became a pathologic correlate for Menière's syndrome. Theories that considered endolymphatic hydrops as the cause of the syndrome will be discussed. More recent studies questioning the old theories and thinking of endolymphatic hydrops as an epiphenomenon in the course of the syndrome rather than the cause of the symptoms will be discussed. Temporal bone studies were the basis of these new theories too. Familial Menière's disease will be discussed and several families will be described in detail. Because the phenotype of siblings on each family studied was variable and migraine was present in many affected members of these families a spectrum was postulated going from migraine alone to full blown Menière's disease. Some siblings had what has been described recently as vertiginous migraine and a detailed description of this syndrome will be provided and the differences between this syndrome and Menière's disease will be made clear. About 20% of Menière's disease patients have a familial history. Sporadic Meniere's disease might have a genetic predisposition and other environmental and behavioral factors contribute for the surfacing of the disease (multifactorial etiology). Because migraine is a central phenomenon and the vertiginous episodes and auditory symptoms are peripheral a hypothesis is presented for the pathophysiology of Menière's disease. Recent research comparing vestibular migraine and Manière's disease reinforcing the concept of these syndromes representing a continuum process with similar etiology are discussed at the end.

Keywords: Menière's disease (MD), endolymphatic hydrops (EH), migraine, familial Menière's syndrome, continuum, vertiginous migraine (VM)

1. Introduction

This chapter will present the etiopathogenesis and pathophysiology of Menière's disease (MD). It is necessary therefore to make clear the definition of Menière's disease that will be considered here.

We consider Menière's disease the Menière's syndrome without a clear etiology. Because vertigo, tinnitus and hearing loss are present in most of the insults to the inner ear there are many known causes for these symptoms. However, there is the Menière's syndrome present in some patients without any definable etiology. This is Menière's disease and will be our subject in this chapter.

1.1 History of Menière's disease

Let us start with following the History of MD. In 1861 Prosper Menière suggested that vertigo, tinnitus and hearing loss were symptoms of vestibular organs injury rather than of brain apoplexy. This paper marked the starting point of a discussion that is now almost 180 years old [1].

In 1938 Hallpike and Cairns described in temporal bone histopathology study hydrops of the endolymphatic compartment in patients who had the Menière's symptoms during life. This was a material proof of the inner ear origin of the Menière's syndrome as stated by Menière in 1861 [2]. In the same year Yamakawa in Japan described the same histopathological findings in temporal bones of patients with the Menière's syndrome [3].

From then on, several temporal bone histopathologists [4–6] found endolymphatic hydrops (EH) in temporal bones of patients with the Menière's syndrome. So, EH was established as the pathological correlate of MD.

Schuknecht [7] in 1978 observed rupture of endolymphatic membranes in patients with EH (**Figures 1** and **2**) in temporal bones of patients who had the Menière's syndrome during their life time. Lawrence in 1864 [8] had shown that rupture of Reisner's membrane in one segment of the chinchilla's cochlear duct and consequent mixing of endolymph with perilymph would cause permanent damage to the organ of Corti in the involved segment.

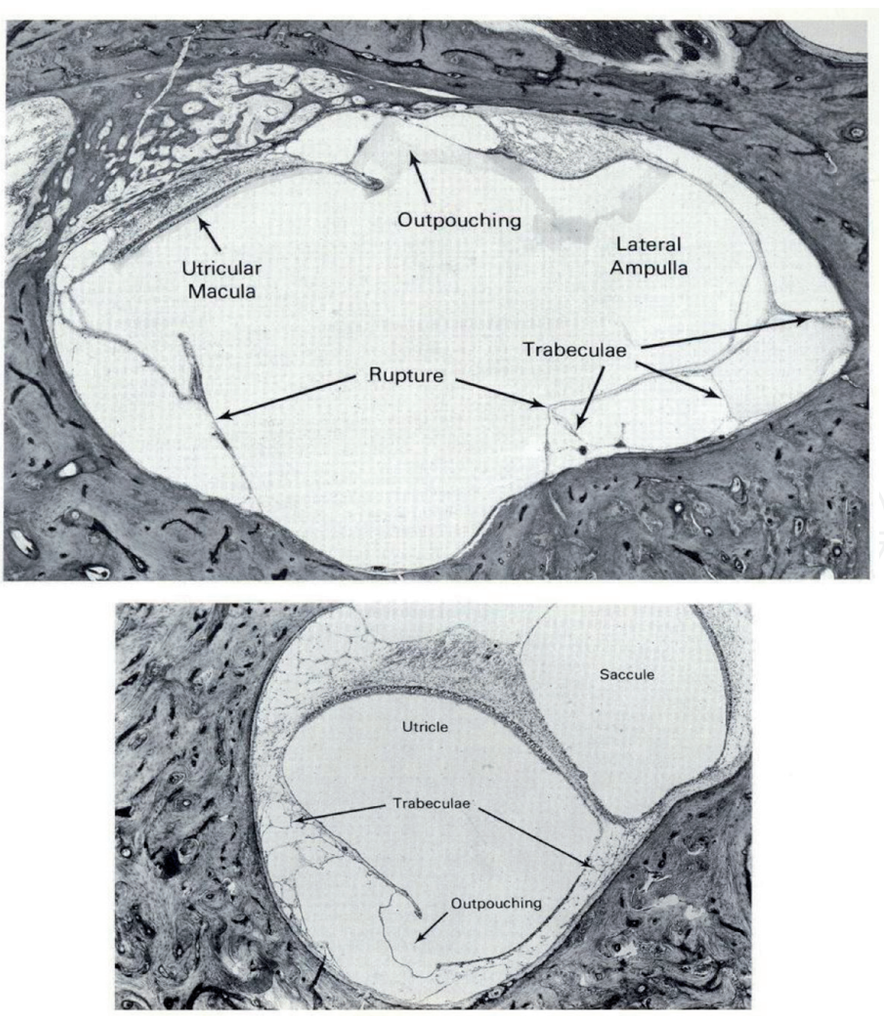

Figure 1.
Membrane rupture in the vestibular labyrinth. Reprinted with permission from Ref. [7].

