FACULTY OF MEDICINE AND HEALTH SCIENCES

The development of a targeted vestibular follow-up protocol for children with a congenital cytomegalovirus infection: data-analysis of 4.5 years of audio-vestibular follow-up

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Abstract

-English-

Objectives: A congenital cytomegalovirus infection (cCMV) is an important cause of neurodevelopmental delay in children. Recently, research has brought to light that cCMV patients are at risk for a vestibular dysfunction (VD). Such paediatric VD could compromise several childhood developmental domains. However, currently clinical awareness for this issue remains limited so that cCMV patients generally do not receive vestibular follow-up. The aim of this study was to provide more insight in the characteristics of cCMV-induced VD and to formulate recommendations regarding a targeted vestibular follow-up protocol.

Methods: 185 patients with a confirmed cCMV diagnosis were subjected to a longitudinal vestibular follow-up study at the Ghent University Hospital. The first vestibular assessment took place around the age of 6 months, follow-up was scheduled around 1, 2, 3, and 4.5 years of age. Patients were on average followed longitudinally for 20.8 months (SD: 16.3 months) and had 1 to 8 vestibular follow-up examinations (mean: 3.2, SD: 1.5).

Results: cCMV-induced VD occurred in 16.2% of the study population. The dysfunction was delayed in onset in 33,3% of the patients with VD. In our study population the oldest patient in whom a dysfunction was found, was 45 months. The VD was unstable (i.e. fluctuating, progressive or improving) in 60.0% of the patients. In 85.7% of the vestibular-impaired ears, both semi-circular canals and otolith organs were affected, and in 5.7% and 8.6% of the vestibular-impaired ears the dysfunction was limited to the semi-circular canals or the otolith organs, respectively. cCMV-induced VD was significantly more prevalent in hearing-impaired patients (51.6%) ($p < 0.001$) and patients with a first trimester seroconversion (27.6%) ($p < 0.001$), compared to normal-hearing patients (9.1%) and patients with a second or third trimester seroconversion (5.3% and 0%), respectively. No statistically significant association between either a symptomatic cCMV-infection or abnormal results on brain imaging, and the occurrence of VD was found ($p = 0.007$, and $p = 0.090$ respectively). The criterion for statistical significance was set at $p < 0.005$ because of Bonferroni correction.

Conclusion: Since cCMV-induced VD is unstable in the majority of the patients and can cause delayed-onset dysfunctions, it is of utmost importance to provide regular, longitudinal vestibular follow-up to cCMV patients. Follow-up is advised until the age of 4 years. To be able to identify both patients with a combined and isolated VD, follow-up should evaluate all five components of the vestibular system. When it is not feasible to follow all cCMV patients, vestibular follow-up should target at least cCMV patients with hearing loss and/or a first trimester seroconversion since they are at higher risk for cCMV-induced VD.

-Nederlands-

Doelstelling: Een congenitale cytomegalovirus infectie (cCMV) is een belangrijke oorzaak van neurologische ontwikkelingsproblemen bij kinderen. Recent onderzoek toonde aan dat cCMV-patiënten een verhoogd risico lopen op het ontwikkelen van een vestibulaire dysfunctie (VD). Dergelijke pediatrische VD kan de ontwikkeling van kinderen hinderen. Tot op heden worden cCMV-patiënten in de klinische praktijk echter nog niet standaard vestibulair opgevolgd en is de kennis van clinici omtrent dit topic eerder beperkt. Het doel van deze studie bestond erin meer inzicht te verwerven in de karakteristieken van cCMV-geïnduceerde VD en aanbevelingen te formuleren omtrent gerichte vestibulaire opvolging van cCMV-patiënten.

Methode: 185 patiënten met een bevestigde cCMV-diagnose werden geïncludeerd in een longitudinale vestibulaire follow-up studie aan het Universitair Ziekenhuis Gent. Het eerste vestibulair onderzoek werd uitgevoerd rond de leeftijd van 6 maanden, opvolgafspraken werden ingepland rond de leeftijd van 1, 2, 3 en 4.5 jaar. Alle patiënten werden gemiddeld 20.8 maanden (SD: 16.3 maanden) opgevolgd en ontvingen 1 tot 8 vestibulaire onderzoeken (gemiddelde: 3.2, SD: 1.5).

