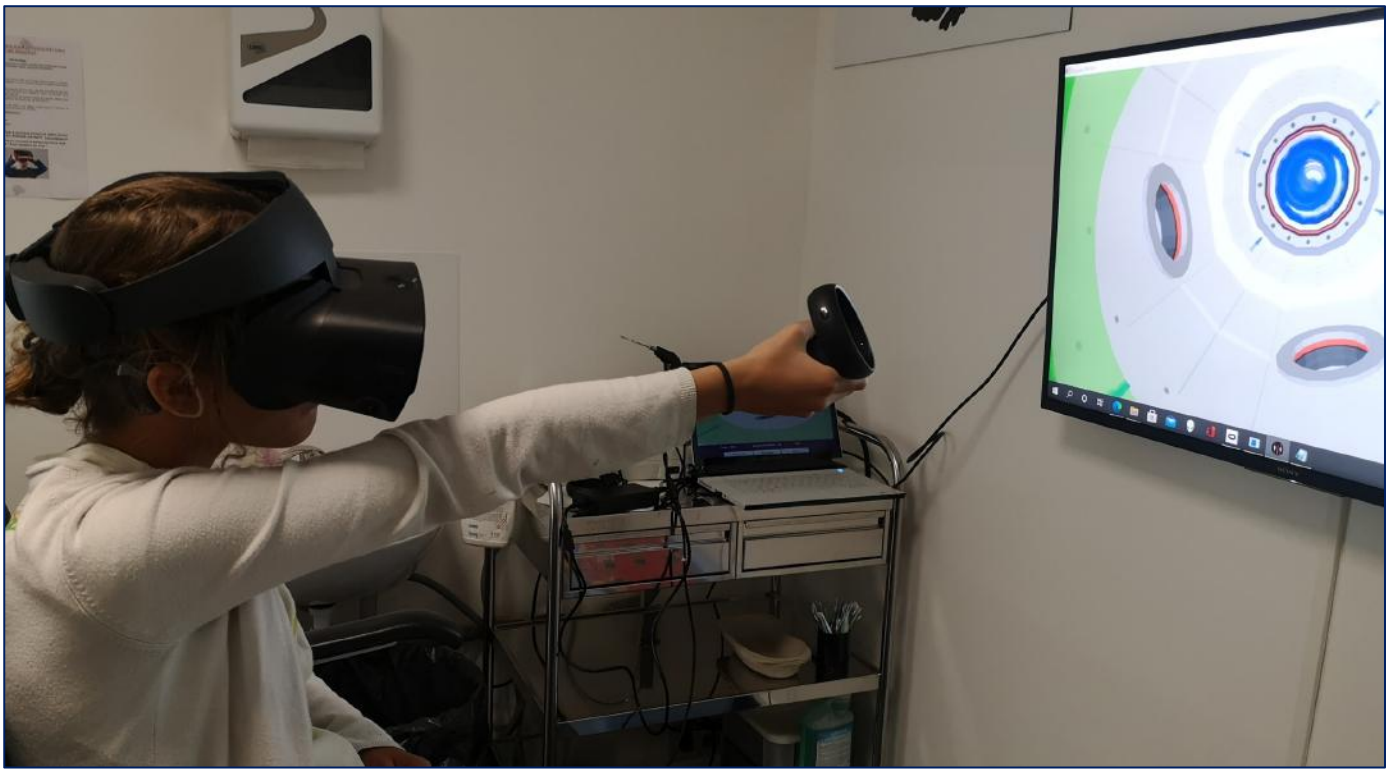
NEWSLETTER



Congenital vestibulopathies

N°3 October – December 2021

Unité GDR 2074

EDITORIAL

➢ François SIMON
PH-universitaire
Hôpital Necker-Enfants Malades
Université de Paris
INCC UMR 8002

➢ Mathieu BERANECK
Research Director CNRS
Université de Paris
INCC UMR 8002

Newsletter 3
Congenital vestibulopathies

Dear colleagues,

We are very happy to take on the role of editors for this 3rd Newsletter of the GDR Vertige! We warmly thank our friend Christian Chabbert for this opportunity to present our GDR Vertige thematic team on congenital vestibulopathies (VesCo).
The objective of the VesCo group is to better characterize the physiological mechanisms and the deficits of multisensory integration associated with congenital vestibular deficits. It associates research teams working on the inner ear, child development and the development of innovative therapies; and hospital services specialising in the management of vestibular pathologies, particularly in children. The GDR Vertige is also seeking to broaden its reader base by offering for the first time a French and English version of the Newsletter!

Have a good reading!

gdrvertige.com/team/pathologies-cochleo-vestibulaires-congenitales/

CONTENTS

Impact of congenital vestibulopathy on child development

The auditory system has always attracted a great interest and research efforts. Up to recently the importance of the vestibular system, in comparison, received relatively scant attention. In fact, vestibular dysfunction leads to one of the most common complaints in medicine, dizziness and/or vertigo, affecting 15–35% of the general population [1-4].

❑ A Maudoux[1,2], J Housset[1], S Wiener Vacher[1], A El-Amraoui[2]

1. Service d'ORL, Hôpital Robert Debré, APHP, Université de Paris, Paris, France.
2. Unité Déficits Sensoriels Progressifs, Pathophysiologie et Thérapie, Institut Pasteur, Institut de l'Audition, INSERM UMRS-1120, Sorbonne Université, Paris, France

In the pediatric population (from 3 y.o. to adolescence), the prevalence of dizziness and/or vertigo has been evaluated by national questionnaires to range from 5.3% to 8% [5, 6]. These numbers are probably underestimated as young children tolerate dizziness better than adolescents and adults. In specialized pediatric vestibular clinic, the prevalence of vestibular dysfunction in children addressed for dizziness/vertigo ranges from 20% to 36.5% [7, 8]. The prevalence of vestibular impairment in children and individuals with sensorineural hearing loss (SNHL) is high, ranging between 20 and 70 percent [9-12]. Study demonstrated that while 50% of children candidate for cochlear implantation had some sort of vestibular dysfunction, up to 20% had a complete bilateral vestibular impairment [11].

Over the last 20 years, the increasing awareness of the actual importance of the vestibular system fueled substantial work that shed light on the multifaceted contributions by the vestibular system.

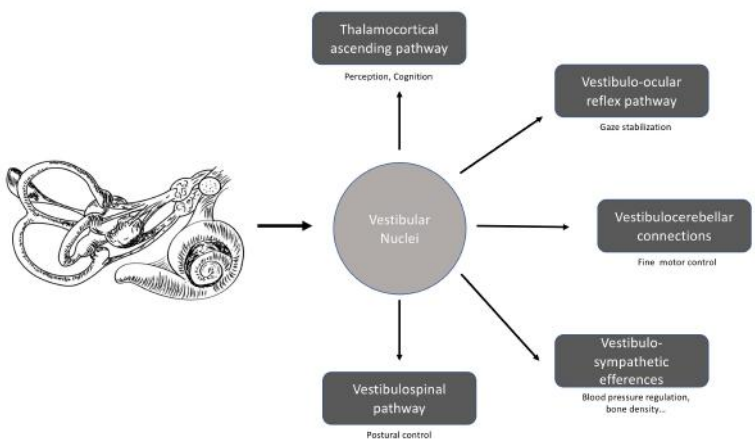


Figure 1: The vestibular system activity supports numerous functions from gaze stabilization and postural control to high-level cortical functions and neurovegetative functions.

Impact of congenital vestibulopathy on child development

The vestibular system activity indeed supports numerous functions from gaze stabilization and postural control to high-level cortical functions involving spatial cognition, including self-body perception, verticality perception, orientation, navigation, and spatial memory [13-17]. At the brainstem and mesencephalic levels, the vestibular organs also influence postural blood pressure regulation, bone density and muscle composition via specific vestibulo-sympathetic efferences [18] and have been shown to act as a powerful synchronizer of circadian rhythms, and a key player in sleep-awake cycles [19] (**figure 1**). Complete vestibular deficit in children can therefore lead to numerous consequences: delayed acquisition of the stages of verticalization, delayed independent walking, repeated falls, impact on the perception of self and space (difficulties in establishment of one's position relative to others in space and surrounding environment, dysfunctional body representation, inaccurate body orientation), laborious construction of their body axis representation (which may explain why certain children with complete vestibular loss are clumsy, with disturbed fine motor control or identified as dyspraxic, dysgraphic and dyslexic), dynamic visual instability with associated reduced visual acuity during movements (impacting playground gaming, reading, sport).

In children, timely detection of vestibular dysfunction is crucial to provide parental counselling and start adequate vestibular rehabilitation in order to limit the effect of vestibular deficit on the child development. Tools to provide clinical measures of vestibular function are available and can provide a considerable amount of information regarding peripherical vestibular defects in children. Evaluation of the vestibular functions during clinical examinations should be more systematic and thorough, to allow accurate appreciation of the real spectrum of vestibular dysfunction in children and their impact. Some recent initiatives have been made in this direction; Belgium has implemented a vestibular infant screening test for hearing impaired children [20, 21] and the French society of Otorhinolaryngology (SFORL) recommends a vestibular assessment for each child ahead of cochlear implantation in its latest guidelines on pediatric cochlear implantation [22]. Systematic vestibular testing should always be proposed in case of hearing loss or delayed posturomotor development. A complete vestibular assessment can be easily performed even in young children (<1 y.o.) and, if possible, should include evaluation of both canal function (at 3 head velocities: bithermal caloric test, evaluation of the vestibulo-ocular reflex (VOR – rotational chair) and video head impulse test (HIT)) and otolithic function (cervical and ocular vestibular evoked myogenic potentials) (**figure 2**). Regarding the impact of vestibular deficit in children, it is known that bilateral loss of vestibular function at birth or early in life results in motor developmental delays [15], but little is known about the impact of vestibular loss on cognitive development in children [17, 23]. There is a crucial need for investigation on the potential impact of vestibular loss on the development of respective spatial and non-spatial cognitive processes. Especially since, similar to the "critical periods" observed for auditory system development, other cognitive functions may have limited developmental windows and that vestibular deficit early in life may have long life repercussion.