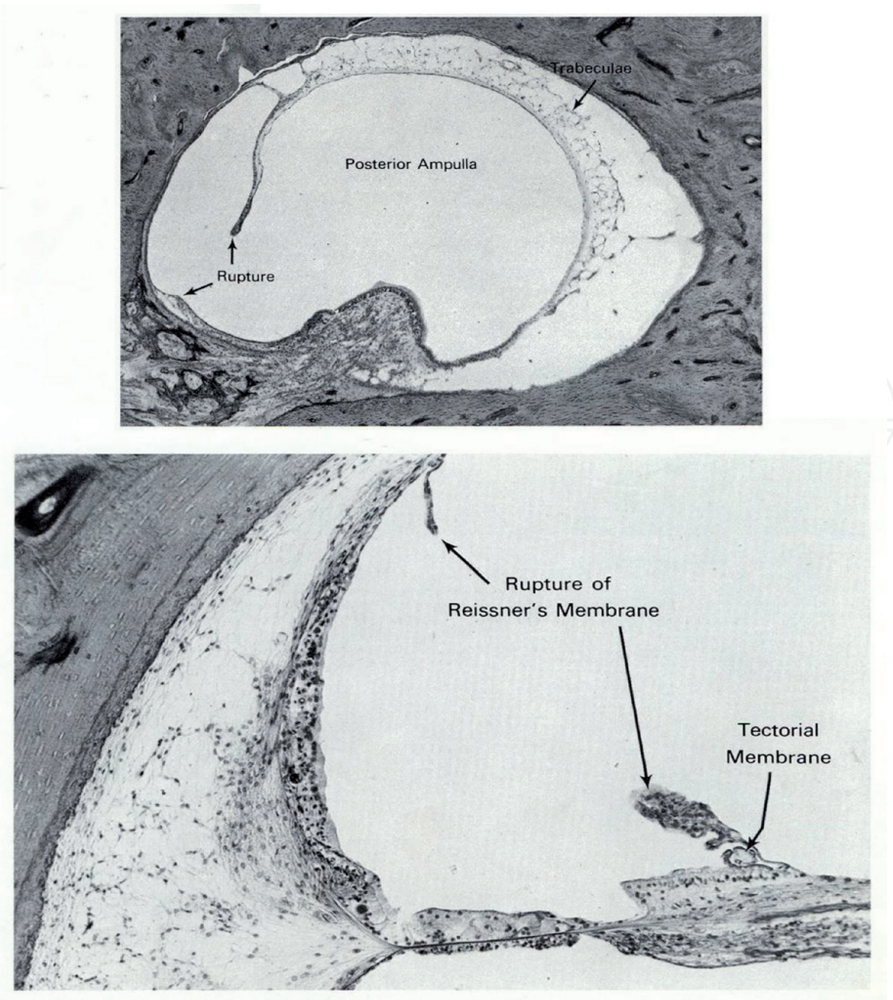

Figure 2.
Membrane ruptures in the semicircular canal and cochlea duct. Reprinted with permission from Ref. [7].

Based on the ruptures of cochlear and vestibular membranes in the hydropic ears Schuknecht proposed that these ruptures and the consequent mixing of endolymph and perilymph would cause the acute Menière's attack.

After the Schuknecht paper EH became more than a pathologic correlate. It was the cause of the Menière's symptoms. For one decade this theory was accepted as true and things appeared to be settled down regarding the etiopathology of Menière's disease.

However, during the year of 1989 Oliveira selected 83 temporal bones of patients who had significant tinnitus during life and tried to find a pathologic correlate for this symptom. Thirty-seven temporal bones had normal histology (44.5%), 23 had EH (27.7%). Among the normal histology bones there were 13 patients who also had episodic vertigo during life. It was notable that 72.2% of the bones had normal histology and EH. He thought of a common cause for MD and EH. In that case EH would not be the cause for MD but both would have a common cause [8].

Rauch et al. in 1989 [9] studied 26 temporal bones from patients who had MD during their life's time but only 13 of them had EH. **Figures 3** and **4** are from Rauch's paper and express the change in position of EH: from the cause of the symptoms to an epiphenomenon also caused by an unknown primary event.

Fraysse in 1990 [10] pointed out that EH may be present in several diseases of the inner ear and that MD patients may not have EH present. Merchant et al. in 1995 found 28 temporal bones from patients with MD who had EH but 19 other patients with EH never had MD symptoms during life [11].

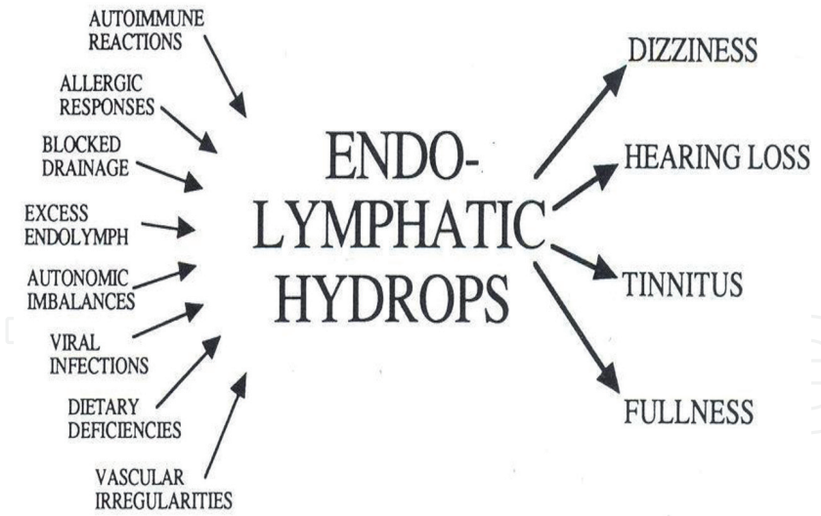

Figure 3.
Reprinted with permission from Ref. [9]. See text for explanation.

In this way the rupture theory put forward by Schuknecht is now discarded. Summarizing what has been said above:

1. EH is present in most cases of MD but it is not the cause of the Menière's symptoms. At most it can be taken as a pathologic correlate for MD. A primary unknown cause produces first the symptoms and later EH as an epiphenomenon.

2. Menière's syndrome is indeed a reaction of the inner ear to many insults (infection, trauma, tertiary syphilis, otosclerosis, autoimmune diseases).

3. EH may be found in the temporal bones from patients with all the above-mentioned insults: it is therefore a common pathologic correlate to many inner ear injuries.

4. We consider as MD the Menière's syndrome without a known cause.

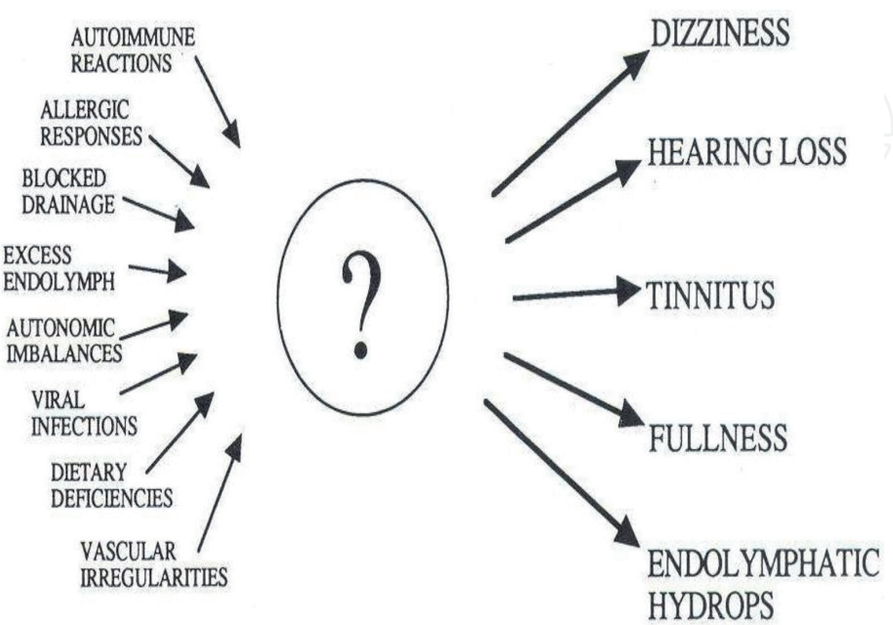

Figure 4.
Reprinted with permission from Ref. [9]. See text for explanation.

2. Familial Menière's disease

Familial MD is not a rare finding. The presence of MD in several siblings of a family points to a genetic etiology for the disease. Studying these families is a way to learn about MD etiology. In this section we will discuss our experience with MD occurring in families.