Resultaten: cCMV-geïnduceerde VD werd teruggevonden in 16.2% van onze studiepopulatie. De oudste patiënt binnen onze studiepopulatie waarbij een VD werd vastgesteld, was 45 maanden oud. Bij 33.3% van de patiënten met VD was er sprake van een delayed-onset dysfunctie. Daarnaast was de VD onstabiel (i.e. fluctuerend, progressief of verbeterend) bij 60% van de cCMV-patiënten. Hoewel geïsoleerde semi-circulair kanaal dysfuncties en geïsoleerde otolietdysfuncties zich voordeden bij respectievelijk 5.7% en 8.6% van de oren met een VD, werden in 85.7% van de gevallen zowel de semi-circulaire kanalen als het otolietsysteem getroffen. cCMV-geïnduceerde VD kwam significant meer voor bij patiënten met gehoorverlies (51.6%) ($p < 0.001$) en patiënten met een eerste trimester seroconversie (27.6%) ($p < 0.001$), in vergelijking met respectievelijk normaalhorende patiënten (9.1%) en patiënten met een tweede of derde trimester seroconversie (5.3% en 0%). De associatie tussen een symptomatische cCMV-infectie of afwijkingen op medische beeldvorming enerzijds en het voorkomen van een cCMV-geïnduceerde VD anderzijds, was niet statistisch significant (respectievelijk $p = 0.007$, en $p = 0.090$). Het criterium voor statistische significantie werd geplaatst op $p < 0.005$ omwille van Bonferroni correctie.

Conclusie: Daar een cCMV-infectie delayed-onset VD kan veroorzaken en in de meerderheid van de patiënten gekenmerkt werd door een onstabiel karakter, wordt er aangeraden om cCMV-patiënten niet eenmalig te testen maar longitudinaal op te volgen tot de leeftijd van 4 jaar. Om zowel patiënten met een volledige vestibulaire uitval als patiënten met een geïsoleerde dysfunctie te kunnen opsporen, evalueert de vestibulaire testbatterij idealiter alle onderdelen van het vestibulair orgaan. Wanneer niet alle cCMV-patiënten onderworpen kunnen worden aan longitudinale follow-up, dienen op zijn minst cCMV-patiënten met gehoorverlies en/of een eerste trimester seroconversie opgevolgd te worden omdat zij meer risico lopen om een cCMV-geïnduceerde VD te ontwikkelen.

1. Introduction

Cytomegalovirus (CMV) is a member of the *Herpesviridae* family. In immunocompetent patients, an infection with this virus often occurs asymptomatically or with mild mononucleosis-like symptoms (Fowler & Boppana, 2018; Kenneson & Cannon, 2007). However, when a CMV-infection occurs during pregnancy, intra-uterine transmission of the CMV-virus from mother to the foetus can take place, causing a congenital cytomegalovirus (cCMV) infection and putting the foetus at risk for morbidity (Fowler & Boppana, 2018; Kenneson & Cannon, 2007). cCMV-infection is the most common congenital infection worldwide and an important cause of neurodevelopmental delay in infants and children (Fowler & Boppana, 2018; Goderis et al., 2014; Kenneson & Cannon, 2007). In industrialised countries the prevalence of cCMV infection is estimated between 0,5% and 0,7% (Fowler & Boppana, 2018). The risk of intra-uterine transmission is higher in maternal CMV-infections that occur in the second or third trimester of pregnancy, compared to maternal CMV-infections that are contracted during the first trimester of pregnancy (Manicklal et al., 2013). However, children born from mothers who were infected in the first trimester of pregnancy, are more vulnerable to cCMV-induced morbidity (Manicklal et al., 2013). In general, the burden of disease is unpredictable and can differ greatly between patients: some infants show severe morbidity from birth, some children develop sequelae later on in life while others remain completely asymptomatic (Fowler & Boppana, 2018; Kenneson & Cannon, 2007). Of all cCMV-infected children, approximately one out of three have symptoms at birth (symptomatic patients) while two out of three show no visible abnormalities during the perinatal period (asymptomatic patients) (Goderis et al., 2016; Keymeulen et al., 2019; Luck et al., 2017).

