Ménière’s Disease
Pathogenesis & Natural History

Gavin Morrison
Guy’s & St Thomas’ Hospital, London.
Section of Otology, RSM
Friday 4th February 2016
Ménière’s Disease

• First described by Prosper Ménière in 1861

• 155 years later, there are still far more questions than answers

• What are some of the Unanswered Questions?
Unanswered Questions

• What is Patho-physiological process?

• Why do we see 80% control of the disease whatever the treatment or surgical procedure?

• Destructive procedures seem effective for unilateral disease but bilateral impairment can be devastating:
  THEREFORE Who gets bilateral disease and when?

• When will it predictably ‘Burn Out’?
How

• Review of Aetiological / Patho-physiological research

• Presentation of Natural History from a Personal Series of patients with Ménière’s Disease
Pathology – Endolymphatic Hydrops
Pathology – Endolymphatic Hydrops
MRI evidence of Hydrops

- Ref 1) Acta Otolaryngol. 2013, Japan
- Endolymphatic hydrops revealed by magnetic resonance imaging in patients with atypical Ménière's disease.
- 3 T MRI after injection of gadolinium enhancement medium intra-tympanically.
Hydrops: Cause or Epiphenomenon?

• Conditions in which we see Endolymphatic Hydrops
  – Ménière's Disease
  – After Head Injury
  – Otosclerosis
  – Infections – Syphilis, Yaws
    Chronic Suppurative Ear Disease
    Viral Infections
  – Autoimmune Inner Ear Disease
  – Low CSF Pressure Syndrome
But

• Hydrops can exist for years without any ear symptoms

Therefore:

• Hydrops can cause MD but hydrops alone is insufficient
The Endolymph System
Radial & Longitudinal flow.

Endolymph formed and reabsorbed in dark cells of vestibular system

Endolymph formed and reabsorbed at Stria Vascularis in Cochlea

Longitudinal flow and drainage/purification of Endolymph to ELS
Hydrops

• Blockage to flow Theories

• Endolymph production / resorption / osmotic gradients theories
Potential sites of Physical Endolymph Obstruction

- Canal Reuniens 0.7 x 0.225 mm
- Utriculo-endolymphatic valve = one way flow?
- Obstruction Endolymphatic duct in VA
Blockage pattern of longitudinal flow in Ménière's disease: Anatomical Studies

3D CT images of the ductus reuniens, saccular duct (SD), and endolymphatic sinus (ES)

2) In MD ears on 3D CT images dimensions were significantly different from normal healthy ears.
   Evaluation of the vestibular aqueduct in Ménière's disease using multiplanar reconstruction images of CT.
   Ref. Auris Nasus Larynx. 2012 Japan
   The external aperture areas of the VA fenestra of the affected and non-affected ears of patients with Ménière's disease were significantly smaller than that for the control ears.

3) Diameter of Vestibular Aquaduct Duct Ref. J Laryngol Otol. 2012 St George's Hospital, London
Endolymph production and cycle

- Strial Cells & Dark cells
- 10 different nearby cell types
  - Fibrocytes, basal cells, intermediate cells, marginal cells
- Rely on:
  - Gap Junctions
  - Ion (K+ and Ca+) and water channels (aquaporins)
  - Pumps
  - Transporters
Molecular Level Studies

- Homeostatic pressure
- Electrolyte Concentrations – Elevated Ca^{++}
  - Osmotic hydrops
- Aquaporins
- ADH Vasopressin
- ERR-B (Oestrogen Related Receptor)
- Cochlin Expression in MD
What causes acute Vertigo attack

- Membrane Rupture?
- Sudden Decompression of Hydrops by valvular opening?
- Sudden Ionic Composition changes?

- I am sure it must be change in normal AP formation. (K+ and then Ca^{2+} influx releases neurotransmitter)

Nystagmus is ‘paralytic’ therefore threshold in disease ear in increased, and vertigo is due to unopposed tonic discharge from normal ear.