This research line started up in 1992 [12]. By that time, we saw a patient who was 69 years old and had a full blown Menière's syndrome: severe episodic rotatory vertigo with drop (falling) attacks, tinnitus and fluctuating hearing loss in his right year. These symptoms started up 5 years before we saw him. His drop attacks were severe and several times he hearts himself during falls. Right sided headaches usually preceded the crisis. Audiogram showed low tone sensorineural hearing loss bilateral and flat severe sensorineural hearing loss on the right ear. Left ear had hearing preserved in the frequencies above 500 Hz (**Figure 5A**). VDRL test was negative and glycerol test was positive bilaterally. An endolymphatic sac procedure

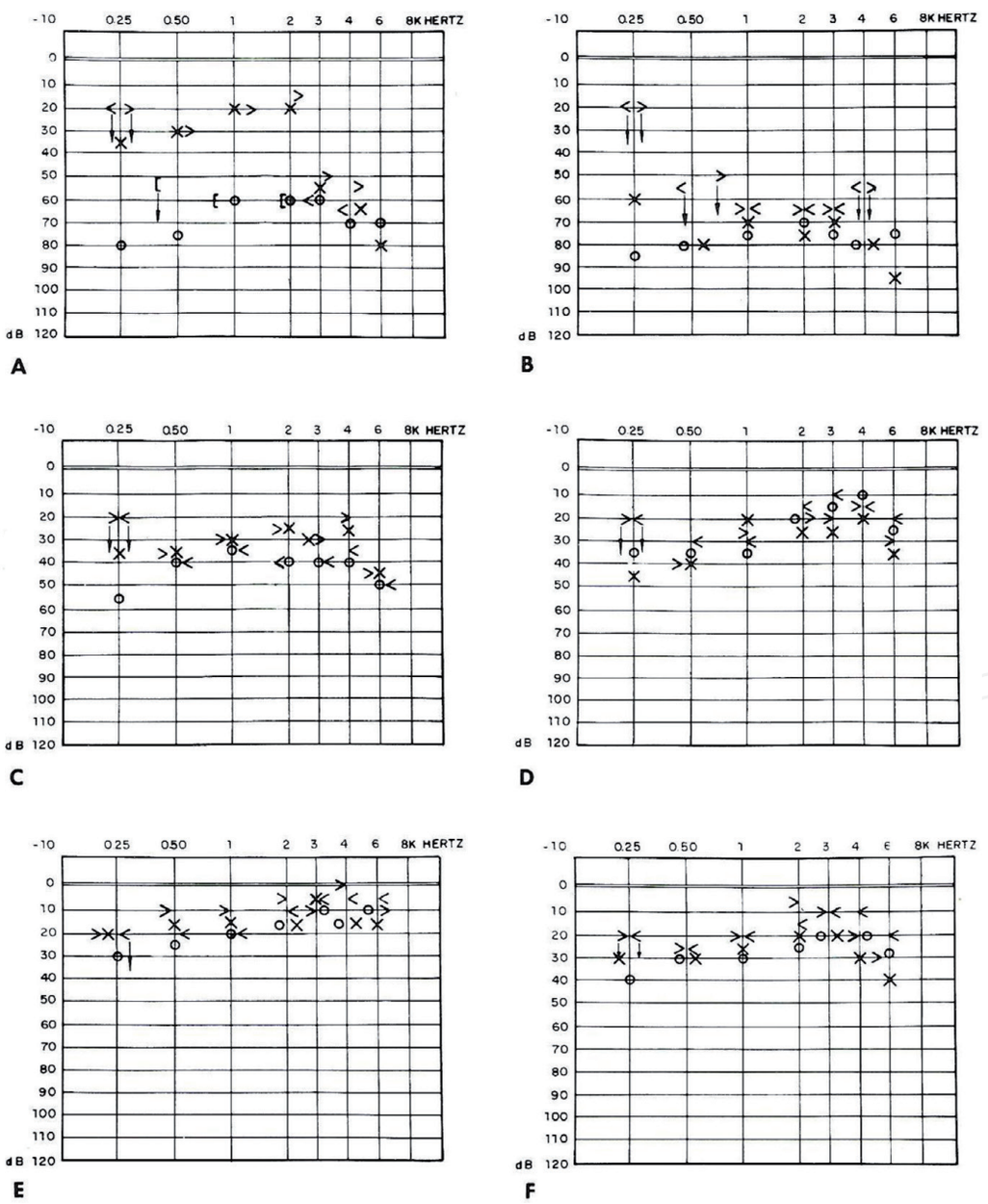

Figure 5.
Audiograms of proband (A and B), one daughter and three sons of his (C–F). Reprinted with permission from Ref. [13].

was performed in his right ear and the drop attacks disappeared. Mild dizziness attacks and headache continued but were controlled on medication. Ten years later in June 1090 his hearing in the right ear had worsened (**Figure 5B**) considerably but the drop attacks had not come back and his dizziness was under control. His headache was unchanged.

The heredogram of this family (**Figure 6**) shows that six of seven sons and daughters of this man had the same complaints as their father and the audiograms on four available siblings showed low tone sensorineural hearing loss (**Figure 5C–F**). One offspring from a second marriage of the index patients also had the same complaints. We did not give attention to the headache these patients complained about so we did not classify this symptom properly.

We found several reports of headache associated with both familial and sporadic Menière's syndrome [13–15] but the headache was not well characterized in any.

Two questions were in our minds after we studied the family described above: (1) how often a family history could be elicited from patients with classic Menière's syndrome; (2) what kind of headache was associated with Menière's syndrome? We started to apply to all the patients with Menière's syndrome seen in our clinic a questionnaire with questions about the presence of similar symptoms in their family members as well as about the presence of migraine symptoms.

Through this questionnaire we identified a large family who had typical Menière's syndrome present in some siblings, migraine and Menière's syndrome in others, and only migraine symptoms in others. Considering all siblings affected with these symptoms we arrived to the heredogram displayed in **Figure 7**. The mode of genetic transmission was clearly autosomal dominant [17]. Of course, we knew that in every day clinic work we find more patients with incomplete than with full blown Menière's syndrome. To consider patients with migraine only as affected siblings was an assumption that was supported by continuing the line of thought.

The summary of all symptoms present on 19 affected members of the family is in **Table 1**. It can be seen there the spectrum of symptoms with some of them present and others absent in different patients. The index patient had full blown Menière's syndrome and fluctuating low tone sensorineural hearing loss (**Figure 8**). Three of his sons had intractable migraine who needed hospitalization for treatment sometimes but they lacked Menière's syndrome symptoms at that point. We concluded that: there was a strong association between migraine and Menière's syndrome in this family and both seemed to be transmitted by a single gene in an autosomal dominant mode. From a physiopathology stand point we do not know how the migraine (central) relates to the Menière's symptoms (peripheral).

Now we had a hypothesis: migraine and Menière's syndrome are related and transmitted in an autosomal dominant mode. To further this hypothesis, we set up to answer two questions: (1) How often is the occurrence of familial

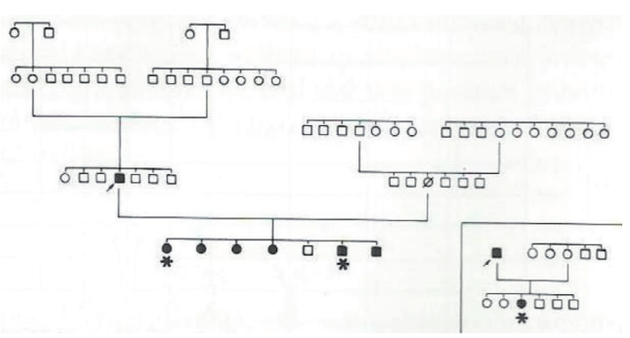

Figure 6.
Heredogram of the 1992 family. Reprinted with permission from Ref. [13]. Black symbols are affected siblings. Circles are male and square are females.