Sensorineural hearing loss (SNHL) is one of the most common sequelae of cCMV, approximately 13% of all cCMV-infected children will develop SNHL (Foulon et al., 2019; Fowler & Boppana, 2018). Moreover, cCMV is the leading cause of congenital nongenetic SNHL in the paediatric population (Foulon et al., 2019; Goderis et al., 2014). Typically, hearing loss in cCMV can be congenital as well as delayed in onset, progressive, fluctuating or stable, mild to profound and unilateral as well as bilateral (Goderis et al., 2016). Hearing loss is much more prevalent in symptomatic children: 63% of the symptomatic children will eventually develop SNHL compared to only 8% of the asymptomatic children (Goderis et al., 2016). Children with a symptomatic infection are more likely to have severe hearing losses and are more often diagnosed with bilateral auditory dysfunctions compared to asymptomatic patients who more frequently have unilateral and/or mild hearing loss (Goderis et al., 2016). In addition to this risk factor, other risk factors for cCMV-induced SNHL have been reported. They include, among others, seroconversion during the first trimester of pregnancy (Craeghs et al., 2020; Foulon et al., 2019), abnormalities on brain imaging (Craeghs et al., 2020; Foulon et al., 2019), and abnormalities on clinical examinations (Rivera et al., 2002; Wu et al., 2019). Thus, it is clear that cCMV-induced SNHL has been thoroughly investigated and more insight has been gained in the characteristics and risk factors of cCMV-associated hearing loss. Consequently, clinical awareness is high and adequate auditory follow-up is often provided to cCMV patients until school-age (Foulon et al., 2019).

Taking into account that the peripheral auditory and vestibular end-organs have a close anatomical and embryologic relationship, cCMV could also cause vestibular dysfunction (VD). This assumption is strengthened by histopathological findings of cCMV-induced cytopathic and inflammatory reactions in both cochlear and vestibular structures (Davis et al., 1981; Gabrielli et al., 2013; Strauss, 1990; Teissier et al., 2011). In the cochlea, pathological changes have been found in the stria vascularis and the Reissner's membrane (Teissier et al., 2011). Damage of the vestibular end-organs predominates in the dark cells of the utricle and semi-circular canals (SCC's) (Gabrielli et al., 2013; Teissier et al., 2011). Both cochlear and vestibular histopathological changes appear to mainly concern these structures that regulate the potassium homeostasis of the inner ear (Gabrielli et al., 2013; Teissier et al., 2016). Since potassium homeostasis constitutes an important element of cochleovestibular signal transduction,

cCMV-induced damage of the endolymphatic structures in the cochlea and the vestibulum can explain potential SNHL and VD, respectively (Gabrielli et al., 2013; Teissier et al., 2016). In addition to histopathological research, a limited number of studies has investigated the vestibular function of cCMV patients. A wide range of occurrence rates of cCMV-induced VD has been reported, ranging from 14% to 91% of the cCMV-infected paediatric population (Bernard et al., 2015; Dhondt et al., 2020; Karltorp et al., 2014; Maes et al., 2017; Pappas, 1983; Pinninti et al., 2021). Further research is necessary to estimate the occurrence of VD in the general cCMV population more accurately. A recently published paper by our study group showed an occurrence rate of 14% by an intermediate analysis of 3 years of data collection in a study population that included both symptomatic and asymptomatic children with and without hearing loss (Dhondt et al., 2020). The higher occurrence rates reported by other studies may be explained by the fact that these studies often included only a small number of patients and/or that the majority of the included patients were symptomatic or had SNHL. Although test protocol and study population differed between studies, several authors addressed recurring characteristics of cCMV-induced VD. Hearing-impaired cCMV patients are more likely to be identified with VD than normal-hearing cCMV patients (Bernard et al., 2015; Dhondt et al., 2020; Karltorp et al., 2014; Maes et al., 2017; Zagólski, 2008). However, researchers reported that the severity and the laterality of SNHL and VD are not always concordant with each other (Bernard et al., 2015; Dhondt et al., 2020). Furthermore, VD tends to occur more in symptomatic compared to asymptomatic patients (Dhondt et al., 2020; Maes et al., 2017; Zagólski, 2008). Lastly, it has been suggested that seroconversion during the first trimester of pregnancy possibly increases the risk of VD (Dhondt et al., 2020; Maes et al., 2017). Despite the fact that previous research has uncovered certain trends, the number of studies investigating cCMV-induced VD remains small. Most research was conducted in a small study population, sometimes only including hearing-impaired patients. Test protocols varied and longitudinal follow-up was often not provided. Because of the small amount of studies and the lack of in-depth research, practical guidelines regarding targeted vestibular follow-up of cCMV patients are lacking and clinical awareness of the impact of cCMV on the vestibular system remains limited.