Impact of congenital vestibulopathy on child development

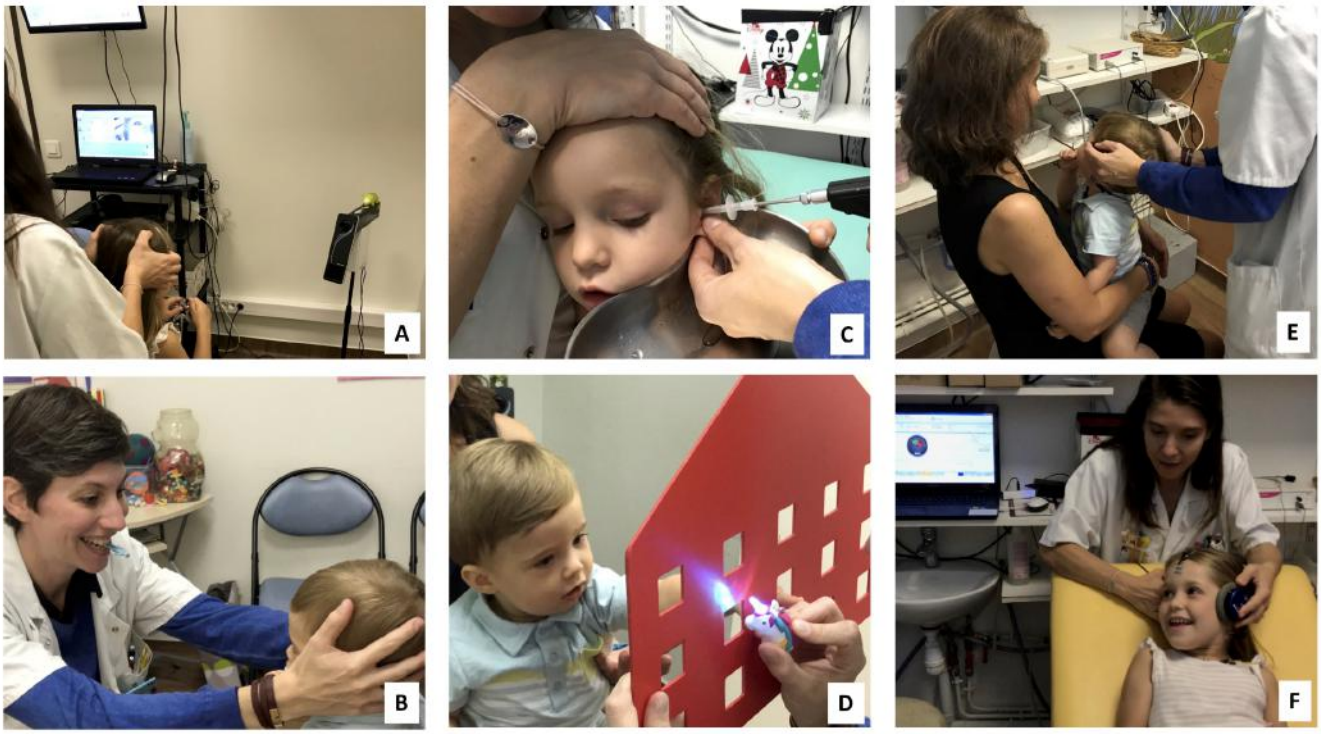


Figure 2: A complete vestibular assessment can be easily performed in clinic even in young children. ***A-B*** *(Video) Head Impulse Test;* ***C*** *Bithermal caloric test;* ***D*** *Study of oculomotricity;* ***E-F*** *Cervical vestibular evoked myogenic potentials.*

For more information:

1. Yardley, L., et al., Prevalence and presentation of dizziness in a general practice community sample of working age people. Br J Gen Pract, 1998. 48(429): p. 1131-5.
2. Gopinath, B., et al., Dizziness and vertigo in an older population: the Blue Mountains prospective cross-sectional study. Clin Otolaryngol, 2009. 34(6): p. 552-6.
3. Mendel, B., J. Bergenius, and A. Langius-Eklöf, Dizziness: A common, troublesome symptom but often treatable. J Vestib Res, 2010. 20(5): p. 391-8.
4. Wiltink, J., et al., Dizziness: anxiety, health care utilization and health behavior--results from a representative German community survey. J Psychosom Res, 2009. 66(5): p. 417-24.
5. Li, C.M., et al., Epidemiology of Dizziness and Balance Problems in Children in the United States: A Population-Based Study. J Pediatr, 2016. 171: p. 240-7.e1-3.
6. Humphriss, R.L. and A.J. Hall, Dizziness in 10 year old children: an epidemiological study. Int J Pediatr Otorhinolaryngol, 2011. 75(3): p. 395-400.
7. Wiener-Vacher, S.R., J. Quarez, and A.L. Priol, Epidemiology of Vestibular Impairments in a Pediatric Population. Semin Hear, 2018. 39(3): p. 229-242.
8. Sommerfleck, P.A., et al., Balance disorders in childhood: Main etiologies according to age. Usefulness of the video head impulse test. Int J Pediatr Otorhinolaryngol, 2016. 87: p. 148-53.
9. Sokolov, M., et al., Vestibular and balance function is often impaired in children with profound unilateral sensorineural hearing loss. Hear Res, 2019. 372: p. 52-61.
10. Cushing, S.L., et al., Evidence of vestibular and balance dysfunction in children with profound sensorineural hearing loss using cochlear implants. Laryngoscope, 2008. 118(10): p. 1814-23.
11. Jacot, E., et al., Vestibular impairments pre- and post-cochlear implant in children. Int J Pediatr Otorhinolaryngol, 2009. 73(2): p. 209-17.
12. Selz, P.A., et al., Vestibular deficits in deaf children. Otolaryngol Head Neck Surg, 1996. 115(1): p. 70-7.
13. Brandt, T., et al., Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans. Brain, 2005. 128(Pt 11): p. 2732-41.
14. Lopez, C., The vestibular system: balancing more than just the body. Curr Opin Neurol, 2016. 29(1): p. 74-83.
15. Wiener-Vacher, S.R., R. Obeid, and M. Abou-Elew, Vestibular impairment after bacterial meningitis delays infant posturomotor development. J Pediatr, 2012. 161(2): p. 246-51.e1.
16. Rine, R.M. and J. Braswell, A clinical test of dynamic visual acuity for children. Int J Pediatr Otorhinolaryngol, 2003. 67(11): p. 1195-201.
17. Ray, C.A. and K.D. Monahan, The vestibulosympathetic reflex in humans: neural interactions between cardiovascular reflexes. Clin Exp Pharmacol Physiol, 2002. 29(1-2): p. 98-102.
18. Martin, T., et al., Exploration of Circadian Rhythms in Patients with Bilateral Vestibular Loss. PLoS One, 2016. 11(6): p. e0155067.
19. Martens, S., et al., Vestibular Infant Screening - Flanders: The implementation of a standard vestibular screening protocol for hearing-impaired children in Flanders. Int J Pediatr Otorhinolaryngol, 2019. 120: p. 196-201.
20. Martens, S., et al., Vestibular Infant Screening (VIS)-Flanders: results after 1.5 years of vestibular screening in hearing-impaired children. Sci Rep, 2020. 10(1): p. 21011.
21. Simon, F., et al., Guidelines (short version) of the French Society of Otorhinolaryngology (SFORL) on pediatric cochlear implant indications. Eur Ann Otorhinolaryngol Head Neck Dis, 2019. 136(5): p. 385-391.
22. Wiener-Vacher, S.R., D.A. Hamilton, and S.I. Wiener, Vestibular activity and cognitive development in children: perspectives. Front Integr Neurosci, 2013. 7: p. 92.
23. Lacroix, E., et al., Neuropsychological profiles of children with vestibular loss. J Vestib Res, 2020. 30(1): p. 25-33.

Ontogeny of human locomotion: Newborn prone skateboarding

❑ Vincent Forma, Marianne Barbu-Both
INCC, CNRS UMR 8002 Université de Paris

BACKGROUND AND OBJECTIVE:

The advent of bipedal walking is an essential step in a child's development. However, walking on two legs is not the only way for a child to get around. Long before bipedal walking, most infants begin to walk on all fours. Adults themselves retain the ability to move in a quadrupedal manner by coordinating arms and legs, for example when crawling, climbing or swimming. In fact, even bipedal walking is a quadrupedal activity, which researchers have demonstrated by observing coordinated muscle contractions between the arms and legs. This quadrupedal activity of walking is thought to result from the stimulation of a network of neurons located in the cervical (for the arms) and lumbar (for the legs) spinal cord. When and how does this quadrupedal organisation, essential for future bipedal walking, emerge during the child's development? Should we wait until the child starts to walk on all fours at around 8-10 months of age? Or is it possible that this quadrupedal network is already functional from the child's birth even in a primitive form? How can this question be studied when the newborn on its stomach has great difficulty moving, crushed by the weight of gravity and unable to lift its head, its arms being blocked under the weight of its body?

Ontogeny of human locomotion: Newborn prone skateboarding

METHOD:
To answer this question, we built a mini skateboard, the Crawliskate, on which the newborn is placed on his or her stomach and secured by a fastening system. Thanks to the sloping shape of the Crawliskate, the head and trunk of the newborn are slightly elevated, allowing the arms to move freely. The child can also move in all directions thanks to the wheels on the bottom of the skate. We then tested 60 2-day-old full-term infants in two different randomly ordered conditions: (i) either lying on a mattress without any assistance (Mattress condition), (ii) or lying on the mini skateboard (Crawli condition). Using simultaneous 2D and 3D recording of leg and arm movements, we then analysed the number and characteristics of these movements and their coordination. If newborns were already able to move using a quadrupedal system by coordinating arms and legs, we hypothesised that we should observe this in the Crawli condition but not in the Mattress condition.

RESULTS:
This is indeed what we found. In the Crawli condition, analyses of the number and types of limb movements and their characteristics, co-activation of limb pairs and distance travelled revealed that neonates are able to use their arms and legs to propel themselves with locomotor patterns similar to those described for quadrupedal locomotion in animals and adult humans. In contrast, left alone on a mattress and without the assistance of the Crawliskate, newborns are unable to move their arms and propel themselves, due to the weight of their head and trunk.