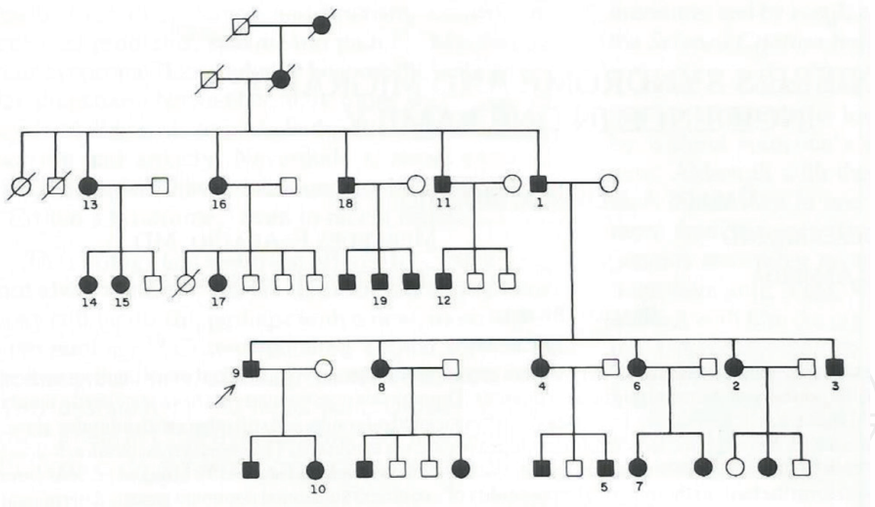

Figure 7.
Heredogram of 1997 family. Reprinted with permission from Ref. [16]. Black symbols are affected siblings. Circles are males and square are females.

Migraine–Menière's syndrome in our population? (2) How is the evolution of these symptoms as time goes by? In other words: what is the Natural History of this symptom's complex?

We then started to apply a questionnaire inquiring about the family history of every patient with typical Menière's syndrome seen in our Otology Clinic prospectively beginning in January 1997 and finishing in December 1998.

All index patients were required to have typical Menière's syndrome according to the American Academy of Otolaryngology—Head and Neck Surgery criteria. The work up included audiometry, tympanometry, vectoeletronystagmography and a glycerol test in order to seal the diagnosis of idiopathic typical Menière's syndrome (Menière's disease). At this point the included patients were questioned about migraine symptoms. Next the questionnaire about their family history regarding Menière's and migraine's symptoms present in other family members was applied. It is worth to mention that any symptom of one of these syndromes were noted and used to construct the heredogram of each family. Every available affected member of these families went through the same work up of the index patients.

Eight patients with typical, complete Menière's syndrome were collected in 2 years from our otology clinic in Brasília. Six of the eight had positive family history for Menière's and/or migraine. **Table 2** shows that only one index patient had low tone sensorineural hearing loss. All others displayed high tone sensorineural hearing loss in between crisis. **Table 3** shows the presence/absence of Menière's and migraine symptoms in the affected members as well as demographic data.

Age of the index patients varied from 26 to 63 years old. Symptoms appeared between 15 and 40 years. Six patients had unilateral symptoms and two had both ears affected. Most of the time migraine occurred before the vestibular symptoms, sometimes it came after the vestibular crisis and a minority had migraine unrelated to the vertiginous attack. In six of the eight indices patient's headache fit the classification of the International Headache Society of 1988 as migraine. There were six female and two male probands [16].

Figures 9–11 show heredograms of the six affected families. It is clear from them that the pattern of genetic transmission is autosomal dominant and there is great variability with some siblings having typical Menière's disease and migraine, others having migraine alone and others having symptoms of Menière's syndrome incomplete with or without migraine. If we assume a monogenetic transmission then variable penetrance of the gene is probably the cause of this variability.

Patient	Age	Sex	Tinnitus	Hearing Loss	Vertigo	Headache	Vomiting	Nausea	Scotomas
1	22	M	+	+	+	–	+	+	–
2	41	F	+	+	+	+*	+	+	+
3	50	M	+	+	+	+*	+	+	+
4	46	F	+	+	+	+*	+	+	+
5	17	M	–	–	–	+*	+	+	+
6	41	F	+	+	+	+	+	+	+
7	19	F	–	–	–	+*	+	+	+
8	56	F	+	–	+	+	–	+	+
9	58	M	+	+	+	+*	+	+	+
10	15	F	+	–	+	+*	+	+	+
11	77	M	+	+	+	–	+	+	–
12	51	M	+	+	+	+*	–	–	+
13	71	F	+	+	+	+	+	+	–
14	49	F	–	–	–	+*	–	–	–
15	47	F	+	+	+	+	–	–	–
16	80	F	+	–	+	+	–	–	–
17	59	F	+	+	+	+*	–	+	+
18	75	M	+	+	+	+	+	+	+
19	45	M	–	–	–	+*	–	–	–

ENG — electronystagmography, N — normal, SNHL — sensorineural hearing loss, ND — not done, MS — Meniere's syndrome, HL — hyperactive labyrinth.

*Headache was described by patient as typical migraine.

Patient	Anopsia	Paresthesia	Age (y) at Which Symptoms Appeared	Time Sequence of Headache and Vertigo	Blood Tests	Audiometry	Tympanometry	ENG
1	+	–	30		N	SNHL, bilateral, down-sloping	N	ND
2	+	–	10	Headache precedes vertigo	ND	ND	ND	ND
3	–	–	10	Variable	ND	ND	ND	ND
4	–	+	13 migraine, 30 MS	Migraine only for 17 years, MS only afterward	N	Mild SNHL, bilateral, 500 and 1,000 Hz	N	N
5	+	–	15		ND	Mild SNHL, bilateral, 500 and 1,000 Hz	ND	N
6	–	+	14	Headache precedes vertigo	N	Bilateral moderate SNHL, down-sloping	N	HL left side
7	–	–	10		ND	ND	N	N
8	+	+	9	Headache and scotomas precede vertigo	N	Mild SNHL, 500 and 1,000 Hz, right	N	HL left side
9	–	–	39	Headache precedes vertigo	N	Bilateral moderate SNHL, down-sloping	N	HL left side
10	–	–	7	Headache precedes vertigo	ND	ND	ND	ND
11	–	–	18		ND	Bilateral moderate SNHL, down-sloping	N	HL left side
12	+	–	17 migraine, 25 MS	Migraine only for 8 years, then MS only	ND	Bilateral moderate SNHL, down-sloping	N	HL bilateral
13	–	–	30	Variable	N	Bilateral mixed hearing loss, worse on left	ND	HL bilateral
14	–	–	20		ND	ND	ND	ND
15	–	–	35	Variable	N	Mild SNHL, left	N	HL bilateral
16	–	–	21	Variable	ND	ND	ND	ND
17	+	+	43	Variable	ND	ND	ND	ND
18	–	–	15	Headache precedes vertigo	ND	ND	ND	ND
19	–	–	20		ND	ND	ND	ND

ENG — electronystagmography, N — normal, SNHL — sensorineural hearing loss, ND — not done, MS — Meniere's syndrome, HL — hyperactive labyrinth.

*Headache was described by patient as typical migraine.