- Depolarisation Blockade
Endolymphatic hydrops may cause a rupture of the membranous labyrinth or may force open the utriculo-saccular duct

- Ref. Hear Res. 2013 (guinea pigs) Daniel Brown, Sydney
What causes characteristic audiometry

- Cochlear Hydrops greatest at points of natural weakness (increased compliance of Reissner’s & Basilar membrane)
- This is at Apex of Cochlea
- Hydrops/Displacement of BM decreases Endocochlear potential (+80 mV)
- This increases threshold for Action Potential
- Causes Low Frequency Hearing loss
Division of Molecular Genetics,
Institute of Biomedical and Life Sciences (IBLS),
University of Glasgow, Scotland, UK

Co-workers: Dr Mark E S Bailey & Miss Yvonne Lowe
Genetic Studies

- HLA associations – Chr 6p
- Migraine Associations (known genetic factors – 9 loci common migraine)
- Genetic Polymorphins in Aquaporin 5 (not AQP4 and OE receptors ) in MD

- FAMILIAL MÉNIÈRE’S DISEASE: CLINICAL & GENETIC ASPECTS

  A W MORRISON, MB ChB FRCS DLO, M E S BAILEY, B.Sc. Ph.D., G A J MORRISON, MA MB.BS FRCS
  J of Laryngology & Otology, 2009 123: 29-37

  - 5% Patients with MD have a Positive FH, 46 families, Autosomal dominant

- MD Linkage studies:
  - Morrison, Bailey, Lowe - Region of Chr 14q11-13 - Highly Likely Heterogeneic Factors in families and Sporadic MD (unpublished)
  - Swedish Group - Chr 12p12.3
  - Danish Group – COCH gene DFNA2 Chr 14p11.2
  - others

- Sporadic MD: Genome Wide Association Study (GWAS) in large numbers of Sporadic MD patients
  DNA Microchip Technology
  Rapid automated analysis of thousands of genes simultaneously
Personal Series of Patients with Ménière's Disease

• N = 124

• 111 Definite MD, 9 probable MD, 4 Possible MD (ecogs +ve)

• Sex F = 62 : M = 60

• Quantitative and Descriptive data review
Ménière’s series

• Follow Up
  – Seen over 18 Years (1997 - 2015)
  – Range: Diagnosis to last review – up to 40 years, (median 10 years)
  – Mean personal FU 5.2 years (Median 4 years)

• Unilateral Throughout 97
• Bilateral Disease 26 (20.9%)
Age distribution Onset of Symptoms

n=124

Mean 44.8 years
Natural History - Evolution

• Highly variable

  – Bad Vertigo attacks, hearing loss not spared

  – Hearing loss (with fluctuations then progression), infrequent vertigo over many years.
Analysis of Vertigo Attacks

• Predominant *Clustering*
  – Very frequent & severe attacks over 6 weeks to 2-3 months
  – Followed by relative quiescent period often for over a year
  – AAO-HNS 1995

![Hypothetical Chart of Attacks vertigo per week for one Patient](chart.png)
Analysis of Severe Vertigo Attacks II

<table>
<thead>
<tr>
<th>Bad Clusters</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 years:</td>
<td>25</td>
</tr>
<tr>
<td>2-5 years:</td>
<td>16</td>
</tr>
<tr>
<td>5-8 years:</td>
<td>8</td>
</tr>
<tr>
<td>8-11 years:</td>
<td>8</td>
</tr>
<tr>
<td>11-15 years:</td>
<td>5</td>
</tr>
<tr>
<td>15-20 years:</td>
<td>2</td>
</tr>
</tbody>
</table>

56 Patients: 12.5%

After 10 -11 Years per ear – attack of vertigo diminish greatly
Hearing Outcomes

- 86% fluctuant then progressive
- 14% relentlessly progressive loss

Audiogram Pattern
- Peaked pattern 14% (early years)
- Low tone loss 36%
- Flat 42%
- Ski-slope high tones 8%

- Stabilised often at 65-75 dB

- 5 of the 124 patients ended with profound HL in 1 or 2 ears

After 10 years if hearing 65-75 dB it is more likely to burn out
Bilateral Disease (n=26, 21%)

- Age of onset of first ear
  - Range 15 yrs – 60 years old
  - Mean 40.8 years

- 16% devpd. Bilateral simultaneously or within 2 years
  - Mean age onset 46 yrs

- Natural Hx of 2nd ear follows same time course as Nat. Hx of first ear except in old age
Bilateral Disease – interval to onset of 2\textsuperscript{nd} ear

Duration between onset first and onset 2\textsuperscript{nd} ear
- Range 0 – 33 years
- Mean 8.5 years
- Median 5.5 years

Mean FU of Bilateral patients 18 years.