CONCLUSIONS :
This finding challenges the tendency to study newborns as if they were bipedal and suggests instead that all forms of locomotion, including bipedal walking, may be organised in a quadrupedal fashion with neural networks already functional at birth. We propose that humans are born quadrupedal and develop bipedal skills later, both through progressive changes in their anatomy, linked to maturation and experience, and through their practice of locomotion in a variety of different contexts. This proposal has very important implications, although they still need to be experimentally verified, for the design of interventions for infants at risk of locomotor delay. Indeed, to accelerate the onset of independent walking, our study suggests that such interventions might be more effective if we stimulate quadrupedal locomotion from the first months of life.

Reference:
Forma V., Anderson D.I., Provasi J. , Soyez E., Martial M., Huet V., Granjon L., Goffinet F., Barbu-Roth M. (2019). What does prone skateboarding in the newborn tell us about the ontogeny of human locomotion? *Child Development*, 90 (4), 1286–1302. DOI: 10.1111/cdev.13251

Cytomegalovirus: the first non-genetic cause of congenital vestibular disorder

Congenital cytomegalovirus (cCMV) infection is the leading infectious cause of developmental and neurological disabilities and sensorineural hearing loss (SNHL) in children[1]. Although SNHL is well-described in cCMV infections, affecting 21% to 33% of children depending on the symptomatic status at birth[2], few publications have assessed vestibular disorders induced by cCMV. These studies suggest that the prevalence of vestibular disorders is probably underestimated despite the consequences of vestibular loss on the psychomotor development of these children[3,4].

❑ E. Chebib[1], A. Maudoux[1], N. Teissier[1,2]

1. Service d'Otorhinolaryngologie, Hôpital Robert Debré, Assistance Publique Hôpitaux de Paris (APHP), Université de Paris, Paris, France
2. Université de Paris, UMR1141, Equipe NeuroDev, INSERM co-tutelle, Paris, France.

Histological studies suggest a particular viral tropism for the inner ear of the CMV where the lesions are particularly intense in the secretory structures of the inner ear, such as the stria vascularis in the cochlea and the dark cells in the vestibule (Figure 1). Vestibular lesions were systematically more frequently observed than cochlear lesions in histopathological studies[5].
To illustrate the importance of vestibular impairment, a complete hearing and vestibular (bithermal caloric test, video head impulse test and cervical vestibular evoked myogenic potential) assessments were performed in our tertiary center in 130 children with cCMV infection (median age of 21 months).

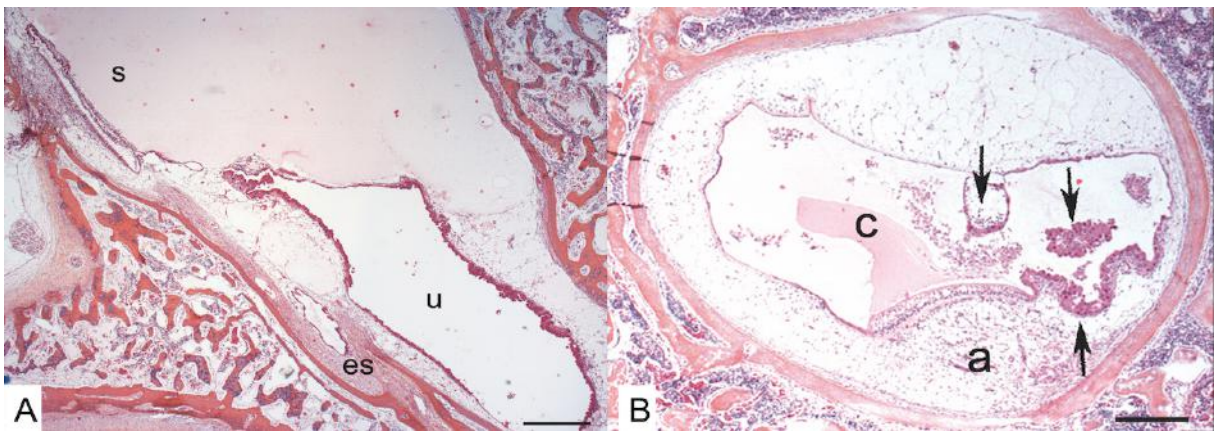


Figure 1. Histopathological sections of vestibular lesions of a fetopathological sample. (A) Low magnification of the vestibule containing the saccule (s) and utricule (u); the endolymphatic sac (es) is located below the utricule. The majority of the epithelial cells of the utricule and saccule are cytomegalic cells containing CMV inclusion bodies (HES). (B) The semicircular canal and crista ampullaris (a) covered by the cupula (c) are shown.

Cytomegalovirus: the first non-genetic cause of congenital vestibular disorder

Eighty-three children (64%) showed an inner ear impairment (both cochlear and vestibular). The vestibular part of the inner ear was significantly more frequently impaired than the cochlear part (p =0.003). The vestibular assessment showed a canal function disorder in 67 children (88%) and an otolith function disorder in 63 children (83%) (non-significant difference). For the children with inner ear impairment who passed the hearing-screening test at birth (n = 36), vestibular disorders were later found in 35 children (97%) and 17 of them (47%) developed hearing loss secondarily.

This underlines the importance of vestibular evaluation in the follow-up of CMV-infected children associated with hearing assessment (article submitted).

These results are supported by other recent studies which confirmed the association between hearing loss and vestibular impairment, highlighting the importance of vestibular assessment in cCMV-infected children and suggesting a higher proportion of damage in the vestibular part than in the cochlear part of the inner ear6,7.

Although less described than cCMV-induced SNHL because of the difficulty of performing a complete vestibular assessment in children younger than 1 year of age, cCMV infection is a major cause of vestibular impairment in children8. Early detection and prolonged auditory and vestibular follow-up (from 6 months of age to at least 5 years-old) of children with cCMV infection is a priority in order to limit neurosensory sequelae.

To go further:

1. Cannon MJ. Congenital cytomegalovirus (CMV) epidemiology and awareness. *J Clin Virol Off Publ Pan Am Soc Clin Virol*. 2009;46 Suppl 4:S6-10. doi:10.1016/j.jcv.2009.09.002
2. Foulon I, Naessens A, Foulon W, Casteels A, Gordts F. A 10-year prospective study of sensorineural hearing loss in children with congenital cytomegalovirus infection. *J Pediatr*. 2008;153(1):84-88. doi:10.1016/j.jpeds.2007.12.049
3. Wiener-Vacher SR, Obeid R, Abou-Elew M. Vestibular impairment after bacterial meningitis delays infant posturomotor development. *J Pediatr*. 2012;161(2):246-251.e1. doi:10.1016/j.jpeds.2012.02.009
4. Bernard S, Wiener-Vacher S, Van Den Abbeele T, Teissier N. Vestibular Disorders in Children With Congenital Cytomegalovirus Infection. *Pediatrics*. 2015;136(4):e887-895. doi:10.1542/peds.2015-0908
5. Teissier N, Delezoide A-L, Mas A-E, et al. Inner ear lesions in congenital cytomegalovirus infection of human fetuses. *Acta Neuropathol (Berl)*. 2011;122(6):763-774. doi:10.1007/s00401-011-0895-y
6. Dhondt C, Maes L, Rombaut L, et al. Vestibular Function in Children With a Congenital Cytomegalovirus Infection: 3 Years of Follow-Up. *Ear Hear*. 2020;42(1):76-86. doi:10.1097/AUD.0000000000000904
7. Pinninti S, Christy J, Almutairi A, Cochrane G, Fowler KB, Boppana S. Vestibular, Gaze, and Balance Disorders in Asymptomatic Congenital Cytomegalovirus Infection. *Pediatrics*. 2021;147(2):e20193945. doi:10.1542/peds.2019-3945
8. Wiener-Vacher SR, Quarez J, Priol AL. Epidemiology of Vestibular Impairments in a Pediatric Population. *Semin Hear*. 2018;39(3):229-242. doi:10.1055/s-0038-1666815

Cochlear implantation and vestibular function in the toddler

❑ Marine Parodi[1], François Simon[1,2], Natalie Loudon[1]
1. Hôpital Necker-Enfants Malades, APHP, Paris
2. INCC, CNRS UMR 8002 Université de Paris

➢ The development of vestibular function assessment in children followed the development of cochlear implantation (CI) in paediatrics in the late 1990s. The study of the vestibule in paediatrics then developed in France under the impetus in particular of Dr Sylvette Wiener Vacher. The appearance of new vestibular exploration tools such as the Video Impulse Test (VHIT) and the Myogenic Otolithic Potentials (MOEP) also made the assessment of young children more accessible.

In parallel with the development of knowledge about the CI, new knowledge about its influence on vestibular function has emerged.

Numerous studies have shown a modification of vestibular function following CI with results that vary greatly from one study to another (from 0% to 71% depending on the study).

Canal function could vary from 0 to 77% on caloric tests (1)(2). Otolith function could also be modified, in particular saccular function (3).

A recent study at Necker Hospital showed that among 71 patients included, 15 patients (21%) had a deterioration of saccular otolith function (PEOM) and 13 patients (18.3%) had a deterioration of canal function (VHIT and/or caloric tests).

In the multivariate analysis, this study found a statistically significant positive correlation between increasing age at implantation and the risk of degradation of vestibular function ($p=0.037$), i.e. the younger a patient is operated on, the lower the risk of degradation of vestibular function, this data is supported by the literature.

Cochlear implantation and vestibular function in the toddler

At a time when the French ENT Society (SFORL) recommends early cochlear implantation before 12 months of age in cases of severe to profound bilateral deafness, bilateral implantation (simultaneous or sequential bilateral depending on the habits of each implantation team) as well as a vestibular assessment prior to each implantation, two challenges are imposed on cochlear implantation teams (4).