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Table 1.
Summary of clinical, laboratory, audiometric, and electronystagmographic findings in 19 affected members of family studied in 1997.[*]

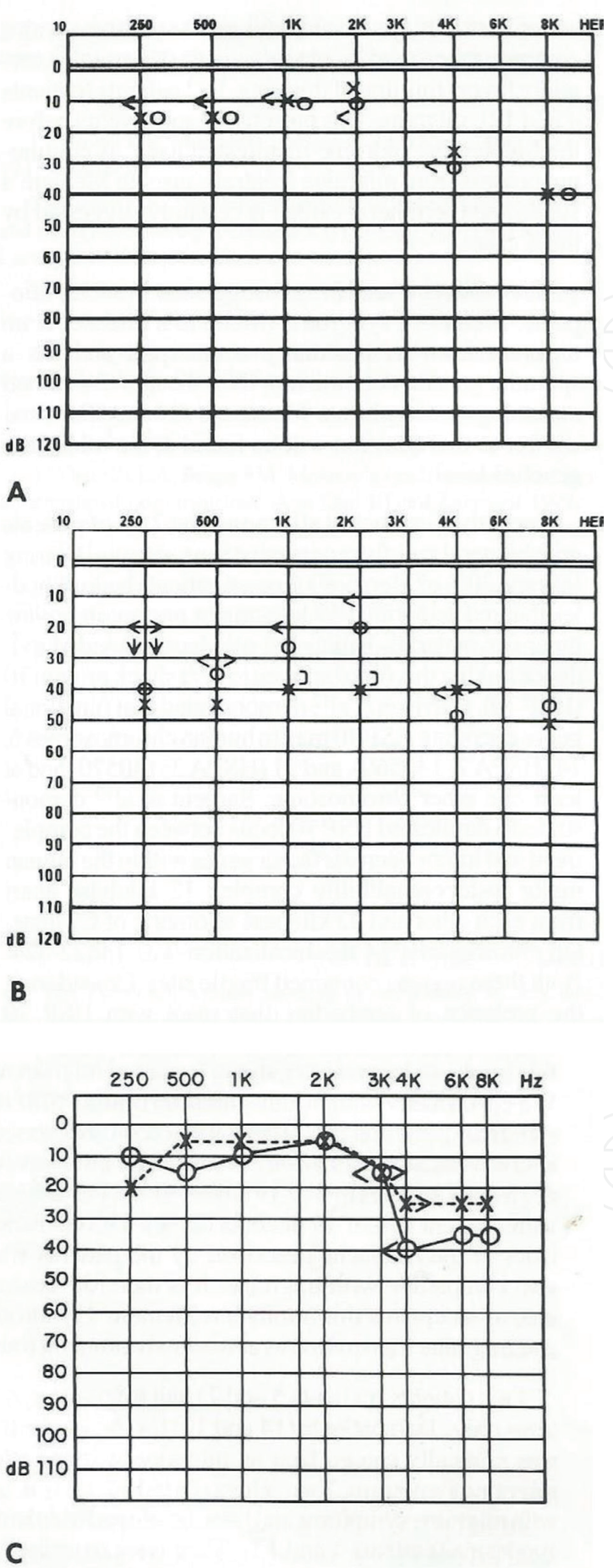

Figure 8.
Audiograms of the proband of the 1997 family. (A–C) Document fluctuating low tones sensorineural hearing loss. Reprinted with permission from Ref. [16].

Proband	Age (y)	Sex	Audiometry
1	62	M	Bilateral moderate SNHL, downsloping on R, flat on L
2	43	F	Bilateral downsloping SNHL, moderate on R, severe on L
3	30	F	Normal
4	46	F	Normal
5	43	F	Flat moderate SNHL on R, normal on L
6	26	F	Normal
7	45	M	Bilateral moderate SNHL low and high tones, worse on L, middle tones normal
8	35	F	Moderate low-tone SNHL on L, normal on R

Speech discrimination score was compatible with pure tone loss in all patients.

SNHL — sensorineural hearing loss.

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Table 2.
Summary of audiometric findings in eight probands (2002 paper).[*]

Probands	Affected Family Members	Age (y)	Sex	Tinnitus	Fluctuating Hearing: Aural Fullness	Fluctuating Hearing: Loss	Vertigo	Nausea	Vomiting	Audiometry	VENG	Scotoma	Photophobia	Atypical Headache	Hemicranial Headache	Pulsatile Headache
III-5		30	F	+	+	+	+	+	+	N	PIS R	+	+	–	+	+
(Family 3)	I -2	Deceased	F	+	+	+	+	+	–	ND	ND	+	+	–	+	+
	II-2	60	F	–	–	–	–	+	–	ND	ND	+	+	–	+	+
	III-6	16	F	+	–	+	+	–	–	SNHL bilat	PIS R	+	+	–	+	+
	III-8	37	F	–	–	–	–	+	–	ND	ND	–	+	–	+	+
	IV-1	10	M	+	+	+	+	–	–	N	N	–	–	+	–	–
III-2		46	F	+	+	+	+	+	+	N	PIS R	–	–	+	–	–
(Family 4)	II-2	60	F	+	–	–	+	–	–	N	N	–	+	–	+	+
	II-3	58	F	+	–	–	+	–	–	N	N	+	–	–	+	+
	II-4	65	F	+	+	–	+	+	+	N	PIS L	–	+	–	+	+
	III-3	43	F	–	–	–	+	–	–	N	PIS bilat	+	+	–	+	+
	III-7	33	F	–	–	–	–	–	–	ND	ND	–	+	–	+	+
	III-8	32	F	–	–	–	–	–	+	ND	ND	–	+	–	–	–
	IV-1	25	F	–	–	–	+	+	–	ND	ND	–	–	–	–	–
III-5		43	F	+	+	+	+	+	+	SNHL R	ND	+	+	–	+	+
(Family 5)	III-4	46	F	+	–	–	+	–	–	N	N	–	–	+	–	–
	IV-3	14	F	+	–	+	–	–	–	N	N	–	–	–	–	–
III-9		26	F	+	+	+	+	+	+	N	PIS bilat	+	+	–	+	+
(Family 6)	II-5	75	M	+	–	–	+	+	+	SNHL L	N	–	+	–	+	+
	III-8	32	F	+	–	–	+	–	–	ND	ND	–	+	–	+	+
	II-4	65	F	–	–	–	–	+	–	ND	ND	–	+	–	+	+
	III-2	46	M	–	–	–	–	–	–	ND	ND	–	+	–	–	–
	III-6	36	F	–	–	–	+	+	–	ND	ND	–	+	–	+	+
	II-1	40	F	–	–	–	–	+	–	ND	ND	+	+	–	+	–
	II-2	50	F	–	–	–	–	–	–	ND	ND	+	–	–	+	+
	II-4	52	F	–	–	–	–	+	+	ND	ND	–	+	–	+	+
II-22		45	M	+	+	+	+	+	+	SNHL L	N	–	–	–	–	–
(Family 7)	II-13	62	M	+	+	–	+	+	–	SNHL bilat	ND	+	–	+	+	+
	II-18	58	M	–	–	+	+	–	–	SNHL bilat	ND	–	–	–	–	–
	II-17	56	F	+	–	+	–	–	–	SNHL bilat	ND	+	–	+	+	+
	III-4	20	F	+	+	+	–	–	–	ND	ND	–	+	–	+	+
	III-5	12	F	–	–	–	–	–	–	N	N	–	+	–	+	+
III-5		35	F	+	+	+	+	+	+	N	PIS bilat	+	+	–	+	+
(Family 8)	II-5	54	F	+	–	+	–	+	–	ND	ND	+	+	–	+	+
	II-1	50	F	–	–	–	+	+	–	ND	ND	–	–	–	+	+

Tympanometric and stapedial reflex results were normal in all patients who had them done. Proband 1 had full-blown Meniere's syndrome and atypical headache. Proband 2 had both Meniere's and migraine symptoms.

VENG — vectoelectronystagmography, N — normal, PIS — peripheral irritative syndrome, ND — not done.