There are a number of reasons why paediatric VD has long been overlooked in research and clinical practice. Vestibular-impaired children often do not report typical vestibular symptoms like vertigo because they have good compensation skills and lack experience and sufficient language proficiency to detect and express abnormal vestibular sensations (Cushing & Papsin, 2018; Weiss & Phillips, 2006). Furthermore, vestibular assessment in the paediatric population is challenging. However, recently several research groups have demonstrated that paediatric vestibular assessment is feasible, provided that the test protocol is adapted to the child's age and that age-appropriate normative data are used (Dhondt et al., 2019; Janky & Rodriguez, 2018; Phillips & Backous, 2002; Verrecchia et al., 2020). At present there is a growing interest in paediatric vestibular function. It is believed that VD can seriously hamper the development of the child, possibly compromising motor development, cognitive development, psychosocial development, and school performance. Firstly, concerning motor development, both gross motor skills (Inoue et al., 2013; Kaga, 1999; Singh et al., 2021) and postural control (De Kegel et al., 2012; Wiener-Vacher et al., 2013) can be affected in vestibular-impaired patients, these difficulties are more pronounced in children with a bilateral dysfunction. Furthermore, VD can impede adequate vestibulo-ocular reflex function, hence hampering gaze stability which is crucial for eye-hand coordination and fine motor skills (Wiener-Vacher et al., 2013). Secondly, the link between bilateral VD and significantly impaired visuospatial cognition has been well-established in the adult population (Bigelow & Agrawal, 2015; Dobbels et al., 2019; Popp et al., 2017). Therefore, it has been suggested that a VD can hamper a child's cognitive development (Janky et al., 2022; Lacroix et al., 2020; Wiener-Vacher et al., 2013). Cognitive difficulties secondary to VD can on the one hand be attributed to altered vestibular projections from the vestibular end-organs throughout the cerebral cortex and subcortex (Hitier et al., 2014; Jacob et al., 2020). On the other hand they can be attributed to the fact that gaze stabilization and postural control no longer occur automatically, therefore requiring more

cognitive resources to maintain balance resulting in fewer cognitive reserve to perform concurrent tasks (McIsaac et al., 2015). Thirdly, vestibular-impaired patients can show anxiety, signs of depression, panic reactions, etc. which was hypothesised to impact the psychosocial development of vestibular-impaired children (Bigelow et al., 2016; Lee et al., 2014). Fourthly, since important prerequisites for reading acuity and other school skills (i.e. gaze stability, postural control, and spatial cognition) can be disturbed in children with a bilateral VD, these children could experience difficulties at school (Braswell & Rine, 2006; Grossman & Leigh, 1990; Smith et al., 2010). Based on a growing body of research that demonstrates the adverse impact of paediatric VD, it seems evident that timely detection and intervention are needed to improve the developmental outcome of the child.

In conclusion, cCMV patients are at risk for VD, which can have an impact on several childhood developmental domains. Hence it is clear that cCMV patients should receive a timely diagnosis, vestibular follow-up, and appropriate therapy to enhance their development. However, contrary to the hearing status, vestibular function is not standardly evaluated and followed in cCMV patients. Ideally, all cCMV patients should receive regular, longitudinal vestibular follow-up. However, such approach is not always feasible in clinical practice. On the one hand, vestibular follow-up of all cCMV patients is often logistically not attainable for reference centra because of the large number of patients. On the other hand, parents can perceive regular vestibular testing as burdensome. A more targeted follow-up of this population is therefore needed. To date, due to the paucity of in-depth research, no clear recommendations regarding an ideal vestibular follow-up protocol have been made. To optimize the follow-up of cCMV patients, research elucidating potential predictive factors and characteristics of cCMV-induced VD is needed. Therefore, since 2016, a prospective longitudinal follow-up study has been initiated at the Ghent University Hospital where vestibular follow-up was provided to a large sample that included both symptomatic and asymptomatic cCMV patients. This masters dissertation aimed to identify risk factors for developing cCMV-induced VD and to formulate recommendations concerning targeted vestibular follow-up of cCMV patients.

2. Method

2.1 Study design

A prospective longitudinal follow-up study was initiated at the otolaryngology department of the Ghent University Hospital and covered the period between June 2016 and November 2021. This study was approved by the local Ethical Committee (EC UZG BC-03014 E06). Informed consent was obtained from the patient's parents prior to participation in accordance with the Declaration of Helsinki.