- The first is the need for a reliable pre- and post-implant vestibular assessment in infants from the age of 6 months onwards, with the need to adapt the investigation techniques in order to reconcile a child-friendly assessment with one that is sufficiently robust to assess the vestibular function of young children (5). It requires a bright and welcoming environment, the use of varied, bright and colourful visual targets. The use of tablets can also help to improve the child's cooperation and visual fixation. For the assessment to be successful, the choice of tests must be relevant and must start with the tests that are least difficult for babies and their parents, such as the clinical assessment, the VHIT or the PEOM.

- The second challenge for paediatric CI teams and their surgeons is to preserve as much vestibular function as possible during surgery. Surgical techniques have been adapted (insertion of the electrode bundle through the round window rather than through a cochleostomy), as well as the equipment used (development of thin, less traumatic electrodes). Finally, the development of a robotic tool (Robotol®) allowing a slow and very progressive insertion of the electrode, already used in adults and in the process of being applied to children in a few French hospitals, including the Necker Hospital.

References:
1. Cushing S, Papsin B. Cochlear Implants and Children with Vestibular Impairments. Semin Hear. août 2018;39(03):305-20.
2. Fina M, Skinner M, Goebel JA, Piccirillo JF, Neely JG. Vestibular Dysfunction after Cochlear Implantation: Otology & Neurotology. mars 2003;24(2):234-42.
3. Tien H-C, Linthicum FH. Histopathologic Changes in the Vestibule after Cochlear Implantation. Otolaryngol Head Neck Surg. oct 2002;127(4):260-4.
4. Simon F, Roman S, Truy E, Barone P, Belmin J, Blanchet C, et al. Guidelines (short version) of the French Society of Otorhinolaryngology (SFORL) on pediatric cochlear implant indications. European Annals of Otorhinolaryngology, Head and Neck Diseases. oct 2019;136(5):385-91.
5. Cushing SL, Papsin BC. Special Considerations for the Pediatric Patient. In: Lea J, Pothier D, éditeurs. Advances in Oto-Rhino-Laryngology [Internet]. S. Karger AG; 2019 [cité 19 sept 2021]. p. 134-42. Disponible sur: https://www.karger.com/Article/FullText/490282

The vestibule in inner ear research: insights from mouse models for cochleovestibular deficits

❑ Saaid Safieddine[1], Aziz El-Amraoui[2]
1. Technologies et thérapie génique pour la surdité, Institut Pasteur, Institut de l'Audition, INSERM UMRS-1120, Paris, France
2. Déficits Sensoriels Progressifs, pathophysiologie et thérapie, Institut Pasteur, Institut de l'Audition, INSERM UMRS-1120, Paris, France

The inner ear, whose origin dates to more than 500 million years, was initially composed of only a gravitational organ to sense gravity, then motion and balance (Delmaghani & El-Amraoui 2020). As a key player during the evolution of sound-based communication and language, the auditory system has attracted much of interest and research over the last few decades.

The growing awareness of the role played by the vestibular system in daily life has recently fueled increasing efforts to better discriminate and understand the multiple contributions of the vestibular system. Untreated loss of vestibular function will be greatly disabling for humans in many ways, ranging from gaze stabilization and postural control to high-level cortical functions involving self-body perception, verticality perception, orientation, navigation and spatial memory. Thus, total, or partial loss of vestibular function will have a dramatic socio-economic impact on quality of life and health care systems worldwide.

Over the last twenty years, the generation and the characterization of animal models has been at the core of research on inner ear disorders, aiming to: i) understand how the sensory sub-organs develop and function; ii) elucidate the molecular, cellular, and physiological mechanisms underlying the inherited or acquired sensory disorders; iii) develop and implement accurate diagnostic tools; and iv) evaluate and validate effective rehabilitation and/or treatment strategies to prevent and/or restore sensory deficits (Delmaghani & El-Amraoui 2020).
Of note, most current knowledge on vestibular disorders come from investigations originally initiated to understand the mechanisms underlying the deafness caused by a given defective gene. To date, about 130 genes responsible for non-syndromic deafness and about 300 genes responsible for syndromic forms (defects of the inner ear and other organs) have been identified (http://hereditaryhearingloss.org/). Mouse models exist for most of these identified genes in humans (Delmaghani & El-Amraoui 2020, Safieddine *et al.* 2012). In an ongoing analysis of published, and publicly accessible, clinical and research datasets, we found that the number of genes in humans for which deafness is associated with a vestibular phenotype is largely underestimated (Maudoux *et al.* 2021).

The vestibule in inner ear research: insights from mouse models for cochleovestibular deficits

Redundancy and visual and proprioceptive compensation mechanisms could mitigate the dysfunction of the vestibular organs, making difficult their detection during clinical examinations in human patients. In such context, animal models, amenable to invasive analyses, help provide additional and more in-depth information on vestibular functions, even in the absence of overt balance deficits. Thanks to ongoing international collaborative programs to model and phenotype potential diseases for all human genes, the number of mutant mice with auditory and balance/vestibular deficits will continue to increase significantly (see Bowl M *et al.* 2017, Potter P *et al.* 2016); http://www.mousephenotype.org/; https://www.mousephenotype.org/). These mouse models are available to researchers worldwide. We expect that their study using dedicated vestibular experimental tools should lead to a better understanding of the properties and peculiarities of the vestibular organs.

In this context, within our teams, recently set at the Institut de l'Audition (https://www.institut-audition.fr/fr), we have implemented experimental protocols for a more systematic and full investigation of auditory and vestibular functions. Different behavioral tests are routinely used to quantify vestibular functions: (i) Observation of the mouse behavior, including mouse tendency to circle "circling" or permanent head bobbing "head bobbing"; this can be complemented by video tracking analysis of exploratory behavior "open field test"; (ii) trunk curl test , (iii) "contact righting"; (iv) platform test, or v) swim test (see Dulon D *et al.* 2018, Emptoz A *et al.* 2017 , Michel V *et al.* 2017). To further monitor vestibular functions, a collaboration was established with François Simon and Mathieu Beraneck (University of Paris) to investigate the vestibulo-ocular reflex in mice, in response to specific rotation of the turntable.

In addition, in collaboration with Pierrick Bordiga and Paul Avan (Institut de l'Audition, and Université Clermont-Auvergne), we sought direct measurements of peripheral vestibular function using recordings of the vestibular compound action potentials in the vestibular neurons in response to a linear acceleration of animal head. Collected datasets are used for comparative analyses of response thresholds, peak amplitudes, and peak-to-peak latencies, providing more accurate metric values to document the sensitivity of the vestibular macular organs. These experimental protocols are being used in ongoing work on Usher syndrome type 1, characterized by profound deafness associated with severe balance disorders that are followed by progressive retinitis pigmentosa leading to blindness. As in Usher 1G patients, mice deficient for the Sans gene, *Ush1g*$^{-/-}$, show profound deafness and a bilateral vestibular dysfunction. These deficits have been ascribed to early onset disorganization and dysfunction of the mechanoelectrical transduction apparatus of auditory and vestibular hair cells, the hair bundle (Geleoc & El-Amraoui 2020).

The vestibule in inner ear research: insights from mouse models for cochleovestibular deficits

Viral transfer at birth, through the round window membrane, of cDNA (complementary DNA) encoding normal Sans protein to the inner ear hair cells in *Ush1g*$^{-/-}$ mice restores the structure of auditory and vestibular sensory cells and sustainably restores balance function in these mice (Calvet C *et al.* 2018, Emptoz A *et al.* 2017). Measurements of vestibulo-ocular responses in treated mice showed full recovery of semicircular canal and otolith organ activity (Calvet C *et al.* 2018, Emptoz A *et al.* 2017). In the utricle, scanning electron microscopy analyses show that the staircase pattern arrangement of the stereocilia that compose the hair bundle is comparable to that of wild-type mice (Emptoz A *et al.* 2017). Similar work is ongoing using mouse models of Usher syndrome type 3 (Dulon D *et al.* 2018, Dunbar LA *et al.* 2019), characterized by late-onset, progressive hearing loss, and variable degrees of severity and progression of vestibular deficits. Ongoing findings help understand how clarin proteins can substitute for one another in the vestibular and hearing organs.

Altogether, ongoing research in animal models is essential to provide insights into the precise understanding of the evolution, development, physiology, and behavior outcomes of the vestibular system. Findings will also pave the way for better diagnostic tools and a precise and accurate definition and classification of vestibular disorders. Thanks to recent encouraging results, efforts are now being developed to implement gene therapies for the curative treatment of certain forms of cochlear and vestibular disorders in humans. Together, these discoveries will help guide patient management and the search for therapeutic avenues through the study of the effective therapeutic window, optimal route of therapeutic agents' administration, safety, efficacy, and long-term stability of treatment solutions (Delmaghani & El-Amraoui 2020, Geleoc & El-Amraoui 2020).

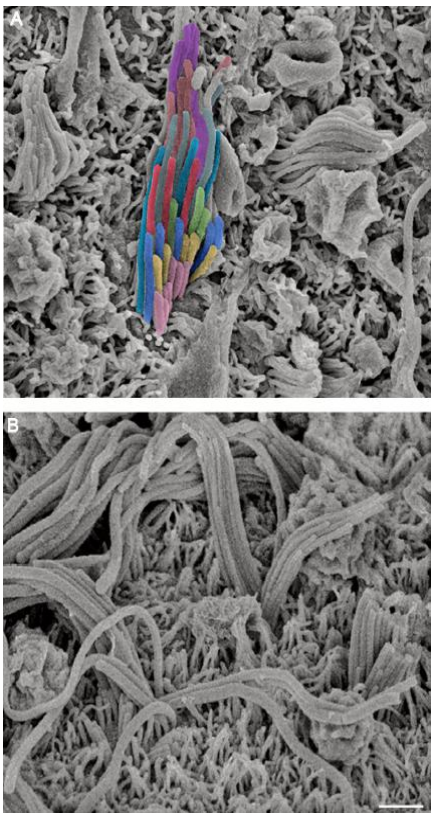


Figure: Scanning electron microscope image of vestibular ciliary tufts from wild-type (A) and Ush1G model mice (B).
Note the complete disorganisation of the stereocilia from the vestibule of the Ush1G mouse. Adapted from Empotz et al. 2017.