[*] *Reprinted with permission from Ref. [18].*

Table 3.
Summary of clinical, audiometric, and VENG findings in affected members of six families.[*]

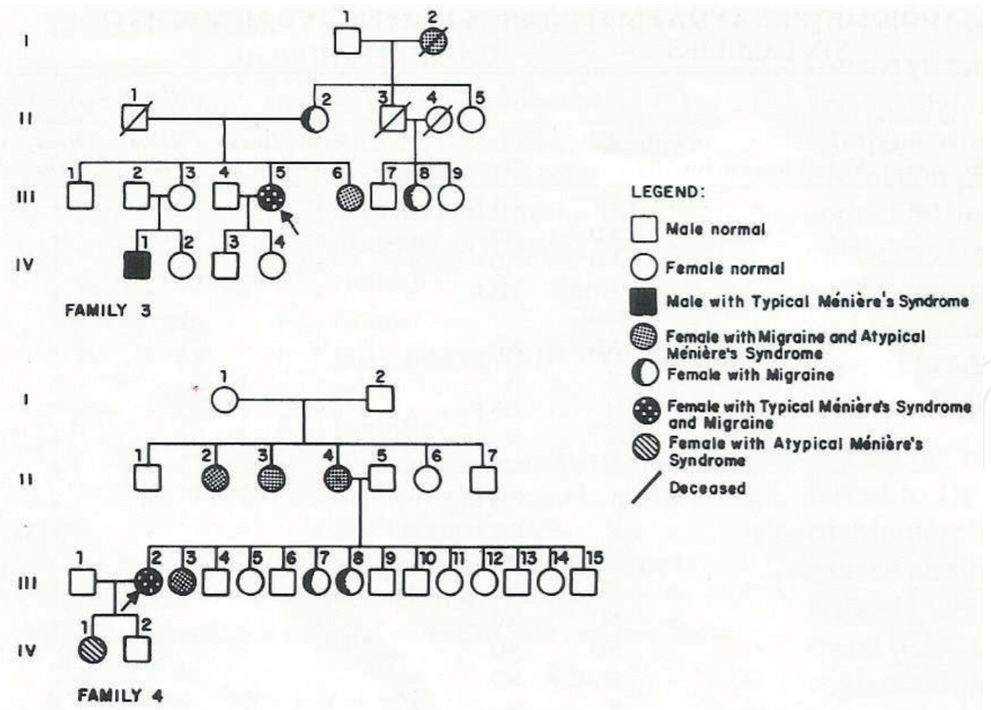

Figure 9.
Heredograms of families 3 and 4 from the 2002 paper. Note the spectrum of migraine and Menière's syndrome present in the affected siblings. Reprinted with permission from Ref. [18].

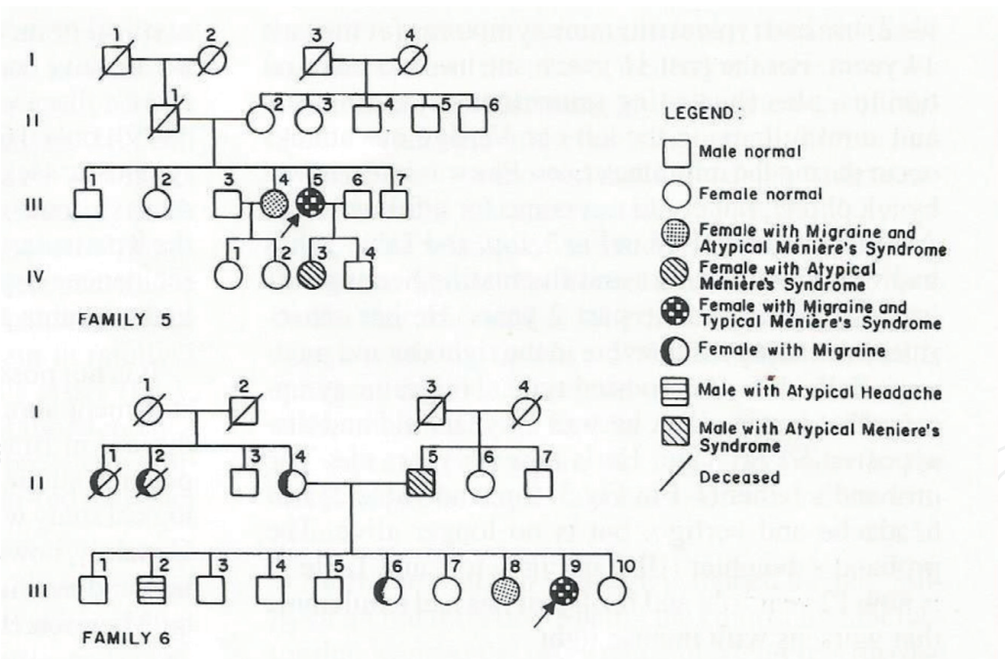

Figure 10.
Heredograms of families 5 and 6 of the 2002 paper. The pattern of symptoms distribution among the siblings are similar to the one present in families 3 and 4 above. Reprinted with permission from Ref. [18].

From these data we reasoned that:

1. Typical Menière's syndrome is not very frequent in Brasília: during 2 years in a very buzzy Otology Clinic we collected only eight cases.

2. On the other hand, the occurrence of familial disease in patients with typical Menière's syndrome (Menière's disease) is quite high (six of eight index

patients). If we consider Menière's syndrome all the spectrum of symptoms seen in these families then the disease is not so infrequent. In other words, we see incomplete Menière's syndrome much more often in our clinics than the typical syndrome. However, migraine can be associated with all the Menière`s spectrum of symptoms.

We wanted to ask: what happens to this spectrum of symptoms as time goes by?

The family we published in 1997 [17] lived in Brasília and we were able to follow them up from 1995 on for 10 years. The following paragraphs will refer to unpublished data from our group.

All affected and unaffected siblings in the heredogram in **Figure 7** were carefully interviewed along the 10 years follow up. Twenty siblings had no qualitative changes in symptoms from 1995 to 2005. Four had changed from atypical headache in 1995 to typical migraine 10 years later. Two had migraine in 1995 and progressed to Menière's syndrome in 2005. Four siblings had vertigo and atypical headache in 1995 and progressed to vertigo and typical migraine in 2005.

Five unaffected siblings in 1995 had symptoms of the migraine—Menière's complex 10 years later: two with aural fullness, one with migraine, tinnitus, vertigo and hearing loss and two with migraine and vertigo. Three affected siblings had remarkable improvement in migraine and vertigo or complete remission of the symptoms.

Fifteen of the 38 affected siblings started out with migraine and the vestibular symptoms appeared in average 17.6 years later. Seven siblings continued with migraine only after 10 years follow up. Over time the intensity and periodicity of the migraine symptoms tended to diminish and the vestibular symptoms tended to become more frequent and intense (**Table 4** and **Figure 12**).