Duration in Years until onset of second ear

No. patients

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34
• Bilateral Disease risk increased over time

• Bilateral Disease often develops up to 18 years later
Burn Out

• Age 50 - 87 (Mean 67 years)
• Hearing loss > 70 dB - Stage 4
• Had disease for 10 - 18 years

• Can get secondary BPPV
• Can be left with ataxia and chronic disequilibrium
Medical treatments used (I)

- Betahistine 16 mg tds to 32 mg tds
- Bendroflumethiazide 5 mg o.d.

- Acetazolamide (Diamox) — carbonic anhydrase inhibitor
- Glycerol

- Prednisolone or Dexamethasone systemically
Medical treatments used (II)

- Furosemide
- Spironolactone (Aldosterone antagonist)
- iv mannitol
- Nimodipine (Ca channel blocker)
- Vitamin D
- Demeclocycline (tetracycline with ADH blockade effect)
- Etanercept (Anti TNF alpha)
- Methotrexate 7.5 mg / wk
- Sildenafil (Viagra)
Surgery – 45 patients (36%): 75 procedures

- Tympanotomy for Gentamicin or TT-gent 29
- Endolymphatic Sac drainage 30
- Trans-tympanic Dexamethasone 10
- Osseous labyrinthectomies 4
- Vestib. N sections 2
- Grommets for Meniett 2

- Only 1 bilateral patient treated with Gentamicin
- One osseous lab. developed bilateral disease afterwards.
Headline Conclusions – Very Difficult Condition to Understand & Manage

• Ca++ elevated in Endolymph is implicated

• Pathophysiol. of V attacks remain uncertain but massive depolarisation blockade must occur

• The clustering nature of attacks renders the 1995 AAOHNS reporting guidelines flawed potentially even for randomised controlled studies.

• Vertigo attacks are likely to be reduced after 10 years (per ear).

• Full Burn Out occurs within 10-18 years in the age range 50-87 yrs

• Bilateral Disease risk increases over time and often takes 18 years to develop.
References

1. Kato M, Sugiura M, Shimono M, Yoshida T, Otake H, Kato K, Teranishi M, Sone M, Yamazaki M, Naganawa S, Nakashima T. Endolymphatic hydrops revealed by magnetic resonance imaging in patients with atypical Meniere’s disease. Department of Otorhinolaryngology, Nagoya University Graduate School of Medicine, Nagoya, Japan. masahirok@med.nagoya-u.ac.jp

2. Takano S, Iguchi H, Sakamoto H, Yamane H, Anniko M. Blockage pattern of longitudinal flow in Meniere’s disease. Department of Otorhinolaryngology, Osaka City University Graduate School of Medicine, Osaka, Japan.

3. Brown DJ, Chihara Y, Wang Y. Changes in utricular function during artificial endolymph injections in guinea pigs. The Brain and Mind Research Institute, Sydney Medical School, The University of Sydney, 100 Mallett Street, Camperdown 2050, Australia. daniel.brown@sydney.edu.au

4. Miyashita T, Toyama Y, Inamoto R, Mori N. The relationship between vestibular aqueduct diameter and sensorineural hearing loss is linear: a review and meta-analysis of large case series. Department of Otolaryngology, Faculty of Medicine, Kagawa University, Kagawa, Japan. takenori@med.kagawa-u.ac.jp

5. Spencer CR. The relationship between vestibular aqueduct diameter and sensorineural hearing loss is linear: a review and meta-analysis of large case series. Department of Head and Neck Surgery, St George’s Hospital, London, UK. drcbekaspencer@doctors.org.uk