References:

Bowl MR, Simon MM, Ingham NJ, Greenaway S, Santos L, et al. 2017. A large scale hearing loss screen reveals an extensive unexplored genetic landscape for auditory dysfunction. *Nat Commun* 8: 886

Calvet C, Lahlou G, Safieddine S. 2018. [Gene therapy progress: hopes for Usher syndrome]. *Med Sci (Paris)* 34: 842-48

Delmaghani S, El-Amraoui A. 2020. The inner ear gene therapies take off: current promises and future challenges. *J. Clin. Med.* 9: 2309-36

Dulon D PS, Patni P, Cortese M, Vincent PF, Tertrais M, Emptoz A, Tlili A, Bouleau Y, Michel V, Delmaghani S, Aghaie A, Pepermans E, Alegria-Prevot O, Akil O, Lustig L, Avan P, Safieddine S, Petit C, El-Amraoui A. 2018. Clarin-1 defect results in a rescuable auditory hair cell synaptopathy in mice. *J. Clin. Invest.* 128: 3382-401

Dunbar LA PP, Aguilar C, Mburu P, Corns L, Wells HR, Delmaghani S, Parker A, Johnson S, Williams D, Esapa CT, Simon MM, Chessum L, Newton S, Dorning J, Jeyarajan P, Morse S, Lelli A, Codner GF, Peineau T, Gopal SR, Alagramam KN, Hertzano R, Dulon D, Wells S, Williams FM, Petit C, Dawson SJ, Brown SD, Marcotti W, El-Amraoui A, Bowl MR. 2019. Clarin-2 is essential for hearing by maintaining stereocilia integrity and function. *EMBO Mol. Med.* 11: e10288.

Emptoz A, Michel V, Lelli A, Akil O, Boutet de Monvel J, et al. 2017. Local gene therapy durably restores vestibular function in a mouse model of Usher syndrome type 1G. *Proc Natl Acad Sci U S A*

Geleoc GSG, El-Amraoui A. 2020. Disease mechanisms and gene therapy for Usher syndrome. *Hear. Res.* Mar 4:107932

Maudoux A, Vitry S, El-Amraoui A. 2021. Vestibular deficits in deafness: clinical presentation, animal modeling and treatment solutions *Front. Neurol.* in preparation

Michel V BK, Patni P, Cortese M, Azaiez H, Bahloul A, Kahrizi K, Labbé M, Emptoz A, Lelli A, Dégardin J, Dupont T, Aghaie A, Oficjalska-Pham D, Picaud S, Najmabadi H, Smith RJ, Bowl MR, Brown SD, Avan P, Petit C, El-Amraoui A. 2017. CIB2, defective in isolated deafness, is key for auditory hair cell mechanotransduction and survival. *EMBO Mol Med.* 9: 1711-31

Potter PK, Bowl MR, Jeyarajan P, Wisby L, Blease A, et al. 2016. Novel gene function revealed by mouse mutagenesis screens for models of age-related disease. *Nat Commun* 7: 12444

Safieddine S, El-Amraoui A, Petit C. 2012. The auditory hair cell ribbon synapse: from assembly to function. *Annu Rev Neurosci* 35: 509-28

Vestibular exploration of the mouse: models of human pathology

❑ **François Simon[1,2], Mathieu Beraneck[2]**
1. Hôpital Necker-Enfants Malades, APHP, Paris
2. INCC CNRS UMR 8002 Université de Paris

Behavioural study of vestibular syndrome in mice

Vestibular syndrome in mice leads to oculomotor, postural-locomotor, cognitive (spatial orientation) and vegetative (salivation - rodents cannot vomit) symptoms. Behavioural studies focus on the observation of postural-locomotor and cognitive symptoms.

Following an acute and brutal vestibular lesion, the mouse will present intense symptoms that will diminish until they are completely compensated a few weeks after the lesion [1]. The most intense sign is tumbling, when the mouse repeatedly rolls to the side ipsilateral to the lesion. Hypotonia of the hemibody ipsilateral to the lesion, ipsilateral torticollis, circling (repeated circular locomotor movements), head bobbing and loss of swimming ability can also be observed.

In mouse models of congenital vestibular dysfunction, the symptoms are less severe. Swimming analysis remains an important element to distinguish between severe and moderate deficits (immediate, delayed drowning, circling swimming and head tilt). An analysis of the behaviour of the mouse suspended by the tail and in particular the falling behaviour is interesting: a normal mouse will have a tendency to have an extended trunk while looking for support and to fall on its legs.

A mouse with a vestibular deficit is rather flexed on itself during tail suspension and the fall reception is poor [2]. Other tests can be used, such as a video-tracking analysis of the number of circling movements performed during a 120 second period or a balance analysis by positioning the mouse on a small 7 x 7 cm platform and counting the number of falls during 60 seconds [3].

Although these behavioural tests are very easy to implement, they are not specific and are difficult to quantify accurately. Only vestibular exploration by video-oculography allows a fine and specific analysis of the vestibular system of the mouse.

Vestibular exploration of the mouse: models of human pathology

Vestibular exploration in the mouse

For the precise study of vestibular function in mouse models, it is possible to impose movements on the mouse in all planes of space, and thus to specifically stimulate the semicircular canals or the otolith system. The vestibular stimulations are coupled to a video-oculography system which allows the measurement and quantification of the vestibulo-ocular reflex; this system constitutes the most precise functional test used in research as well as in the clinic (table 1).

Videonystagmography is first recorded without stimulation in the dark and in the light to report the direction and number of spontaneous nystagmus per minute. Then different stimuli are applied to analyse the different functional aspects of the vestibulo-ocular reflex.

Tableau 1: Différents réflexes vestibulaires analysés chez la souris

Stimulation	Réflexe analysé	Mesure	Fonction analysée	Equivalent chez l'Homme
Rotation sinusoïdale dans le plan horizontal	aVOR	Gain et phase	Canal semi-circulaire horizontal	SHA sur fauteuil rotatoire
Off-vertical axis rotation (OVAR)	$_{OVAR}$MOR	Biais	Intégrité du système otolithique, canalaire et central	OVAR sur fauteuil rotatoire
Inclinaison statique de la tête en roulis (static roll head tilt)	$_{tilt}$MOR	Gain (position verticale oculaire sur l'angle d'inclinaison de la tête)	Système otolithique surtout utricule	vOCR
Rotation impulsionnelle dans le plan horizontal (hsteps)	velocity storage	Constante de temps et gain	Intégrité du système canalaire et central	Rotation impulsionnelle sur fauteuil rotatoire

L'ensemble de ces tests se font à tête fixe et dans le noir

Vestibular exploration of the mouse: models of human pathology

Vestibular exploration in the mouse

Specifically, mice are vigorously fixed thanks to headposts so as to horizontalize the lateral semi-circular canals on a table [4], in order to perform videonystagmography (Figure 1). The lateral semi-circular canals can be studied from the angular vestibulo-ocular reflex during table rotation movements at different amplitudes or frequencies. The otolith system can also be studied from a continuous rotation of the table in an inclined axis (OVAR - Off-Vertical Axis Rotation) and more particularly the utricular system by studying the vertical movement of the pupils during a static lateral tilt of the head.

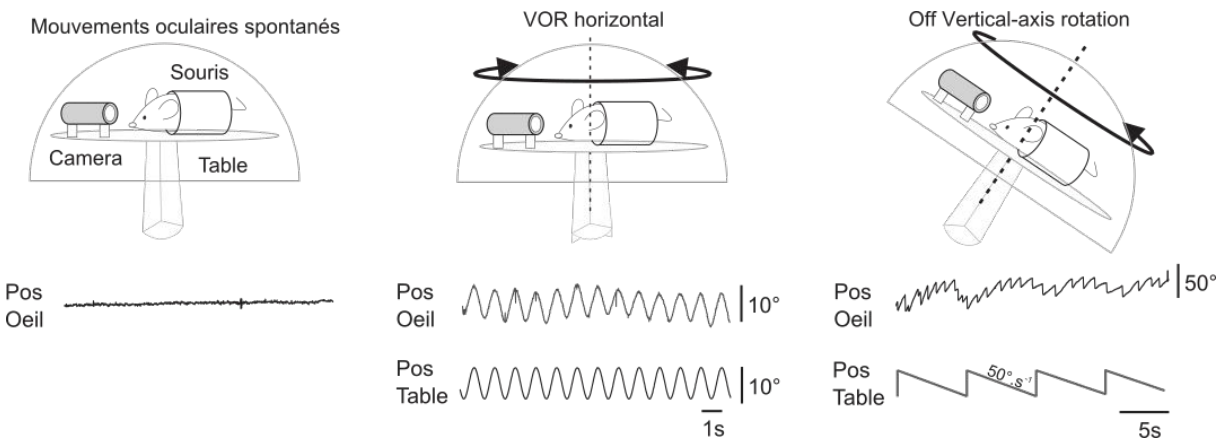


Figure 1 : Mesures des mouvements oculaires spontanés, VOR et OVAR pour une souris normale. Lors du VOR, la table oscille à une fréquence et amplitude donnée. Lors de l'OVAR la table fait plusieurs rotations. Le gain est calculé en comparant la position de l'œil par rapport à celle de la table

References

1. Simon, F., Pericat, D., Djian, C., Fricker, D., Denoyelle, F., Beraneck, M., 2020. Surgical techniques and functional evaluation for vestibular lesions in the mouse: unilateral labyrinthectomy (UL) and unilateral vestibular neurectomy (UVN). J Neurol. https://doi.org/10.1007/s00415-020-09960-8

2. Cassel, R., Bordiga, P., Carcaud, J., Simon, F., Beraneck, M., Le Gall, A., Benoit, A., Bouet, V., Philoxene, B., Besnard, S., Watabe, I., Pericat, D., Hautefort, C., Assie, A., Tonetto, A., Dyhrfjeld-Johnsen, J., Llorens, J., Tighilet, B., Chabbert, C., 2019. Morphological and functional correlates of vestibular synaptic deafferentation and repair in a mouse model of acute onset vertigo. Dis Model Mech 12. https://doi.org/10.1242/dmm.039115