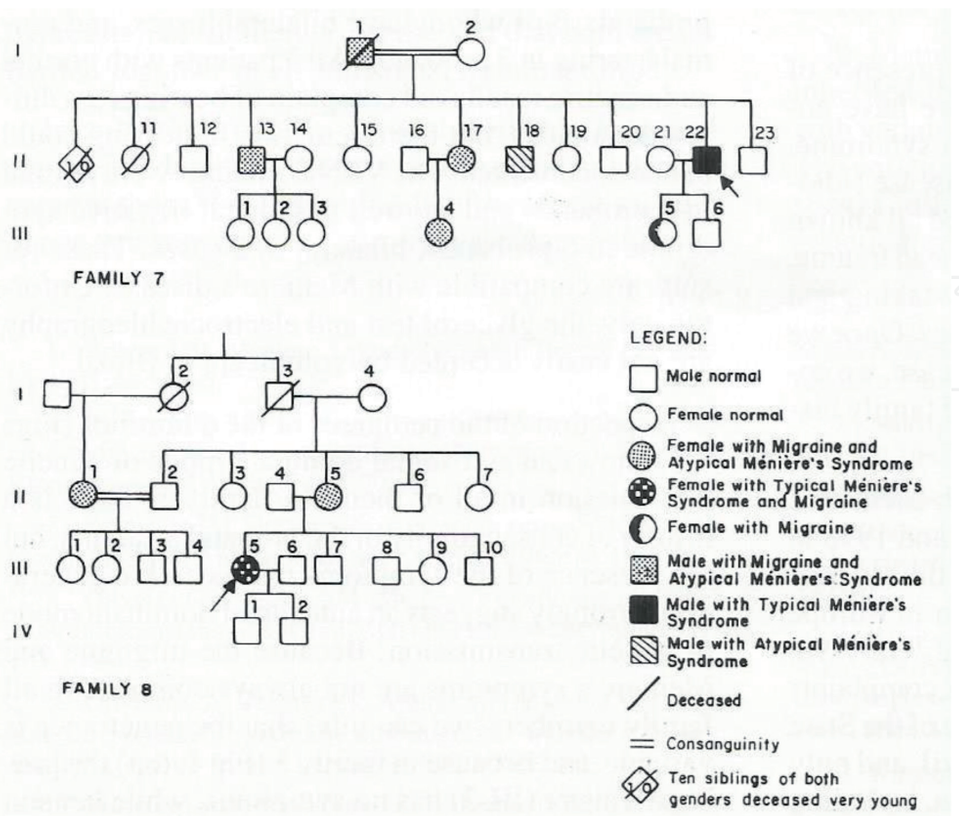

Figure 11.
Heredogram of families 7 and 8 of the 2002 paper. The pattern of symptoms among the siblings is similar to the families 3to 6. Reprinted with permission from Ref. [18].

Patient	Age at the moment (2005) (y)	Periodicity* (1995)		Periodicity* (2005)		Intensity (1995)		Intensity (2005)	
		Migraine	Menière	Migraine	Menière	Migraine	Menière	Migraine	Menière
1	81	2/w	1/w	1/w	1/w	9/10	Moderate	6/10	Severe
2	90	—	—	—	—	—	—	—	—
3	82	2/w	2/m	2/m	1/w	8/10	Moderate	6/10	Severe
4	87	1/w	1/m	1/m	1/w	6/10	Moderate	6/10	Severe
5	92	1/w	1/w	2/m	2/w	9/10	Severe	9/10	Severe
11	62	2/m	—	2/m	1/m	8/10	—	7/10	Severe
12	58	2/m	—	2/m	—	7/10	—	6/10	—
21	69	1/m	1/m	1/m	2/m	8/10	Moderate	5/10	Moderate
31	61	1/m	1/m	1/m	2/m	9/10	Moderate	6/10	Moderate
32	64	3–4/m	—	2/m	—	9/10	—	6/10	—
33	63	1/m	—	1/m	—	10/10	—	6/10	—
41	61	2/w	1/w	2/m	2/w	9/10	Moderate	7/10	Severe
51	68	1/m	1/m	1/m	2/m	9/10	Severe	8/10	Severe
52	66	1/m	—	1/m	—	8/10	—	8/10	—
53	54	1/m	2/y	1/m	4/y	7/10	Moderate	7/10	Severe
54	51	2/y	3/y	2/y	1/m	8/10	Moderate	8/10	Moderate
55	51	3/y	1/y	3/y	3/y	8/10	Moderate	6/10	Moderate
56	60	1/m	2/y	1/m	1/m	9/10	Moderate	8/10	Moderate
512	37	6/y	1/y	2/m	4/y	8/10	Moderate	8/10	Moderate
524	37	1/m	—	1/m	—	8/10	—	8/10	—
531	32	3/y	—	3/y	—	7/10	—	7/10	—
533	25	3/y	—	3/y	—	7/10	—	7/10	—
541	29	4/y	1/y	1/m	4/y	8/10	Moderate	8/10	Moderate

*Unpublished observations.

Table 4.
*Natural history of migraine and vestibular symptoms during 10 years follow-up (1997 family) (N = 23 affected siblings).**

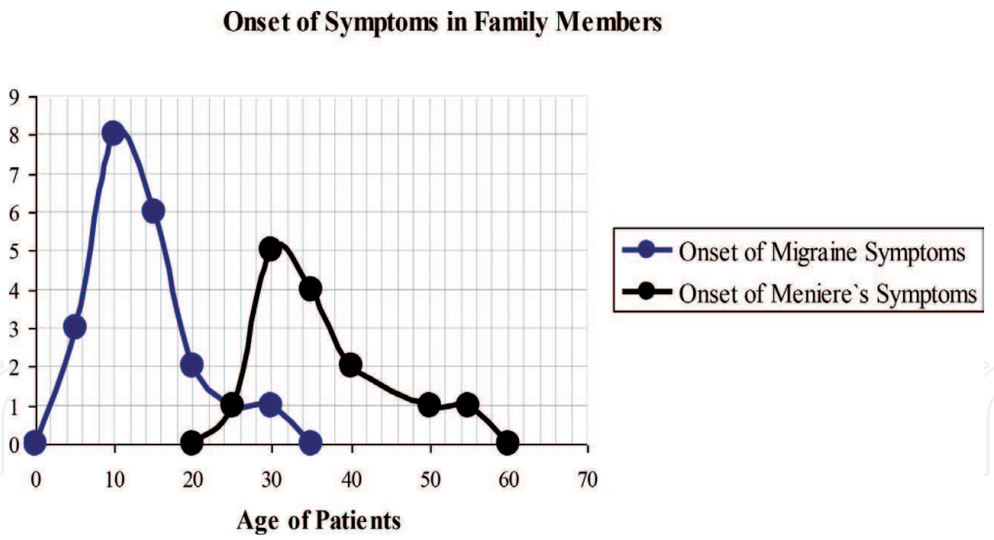

Figure 12.
Graphic representation of the natural history of this symptom complex during 10 years follow up of the 1997 family.

Patient	Audiogram result (1995)	Audiogram result (2005)
1	Moderate to profound mixed hearing loss bilaterally	Profound mixed hearing loss bilaterally
2	Mild high frequency SNHL	Mild to moderate high frequency SNHL
3	Moderate high frequency SNHL	Moderate high frequency SNHL
4	Moderate mixed hearing loss bilaterally	Moderate mixed hearing loss bilaterally
5	Moderate high frequency SNHL bilaterally	Moderate to severe high frequency SNHL bilaterally
11	Normal	Normal
12	Normal	Normal
13	—	—
21	Normal	Normal
22	—	—
23	—	—
24	—	—
31	—	—
32	Normal	Mild high frequency SNHL bilaterally
33	—	—
41	Mild high frequency SNHL	Mild to moderate high frequency SNHL bilaterally
42	—	—
43	—	—
51	Moderate high frequency SNHL bilaterally	Profound high frequency SNHL bilaterally
52	Normal	Normal
53	Normal	Normal
54	Mild high frequency SNHL bilaterally	Mild to moderate high frequency SNHL bilaterally
55	Mild high frequency SNHL bilaterally	Mild to moderate high frequency SNHL bilaterally
56	Moderate high frequency SNHL	Profound high frequency SNHL bilaterally

Patient	Audiogram result (1995)	Audiogram result (2005)
511	—	—
512	Normal	Mild high frequency SNHL bilaterally
521	—	—
522	—	—
523	—	—
524	—	—
531	—	—
532	—	—
533	Normal	Normal
541	Normal	Normal
542	—	—
551	—	—
552	—	—
553	—	—

**Reprinted with permission from Ref. [19].*

Table 5.
Hearing loss during 10 years follow-up (N = 19).[*]

Hearing loss worsened in most patients. The loss was in high frequency tones and bilateral (**Table 5**). We were not able to document low tone fluctuating sensorineural hearing loss during the crisis of vertigo/migraine in all siblings but we did document this feature clearly only in the index patient (**Figure 8**).

Now we had the natural history of this complex of symptoms described. We were therefore able to organize the clinical data in order to define a phenotype of this syndrome in the large family from Brasília.