6. Gacek RR. A perspective on recurrent vertigo. Department of Otolaryngology, Head and Neck Surgery, University of Massachusetts Medical School, Worcester, MA 01655, USA. gacekR@ummc.edu
References 2

- High-dosage betahistine dihydrochloride between 288 and 480 mg/day in patients with severe Menière's disease: a case series.
  - Lezius F, Adrion C, Mansmann U, Jahn K, Stupp M.
  - Department of Neurology, Klinikum Grosshadern, Marchioninistrasse 15, 81377 Munich, Germany. franziska.lezius@med.uni-muenchen.de

- Effect of a fixed combination of nimodipine and betahistine versus betahistine as monotherapy in the long-term treatment of Ménière's disease: a 10-year experience.
  - Monzani D, Bartieri MB, Affendri Cuifelli M, Aggazzotti Cavazza F, Neri V, Presutti L, Genovese F.
  - ENT Clinic, Dept of Head and Neck Surgery, University Hospital of Modena, via Largo del Pozzo 71, Modena, Italy. daniele.monzani@unimore.it

- Effect of thirst challenge on ADH levels in patients with bilateral Menière's disease.
  - Steinbach S, Hundt W, Hamann KF, Werner JA, Mandic R.
  - Department of Otolaryngology, Head and Neck Surgery, University hospital Giessen and Marburg, Campus Marburg, Marburg, Germany. ssteinb@med.uni-marburg.de

- Morphological and functional changes in a new animal model of Ménière's disease.
  - Egami N, Kakiyi A, Sakamoto T, Takeda T, Hyodo M, Yamasoba T.
  - Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan.

- Estrogen-Related Receptor β/NR3B2 Controls Epithelial Cell Fate and Endolymph Production by the Stria Vascularis
  - Jichao Chen1 and Jeremy Nathans: Johns Hopkins University School of Medicine, Baltimore

- Cochlin expression in vestibular endorgans obtained from patients with Meniere's disease.
  - Calzada AP, Lopez IA, Beltran Parrazal J, Ishiyama A, Ishiyama G.
  - Department of Head and Neck Surgery, UCLA School of Medicine David Geffen, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA.

- Ref 13) FAMILIAL MÉNIÈRE'S DISEASE: CLINICAL & GENETIC ASPECTS
  - A W MORRISON, MB ChB FRCS DLO, M E S BAILEY, B.Sc. Ph.D., G A J MORRISON, MA MB.BS FRCS
  - J of Laryngology & Otology. 2009 123: 29-37
References 3

- Surgery for Ménière’s disease.
  - Pullens B, Verschuur HP, van Benthem PP.
  - ENT Surgery, University Medical Centre Utrecht, Utrecht, Netherlands.

- Ref 15
  - BMJ. 2003 December 20; 327(7429): 1459–1461. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

  - Paradis J, Hu A, Parnes LS.
  - Department of Otolaryngology, Head & Neck Surgery, Western, London, Canada.

  - Sanz EM, Christiane ZL, Manuel SJ, Teresa MB, Laura RB, De Guzmán RB, Ricardo SF.
  - *Department of Otolaryngology, University Hospital of Getafe Madrid; and †Department of Otolaryngology, University Hospital Casa de Salud, Valencia, Spain.

  - Effect of transtympanic low-pressure therapy in patients with unilateral Menière's disease unresponsive to betahistine: a randomised, placebo-controlled, double-blinded, clinical trial.
  - Department of Oto-Rhino-Laryngology, Head and Neck Surgery, Ludwig Maximilians University of Munich, Germany. Robert.Guerkov@med.uni-muenchen.de

  - Lateral semicircular canal plugging with endolymphatic sac decompression as new surgical treatment for intractable Méniere's disease.
  - Goto F, Tsutsuki T, Oga H.
  - Department of Otolaryngology, Hino Municipal Hospital, Tokyo, Japan. umifumi@bc5.so-net.ne.jp

  - [Short-term efficacy of semicircular canal occlusion in the treatment of intractable Meniere's disease].
  - [Article in Chinese]
  - Fan ZM, Zhang DG, Han YC, Wang RB.
  - Department of Otorhinolaryngology Head and Neck Surgery, Shandong University, Jinan, China.