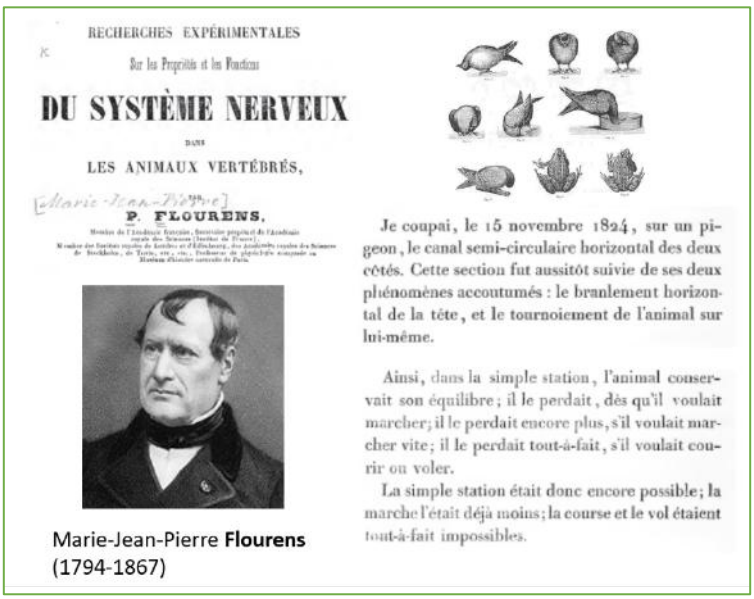
3. Emptoz, A., Michel, V., Lelli, A., Akil, O., Boutet de Monvel, J., Lahlou, G., Meyer, A., Dupont, T., Nouaille, S., Ey, E., Franca de Barros, F., Beraneck, M., Dulon, D., Hardelin, J.P., Lustig, L., Avan, P., Petit, C., Safieddine, S., 2017. Local gene therapy durably restores vestibular function in a mouse model of Usher syndrome type 1G. Proceedings of the National Academy of Sciences of the United States of America 114, 9695–9700. https://doi.org/10.1073/pnas.1708894114

4. Beraneck, M., Cullen, K.E., 2007. Activity of vestibular nuclei neurons during vestibular and optokinetic stimulation in the alert mouse. J. Neurophysiol. 98, 1549–1565. https://doi.org/10.1152/jn.00590.2007

The toad, the chicken and congenital vestibulopathies

❑ **Mathieu Beraneck**
INCC CNRS UMR 8002 Université de Paris

The vestibular system appeared in vertebrates about 450 million years ago. The vestibular organs of the inner ear have been particularly well preserved since then: the anatomy and neurophysiology of these organs is shared by most fish, amphibians, birds and mammals. It was in the pigeon and the frog that a French biologist named Flourens, in a report to the Académie des Sciences in 1824 (Flourens, 1824), first described the existence of balance organs in the inner ear.


RECHERCHES EXPÉRIMENTALES

Sur les Propriétés et les Fonctions

DU SYSTÈME NERVEUX

DANS

LES ANIMAUX VERTÉBRÉS,

P. FLOURENS,

Je coupai, le 15 novembre 1824, sur un pigeon, le canal semi-circulaire horizontal des deux côtés. Cette section fut aussitôt suivie de ses deux phénomènes accoutumés : le branlement horizontal de la tête, et le tournoiement de l'animal sur lui-même.

Ainsi, dans la simple station, l'animal conservait son équilibre ; il le perdait, dès qu'il voulait marcher ; il le perdait encore plus, s'il voulait marcher vite ; il le perdait tout-à-fait, s'il voulait courir ou voler.

La simple station était donc encore possible ; la marche l'était déjà moins ; la course et le vol étaient tout-à-fait impossibles.

Marie-Jean-Pierre **Flourens**
(1794-1867)

This conservation is essential for fundamental research, as it allows researchers to work on different species in order to better understand the physiopathological mechanisms that affect humans. Two examples illustrate the contribution of these animal models to the understanding of congenital deficits.

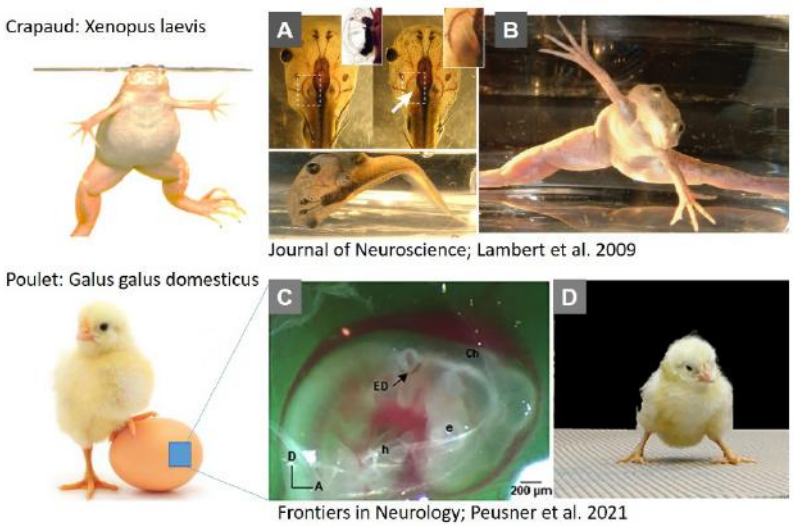
The first concerns studies carried out on the xenopus, a species of amphibian. During its development, this animal grows first as a larva and then, via metamorphosis, transforms into an adult toad.

In the early 2010s, a research team based in Paris (Lambert et al., 2009, 2013) showed that a unilateral lesion of the inner ear in the xenopus larva (Panel A), led to an abnormal development of the skeleton of the toad which was affected by scoliosis (Panel B).

These experiments demonstrated the causal link between the abnormal development of the vestibular system and the consequences on the musculoskeletal systems. Since then, many teams working on scoliosis patients have confirmed the existence of vestibular system abnormalities (Shi et al., 2011; Woo et al., 2019).

The toad, the chicken and congenital vestibulopathies

In collaboration with a team from the University of Washington, we began developing another model in 2014: the chicken (Lilian et al., 2019; Seal et al., 2019). The interest of the model lies in the possibility of carrying out manipulations in the egg and thus very early during embryonic development (Panel C). It is possible to intervene early on in the otic capsule (which will give rise to the inner ear) and thus to disrupt the development of the vestibular organs, for example by changing the orientation of the organ (Lilian et al., 2019), leading to the development of an inner ear with malformations reminiscent of those of many congenital pathologies (Peusner et al., 2021).



Due to their unique characteristics, these animal models allow us to understand the ontogeny of the vestibular system, as well as the functional consequences (Panel D) of malformations acquired early during development. They make it possible to identify pathophysiological cellular mechanisms, and in this respect constitute a hope for the understanding of congenital vestibular deficits.

Pour approfondir

Flourens, P. (1824). *Recherches expérimentales sur les propriétés et les fonctions du système nerveux, dans les animaux vertébrés.* Paris: Crevot.

Lambert, F. M., Malinvaud, D., Glaunès, J., Bergot, C., Straka, H., and Vidal, P.-P. (2009). Vestibular asymmetry as the cause of idiopathic scoliosis: a possible answer from Xenopus. *J. Neurosci. Off. J. Soc. Neurosci.* 29, 12477–12483. doi:10.1523/JNEUROSCI.2583-09.2009.

Lambert, F. M., Malinvaud, D., Gratacap, M., Straka, H., and Vidal, P.-P. (2013). Restricted neural plasticity in vestibulospinal pathways after unilateral labyrinthectomy as the origin for scoliotic deformations. *J. Neurosci. Off. J. Soc. Neurosci.* 33, 6845–6856. doi:10.1523/JNEUROSCI.4842-12.2013.

Lilian, S. J., Seal, H. E., Popratiloff, A., Hirsch, J. C., and Peusner, K. D. (2019). A New Model for Congenital Vestibular Disorders. *J. Assoc. Res. Otolaryngol. JARO* 20, 133–149. doi:10.1007/s10162-018-00705-z.

Peusner, K. D., Bell, N. M., Hirsch, J. C., Beraneck, M., and Popratiloff, A. (2021). Understanding the Pathophysiology of Congenital Vestibular Disorders: Current Challenges and Future Directions. *Front. Neurol.* 12, 1585. doi:10.3389/fneur.2021.708395.

Seal, H. E., Lilian, S. J., Popratiloff, A., Hirsch, J. C., and Peusner, K. D. (2019). Implementing the chick embryo model to study vestibular developmental disorders. *J. Neurophysiol.* 122, 2272–2283. doi:10.1152/jn.00434.2019.

Shi, L., Wang, D., Chu, W. C. W., Burwell, G. R., Wong, T.-T., Heng, P. A., et al. (2011). Automatic MRI segmentation and morphoanatomy analysis of the vestibular system in adolescent idiopathic scoliosis. *NeuroImage* 54, S180–S188. doi:10.1016/j.neuroimage.2010.04.002.

Woo, E. J., Siegmund, G. P., Reilly, C. W., and Blouin, J.-S. (2019). Asymmetric Unilateral Vestibular Perception in Adolescents With Idiopathic Scoliosis. *Front. Neurol.* 10, 1270. doi:10.3389/fneur.2019.01270.

The audiology research network: a platform for clinical vestibular research in children

❑ Géraldine Visentin[1], François Simon[2,3], Natalie Loundon[2]
1. Centre de Recherche en Audiologie (CReA)
2. Hôpital Necker – Enfants Malades, APHP, Paris
3. INCC, CNRS UMR 8002 Université de Paris

Deafness is a societal issue because it affects a very large number of human beings: according to the WHO 466 million people, including 34 million children, have a disabling hearing impairment.

To date, there is no curative treatment for sensorineural deafness, but the development of in vitro research (carried out on a micro-organism, organ or cell or outside its natural context) and in vivo research (carried out on animals) suggests that innovative treatments could be developed in the near future.

In September 2019, a clinical research partnership agreement signed between the Fondation Agir pour l'Audition and the Assistance Publique-Hôpitaux de Paris led to the creation of 2 Audiology Research Centres, selected on the basis of clinical excellence:

The **Pediatric Audiology Research Centre,** located at the Necker Hospital, directed by Dr Natalie Loundon;
The **Adult Audiology Research Centre**, located at La Pitié-Salpêtrière Hospital, directed by Dr Isabelle Mosnier.