Our hypothesis was that this was a genetically determined symptom complex and the genetic transmission was monogenic with incomplete penetrance. Next step was to try to find the genetic locus for these symptoms. Because we were not able to document low tone sensorineural hearing loss in most of the siblings and the high frequency sensorineural hearing loss was bilateral in the majority of the siblings the clinical diagnosis of migrainous vertigo was adopted for these patients. The fact that some of them had typical Menière's syndrome including low tone sensorineural hearing loss was however pointed out in the final paper [18].

Twenty-three family members who were clinically and audiologically evaluated and had image studies also done had genome wide linkage analysis performed with Affymetrix GeneChip Human Mapping 10K microarrays. Genotyping of family members DNA with microsatellite markers was used to further assess candidate loci identified from the whole genome scan.

The results of vestibular testing and imaging studies were unremarkable. The genetic analysis defined a 12.0 MB interval on chromosome 5q35 between loci rs2448795 and D5S2073 that contained the disease gene (logarithm of odd score 4.21).

Molecular genetics studies were performed at the Molecular Genetics laboratory of Harvard Medical School headed by Professor Jonathan Seidman.

3. Discussion of above findings and correlation with current literature

Here we will blend our results with the current literature on the subject and formulate a new hypothesis.

It is important to acknowledge the recently described vertiginous migraine (VM) syndrome [19] which is now listed in the Barany Society and the International Headache Society classification of vestibular diseases [20]. This entity is very frequent, second only to benign paroxistic positional vertigo being probably present in 1% of the general population [8]. We are not going to describe in detail the VM symptoms but it is important to point out the differences between MD and VM.

One marked difference is the absence of hearing loss that fluctuates in the low frequencies in the beginning and that progresses to severe hearing loss along the life in Menière's disease but not in vertiginous migraine. Bilaterally of the symptoms seems to be more frequent in familial MD and VM than in sporadic MD but it is not different between these two syndromes.

There is a significant body of literature dealing with the interfaces of Menière's disease (DM) and VM. We will review briefly some papers on this subject.

Neuhauser et al. [21, 22] prospectively evaluated migraine in 200 patients from a dizziness clinic and 200 ones from a migraine clinic. Prevalence of migraine that satisfied the criteria of the International Headache Society (HIS) II was 38% in the dizziness clinic and 24% in sex and age matched controls ($p < 0.01$). Vertiginous migraine was present in 7% of patients in the dizziness clinic and 9% of the ones in the migraine clinic. In 15 of 32 patient's vertigo was always associated with migraine during the acute attacks. In 16 patients this association was sporadic and two patients never had both symptoms together.

Radke et al. [23] studied 78 patients (40 male and 38 female) aged 29–81 years all with idiopathic uni- or bilateral Menière's disease according to the AAO-HNS criteria. Lifetime prevalence of migraine with and without aura was 50% among these patients and 25% among normal control patients ($p < 0.001$). Furthermore 45% or the Menière's disease patients always experienced at least one migraine symptom (headache, photophobia, aura) during the acute attacks. They postulated a pathophysiologic link between migraine and MD.

Urkur et al. [24] studied VEMPs parameters in VM, MD and migraine patients and found very similar results for all these patients. Gazques et al. [13] published a paper on recent advances in the genetics of recurrent vertigo including familiar episodic ataxias and MD. They found that 20% of MD patients have positive family histories for this disease [25].

Cha et al. [27] described six families with index patients affected by MD and migraine. There were 56 affected siblings. Of these 26 (41%) met the HIS criteria for migraine. Fifty percent had migraine with aura. Three patients had typical aura without headache. Sixty-three family members had recurrent spells of spontaneous vertigo. There were three twin pairs, two monos and one dizygotic. One of the homozygotic pair had migraine and MD while the other one had migraine and episodic vertigo without auditory involvement (VM).

Bertora and Bergman [38] using quantitative EEG (qEEG) studied 120 patients with MD and migraine and 85 patients with MD and no migraine. Eighty-five percent of MDs patients had hemodynamic brain variations like the ones found in migraine. Brain electric depolarizations and cortical irritative focuses are common to migraine and MD. However, MDs patients had important hyperactivity in the limbic lobe [28].

From this brief review of literature, we can say:

1. VM and MD are very often present in one single family and therefore have a common-genetic link.

2. Hearing involvement in MD and not in VM is the main clinical difference between these two syndromes.

3. Migraine is present in both syndromes.

Recently Welfang et al. [29] selected 30 classic MD patients and 30 patients with definite or probable VM matched by age and sex. Three-dimensional real inversion recovery magnetic resonance (3D real IR) was performed in these patients 24 hours after intratympanic gadolinium injection in order to assess endolymphatic hydrops (EH). Response rates, amplitudes, latency and response thresholds of cervical and ocular evoked myogenic potentials (c/o VEMP) were tested using air conducted sound. Pure tone audiometry was used to evaluate the level of hearing loss.

Different degrees of EH were observed in the cochlea and vestibule of MD patients. Some VM patients had 3D real—IR suspicious for cochlea EH and no EH was found in the vestibule of these patients. There was statistically significant correlation between EH and low tone sensorineural hearing loss. Response thresholds for c/o VEMP were no different in VM and MD patients.

Therefore, low frequencies sensorineural hearing loss correlate with EH on MD patients. 3R-real IR showed more severe degrees of EH in patients with MD but suggestion of EH in the cochlea of VM patients was showed. MD and VM patients behaved similarly in vestibular dysfunction and their transduction pathway (VEMP).

Ghawany et al. [30] treated 25 patients with typical MD following protocol to prophylactic migrainous treatment and showed marked improvement in quality of life in 92% of the patients. He states his results point to etiopathogenetic relation between MD and VM.

These results suggest a common etiopathogenesis for MD and VM and that VM may progress to MD as time goes by if EH develops in VM patients.

4. Conclusion

At this point we know that the spectrum of symptoms that goes from migraine alone to migraine with full blown MD including vertigo and migraine (VM), vertigo alone (atypical Menière's syndrome) has high familial incidence and is genetically transmitted in a monogenic autosomal dominant mode [16]. We have found that the locus for this spectrum of symptoms maps to chromosome 5q35 [18].

Studies using VEMP [26] and 3D real IR [27] have shown that EH is present in different degrees in both MD and VM. It may be that absence of low tone sensorineural hearing loss in VM relates to the very small degree of EH present in this entity compared to MD.

Based on all this evidence we have up to now we believe that future efforts should be directed to isolate the gene in chromosome 5q35 and follow up longitudinally patients with VM with VEMP and 3D real IR MRI to test the hypothesis that VM and MD are different stages of the same process.

Sporadic MD and VM should be tested for the presence of the gene we are looking for after we have it isolated. Then we might also have a better idea about the etiology of MD and VM. Probably environmental factors [31] will be also important for the full development of the disease (multifactorial etiology).

We do believe that this research line should be taken to its future.

5. Etiopathogenesis of migraine—Menière's disease

Finally we must consider how migraine, a central syndrome relates to Meniere's disease a syndrome that originates in the periphery of the vestibular system.

Several authors [32–36] have shown that trigeminal vasomotor fibers innervate the inner ear (stria vascularis, cells of the ampullary crests) and through this pathway the vascular changes occurring in the central nervous system reach the

peripheric vestibular system and bring about the symptoms of MD and EH. This certainly would occur in VM too.

Of course this theory needs experimental confirmation before it can be considered proven. Nevertheless the anatomical pathways are in existence and this is factual evidence towards this theory. The natural history of the symptoms in our families supports it.

Dolowitz [37] has studied a big number of patients with MD and showed that headache is a nuclear symptom in sporadic MD but he did not characterize the headache as igraine so this must be done before we can say that migraine is a constant part of sporadic MD.

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