The development of these centres and their operation is made possible thanks to the financial support of the Fondation Agir pour l'Audition.

These centres constitute a network dedicated to research involving the human being and to the creation of cohorts. It is planned that this network, directed by Professor Françoise Denoyelle, will be expanded by the recruitment of other French centres, always selected on the basis of excellence in audiology research. Coordination of the various research projects and protocols will be set up within this network.

The audiology research network: a platform for clinical vestibular research in children

The missions of the Audiology Research Centres

The missions of the Audiology Research Centres are :
To refine the diagnosis and to understand the different physiological mechanisms at the origin of the forms of deafness;
To enable the validation of tools for early detection and diagnosis;
To promote translational research with the development of innovations for the audiological and genetic exploration of deafness;
To accelerate the development of new therapeutic solutions by conducting clinical trials on treatments (such as intra-cochlear or general therapies) and also on medical devices (such as new categories of hearing aids and implants).

Hearing assessment

Hearing can be analysed by so-called "objective" tests performed without the patient's active participation and by so-called "subjective" tests requiring his or her participation. In all tests, sound stimulation is performed and the responses to this stimulation are recorded.

Objective tests include Auditory Evoked Potentials (AEP), Electrocochleography (EcoG), Auditory Steady State Responses (ASSR), and Acoustic Emissions (AEO). They are performed during a child's nap or with a quiet child.

Subjective tests include the tonal or vocal audiogram (using either words or phrases), complex audiometry (tests in noise and spatial localisation), and stereophonic hearing exploration. These tests require the child to participate to give a response ("I hear") or that there is time to observe real auditory reactions in the youngest child.

Depending on the location of the impairment, the following are defined
Conductive hearing loss, which is the result of damage to the external auditory canal, the eardrum or the ossicles. They can be of slight or moderate degree and do not exceed 60-70 dB of hearing loss.
Sensorineural hearing loss, which is the result of a malfunction of the inner ear or the auditory nerve. All degrees of deafness may exist. The treatment modalities depend on the degree of deafness and, in children, on the impact on language.

The audiology research network: a platform for clinical vestibular research in children

Vestibular testing

The vestibulometry room is equipped with a rotating chair.
In particular, the VideoNystagmoGraphy (VNG), the Skull Vibration-Induced Nystagmus Test (SVINT), caloric tests (air and water), the Video Head Impulse Test (vHIT), the subjective vertical test, the measurement of saccular and utricular otolithic evoked potentials (OEPs), and the dynamic posturography (EquiTest) can all be performed.

Vestibular tests can be adapted to the child. In young children, it is quite usual for the child to sit on the attendant's lap to facilitate the test.

Some tests can only be performed from a certain age:
- 3 months for vHIT
- 3 months for saccular auditory evoked potentials (AEP)
- 3 years for ocular OEPs

The Paediatric Audiology Research Centre (Paris)

The Paediatric Audiology Research Centre is located within the Necker-Enfants malades Hospital. It is supported by the presence of the Audiophonology-Cochlear Implant Department of the ENT Department which is a reference in France and internationally in the field of deafness.

The expertise of the Necker ENT department is renewed thanks to the volume of patients consulted each year: more than 5,000 patients in the audiology sector, a vast paediatric cochlear implant programme in France (170 implants/year - the largest in France), more than 500 ear microsurgeries/year and a cohort of 700 children followed up for severe malformation of the external ear (aplasia)

This ENT department has been labelled as a Reference Centre for Rare Diseases for "Rare ENT Malformations" (CRMR MALO) since 2007 and has been attached to the CRMR "Genetic Deafness", coordinated by Dr Sandrine Marlin, a specialist geneticist, since 2004.

The Paediatric Audiology Research Centre (Paris)
What are the research areas of the Necker Paediatric Centre?

Research axis 1: Exploration of central auditory processing
Research area 2: Vestibular exploration
Research area 3: Complex hearing
Research area 4: Specific pathologies and orphan diseases

VIRTUAL REALITY: FROM SPACE TO WORK

❑ Salma Jbyeh[1], François Simon[2,3] Michele Tagliabue[3]

1. Etudiante Master 2 20/21, Université Paris Saclay, interne en ORL
2. Hôpital Necker-Enfants Malades, APHP
3. Ingénieur de recherche, INCC, CNRS UMR 8002 Université de Paris

Virtual reality is a promising technology with various diagnostic and therapeutic applications in the medical field. Thanks to the possibility of actively exploring the virtual environment, it allows a complete immersion of the patient and a precise manipulation of sensory inputs. Thanks to its playful and enjoyable aspect, it offers the possibility of rebuilding the relationship between patients and their pathology. In order to study multisensory integration in healthy adults, the « spatial orientation » team of the Integrative Neuroscience and Cognition Center (INCC) of the Joint Research Unit 8002 of the CNRS has developed experimental protocols using virtual reality in laboratory conditions as well as in microgravity conditions (experiments in parabolic flights and on board the International Space Station).

The ReViCHILD study uses these protocols to better understand multisensory integration in children with and without chronic vestibular disorder.

L'astronaute français Thomas Pesquet portant un casque de réalité virtuelle dans le cadre de l'expérience GRASP réalisée à bord de la station spatiale internationale

VIRTUAL REALITY: FROM SPACE TO WORK

J. McIntyre and M. Tagliabue worked with the European Space Agency by setting up two experiments : GRASP and PILOTE. The GRASP experiment aims to understand how the central nervous system integrates informations from the visual, somatosensory and vestibular systems to coordinate movements of grasping and gripping of the hand. The PILOTE experiment, in which French Astronaut Thomas Pesquet is currently participating, studies how these concepts can be applied to the design of new workstations, more suitable to spacial ergonomics. Since the start of 2021, a collaboration contract was signed between the CNRS, the Assistance Publique des Hôpitaux de Paris (APHP) and the « Fondation pour l'Audition », in order to carry out clinical research between the INCC and the Audiology Research Center (CReA). It's in this context that ReViCHILD study started in April 2021. It's a pilot, prospective, controlled, non-randomized, and monocentric study. Its main objective is to develop a well-tolerated and reproductible virtual reality protocol to study eye-hand coordination in children with and without chronic vestibular disorder. Two groups of children, from 7 to 18 years old, are studied : a « control » group without a history of vestibular or otological pathology and a « vestibular deficit » group. In the « vestibular deficit » group, children are included if they have a chronic unilateral or bilateral vestibular disorder. The non-inclusion criteria are the presence of an ophtalmological, neurological or osteoarticular pathology that may interfere with the virtual reality protocol. The participants undergo a vestibular examination including a Video-Head-Impulse-Test, Vestibular-evoked myogenic potentials and the evaluation of the subjective visual vertical. The virtual reality protocol was built in the form of a video game and consists of performing a task of aligning the hand with a target presented visually or kinesthetically.

VIRTUAL REALITY: FROM SPACE TO WORK

The virtual environment was designed to look like the inside of a space station, which children must protect by shooting a robot (target). Subjects memorize and reproduce the orientation of the target after a delay. Some tasks are performed with visual scene suppression, tilted head or visual conflict. The primary outcome is the degree of precision of children with and without chronic vestibular deficit in these different sensory conditions and the weight given to each sensory input. Thanks to the results of ReViCHILD study, virtual reality could become a diagnostic tool that would allow fun and safe characterization of vestibular deficits in the pediatric population.

ReViCHILD study uses a virtual reality device (A) consisting of a virtual reality headset and a controller adapted to the participant's dominant hand. The virtual reality environment (B) is a cylindrical tunnel designed to look like the inside of a space station, which the participant must protect by shooting a robot.

Vestibular atelectasis…. A myth come true

❑ Charlotte Hautefort[1], Michael Eliezer[2]
1. ORL, Hôpital Lariboisière, APHP, Paris
2. Radiologue, Hôpital Lariboisière, APHP, Paris

In 1988, Merchant and Schuknecht described for the first time "vestibular atelectasis" (1). Vestibular atelectasis was initially observed on post mortem histological sections. It corresponds to the collapse of the endolymphatic structures of the pars superior (utricle and ampulla).

Until now, there was no way to confirm this "in vivo" and atelectasis was progressively forgotten (2). Since the development of imaging of the inner ear with late protocol, morphological analysis of the endolymphatic space is made possible (3,4). It allows to visualize an increase in volume of the endolymphatic space as in hydrops (5,6) or its collapse as in atelectasis (7-10).

Recently, two studies have identified the profiles of patients with vestibular atelectasis. It manifests itself either in a unilateral form (figure 1) (7,8), mimicking a fluctuating unilateral vestibular deficit, or in a bilateral form (figure 2) (9,10), resulting in bilateral vestibular areflexia.

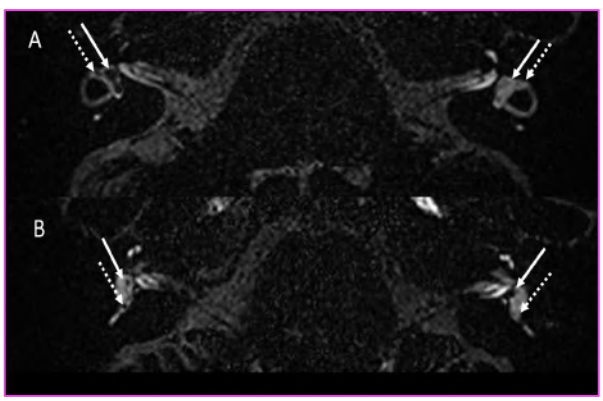


Figure 1 : Patient (male, 43 years old) with a left canalar and utricular deficit associated with a left vestibular atelectasis on the MRI A/ Axial 3D-FLAIR at the level of the upper part of the vestibule where the entire lateral canal semi-circular canal is displayed. The left utricle (white arrow) and lateral ampulla (white dotted arrow) are collapsed compared to the right side. B/ Axial 3D-FLAIR at the level of the lower part of the vestibule, left and right saccule are normal (white arrow) on left side the posterior ampulla (white dotted arrow) is collapsed compared to the right side

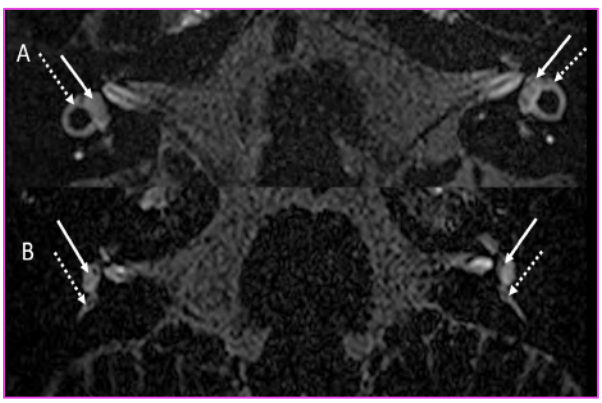


Figure 2 : Patient (female, 53 years old) with a bilateral canalar and utricular deficit associated with a bilateral vestibular atelectasis on the MRI A/ Axial 3D-FLAIR at the level of the upper part of the vestibule where the entire lateral canal semi-circular canal is displayed. Bilateral utricle (white arrow) and lateral ampulla (white dotted arrow) are collapsed. B/ Axial 3D-FLAIR at the level of the lower part of the vestibule demonstrating a bilateral normal saccule (white arrow) while the left and right posterior ampulla (white dotted arrow) are almost collapsed.

Vestibular atelectasis…. A myth come true

Marc and al were able to describe precisely the radio-clinical and electrophysiological presentation of this entity looking into 22 patients with unilateral atelectasis on imaging (8).

In their study, the average age of the affected population at the time of diagnosis was 58.6 +/- 13.7 years with slightly more men than women (R=1.44). As mentioned by Merchant and Shucknecht, the disease onset could take two forms: most often via an acute or sub-acute vestibular syndrome (73%), and more rarely in the form of progressive instability (27%).

The symptoms following this onset evolved in a fluctuating manner with periods of instability and/or recurrent positional vertigo (41%) for the whole population studied. Some of them also described some auditory symptoms on the affected side such as tinnitus or a sensation of fullness in the ear (54%) and in 9% of the cases a Tullio was reported. When vestibular investigations were performed, abolition of responses to utricular potentials on the affected side seemed to be the most consistent feature of this condition (90%) associated with canal involvement at high velocities of one (36%), two (23%) or three (41%) canals. As expected, saccular function was preserved (77%). On the auditory side, 40% had reached an auditory asymmetry on the affected side.

In bilateral forms, the same dissociated vestibular function impairment was found associating a deficit targeting the canal and utricular sensors and preserving the saccular function (10).

This "dissociated" impairment observed on the electrophysiological level is completely consistent with the morphological impairment, affecting the pars superior (utricle and ampulla) visible on MRI and described by Shucknecht on histology (1,11,12).

Interestingly, it seems that a large proportion of idiopathic bilateral vestibular areflexia may ultimately be secondary to a previously unrecognized bilateral vestibular atelectasis. Eliezer and al found 50% vestibular atelectasis on imaging in a group of patients followed for idiopathic bilateral vestibular areflexia (n=42) (10).

Vestibular atelectasis…. A myth come true

For now, the pathophysiology of vestibular atelectasis is unknown. A dysfunction of the Blast valve could be one of the hypotheses (13).

Another hypothesis is the dysfunction of dark cells, the equivalent of cochlear marginal cells involved in endolymphatic homeostasis. Nkcc1, a Na+ K+ 2Cl co-transporter present in both dark cells and marginal cells could be involved in this case.

Indeed, in his work Hibino H and Kurachi described a bilateral vestibular areflexia with vestibular endolymphatic collapse associated with auditory function disorders in Nkcc1-KO mice(14).

To read more:

1. Merchant SN, Schuknecht HF (1988) Vestibular atelectasis. Ann Otol Rhinol Laryngol 97(6):565–576. https://doi. org/10.1177/000348948809700601
2. Maslovara S, Butkovic-Soldo S, Pajic-Matic I, Sestak A (2018) Vestibular atelectasis: Decoding pressure and sound-induced nystagmus with bilateral vestibulopathy. Laryngoscope. https://doi. org/10.1002/lary.27724
3. Eliezer M, Poillon G, Gillibert A et al (2018) Comparison of enhancement of the vestibular perilymph between gadoterate meglumine and gadobutrol at 3-Tesla in Meniere's disease. Diagn Interv Imaging 99(5):271–277. https://doi.org/10.1016/j. diii.2018.01.002
4. Kahn L, Hautefort C, Guichard J et al (2019) Relationship between video head impulse test, ocular and cervical vestibular evoked myogenic potentials, and compartmental magnetic resonanceimaging classifcation in menière's disease. Laryngoscope. https ://doi.org/10.1002/lary.28362
5. Eliezer M, Maquet C, Horion J, Gillibert A, Toupet M, Bolognini B, Magne N, Kahn L, Hautefort C, Attyé A. Detection of intralabyrinthine abnormalities using post-contrast delayed 3D-FLAIR MRI sequences in patients with acute vestibular syndrome. Eur Radiol. 2019 Jun;29(6):2760-2769. doi: 10.1007/s00330-018-5825-0. Epub 2018 Nov 9. PMID: 30413960.
6. Tagaya M, Yamazaki M, Teranishi M et al (2011) Endolymphatic hydrops and blood–labyrinth barrier in Ménière's disease. Acta Otolaryngol 131(5):474–479. https://doi.org/10.3109/00016 489.2010.534114
7. Eliezer M, Attyé A, Guichard J-P et al (2019) Vestibular atelectasis: myth or reality?: vestibular atelectasis. Laryngoscope 129(7):1689–1695. https://doi.org/10.1002/lary.27793
8. Marc M, Hautefort C, Guichard JP, Herman P, Houdart E, Toupet M, Eliezer M. Clinical characteristics in unilateral vestibular atelectasis. J Neurol. 2021 Feb;268(2):689-700. doi: 10.1007/s00415-020-10220-y. Epub 2020 Sep 9. PMID: 32909094.
9. Eliezer M, Toupet M, Vitaux H et al (2019) MRI evidence of vestibular atelectasis in bilateral vestibulopathy and Tullio phenomenon. Otol Neurotol 40(9):e944–e946. https://doi.org/10.1097/ MAO.0000000000002409
10. Eliezer M, Hautefort C, Van Nechel C, Duquesne U, Guichard JP, Herman P, Kania R, Houdart E, Attyé A, Toupet M. Electrophysiological and inner ear MRI findings in patients with bilateral vestibulopathy. Eur Arch Otorhinolaryngol. 2020 May;277(5):1305-1314. doi: 10.1007/s00405-020-05829-8. Epub 2020 Feb 8. PMID: 32036409.
11. Fujimoto C, Murofushi T, Sugasawa K, Chihara Y, Ushio M, Yamasoba T, Iwasaki S. Bilateral vestibulopathy with dissociated deficits in the superior and inferior vestibular systems. Ann Otol Rhinol Laryngol. 2012 Jun;121(6):383-8. doi: 10.1177/000348941212100604. PMID: 22737960.
12. Rosengren SM, Welgampola MS, Taylor RL. Vestibular-Evoked Myogenic Potentials in Bilateral Vestibulopathy. Front Neurol. 2018 Apr 17;9:252. doi: 10.3389/fneur.2018.00252. PMID: 29719527; PMCID: PMC5913369.
13. Hofman R, Segenhout JM, Buytaert JAN, Dirckx JJJ, Wit HP (2008) Morphology and function of Bast's valve: additional insight in its functioning using 3D-reconstruction. Eur Arch Otorhinolaryngol 265(2):153–157. https://doi.org/10.1007/s0040 5-007-0424-8
14. Hibino H, Kurachi Y (2006) Molecular and physiological bases of the K + circulation in the mammalian inner ear. Physiology 21(5):336–345. https://doi.org/10.1152/physiol.0002 3.2006

GDR Vertige

« Researchers, clinicians and vertigo professionals together to reverse the disease»

Call for Donation - Campaign 2021-2022

« Support the research on vertigo...

.... Make a donation»

- Donate is sure and easy with the CNRS Fondation
- All you have to do is connect to the site http://gdrvertige.com under the Donation Campaign section and to follow the indications
- Thank you for your support!

28-29
Janvier 2022

Saintes-Maries-de-la-Mer

The French Society of Vestibular Physiotherapy (SFKV) is a scientific society which mainly brings together physiotherapists specializing in rehabilitation of vertigo and balance disorders of neurosensory origin. Its objectives are to promote and defend this specificity of physiotherapy.

Read our latest publications:

- Status of rehabilitation of the dizzy patient in France: focus on vestibular physiotherapy. Xavier et al. European Journal of Physiotherapy. 2021
- Rehabilitation of dynamic visual acuity in patients with unilateral vestibular hypofunction: earlier is better Lacour et al. European Archives of ORL. 2020.
- Comparaison of passive rotational testing versus active head mouvements testing. Dumas et al. Poster Congrès APTA 2019, Chicago, USA.

➢ The next SFKV congress will be held on **January 28 and 29, 2021 in Saintes Maries de la Mer** (Camargue). For all information: https://www.sfkv.fr/congrès-2022/

New vestibular algorithm

Fast track your patients

- Focus your consultation on the relevant symptoms
- Reduce the clinical tests performed and save time
- Meet well-prepared patients
- Standardize vestibular services
- Patients perceive less waiting time
- Utilize the clinic's resources effectively

Track treatment outcomes

- Take appropriate measures if necessary
- Increase patient satisfaction
- Collect data
- Analyse your data
- Improve clinical processes
- Reduce waiting lists

Ordre in October
40% discount the first year

DIZZYGUIDE

www.dizzyguide.net - jm@dizzyguide.net - available in multiple language

THE NEWSLETTER

GDR Vertige

Chief editor:

Dr Michel LACOUR
(Aix-Marseille University)

- To be edited January 2022
  On the GDRV web site
  http://gdrvertige.com

N°4 – January - March 2022

Unit GDR 2074

cnrs