2.2 Subjects

Two-hundred-seventeen patients with a confirmed cCMV diagnosis who received their first vestibular assessment at Ghent University Hospital before the age of 2 years were included in the study. Seven and five patients were excluded from the study population because no informed consent was obtained or because of additional risk factors for VD [i.e. asphyxia at birth, severe hyperbilirubinemia, toxoplasmosis, and severe hypoxia (> 5 days)], respectively. Additionally, 20 patients were excluded because it was not feasible to obtain at least one reliable vHIT and one reliable cVEMP. The final study population consisted of 185 patients, with a mean age of 38 months (SD 19.4, range: 6 - 80 months) at the end of data collection.

2.3 Procedures

2.3.1 cCMV diagnosis & neonatal follow-up

Patients were enrolled in the study after a confirmed cCMV diagnosis. In Belgium there is no universal neonatal cCMV-screening, but a targeted screening in which newborns are screened for cCMV when they show cCMV-related symptoms in the neonatal period, or because of a known maternal CMV-infection during pregnancy. Whitin the first three weeks of life, this diagnosis was made through polymerase chain reaction (PCR) or viral isolation by culture from saliva or urine. When the patient was older than three weeks of age, a retrospective diagnosis was made through PCR analysis of dried blood spots (Guthrie-card).

cCMV patients received extensive neonatal examinations, including physical examination, laboratory tests, hearing evaluation, brain imaging, and fundoscopy as described by Keymeulen et al. (2019). In addition to these neonatal data, data regarding the prenatal period (e.g. trimester of seroconversion) and other relevant parameters (e.g. antiviral treatment) were collected.

A child was classified as symptomatic when there were one or more significant abnormalities on the extensive neonatal investigations. In concordance with the European Expert Consensus Statement (Luck et al., 2017) symptomatic cCMV-infection was further classified into a mild, moderate, and severe symptomatic cCMV-infection. An infection that was limited to isolated (≤ 2) or transient (≤ 2 weeks) symptoms was classified as mild. When the infection caused multiple (> 2) or persisting (> 2 weeks) symptoms, it was defined moderate. An infection that affected the central nervous system, caused isolated SNHL, severe single organ damage or multiple organ damage, was considered severe. Antiviral treatment was offered to all symptomatic patients with a moderate or severe infection, with the exception of children with isolated bilateral severe SNHL.

2.3.2 Auditory follow-up

cCMV patients were subjected to the Universal Newborn Hearing Screening by means of automated auditory brainstem responses (ABR) around birth. Depending on the results of the diagnostic

ABR the children entered a longitudinal audiological follow-up protocol. Symptomatic patients were followed more frequently than asymptomatic patients. Both symptomatic and asymptomatic patients had their first hearing assessments around the age of 3 months and 1 year, symptomatic patients received an extra intermediate hearing screening around the age of 6 months. Thereafter follow-up appointments were scheduled 6-monthly until the age of 3 years with a final hearing evaluation at the age of 4 years for symptomatic patients, and on a yearly basis until the age of 4 years for asymptomatic patients. To assess the hearing status of the child, ABR or age-appropriate tone audiometry was performed. Normal-hearing ears were followed by means of transient evoked otoacoustic emissions.

Hearing thresholds obtained by ABR were considered normal when they were ≤ 30 dB nHL, mild when they ranged between 31 and 45 dB nHL, moderate when they varied between 46 and 70 dB nHL, severe when they ranged between 71 and 90 dB nHL, and profound when they exceeded 90 dB nHL. When age-appropriate pure tone audiometry was performed, the pure tone average (average hearing threshold at 0.5, 1, 2, and 4 kHz) was evaluated. In accordance with an adapted version of the recommendations of the International Bureau for Audiophonology, patients were characterised as normal-hearing or hearing-impaired when hearing thresholds were ≤ 25 dB HL or > 25 dB HL, respectively. Hearing thresholds between 26 and 40 dB HL, 41 and 70 dB HL, 71 and 90 dB HL, and ≥91 dB HL, were classified as a mild, moderate, severe, and profound hearing loss, respectively. When the hearing loss became apparent around birth it was considered congenital. The SNHL was considered delayed in onset when it occurred after a period of objectified normal hearing. When the hearing loss progressed from a unilateral to a bilateral hearing loss or from one hearing loss-category to a more severe category, it was considered a progressive hearing loss. A hearing loss that transitioned to a better hearing loss-category was defined an improvement. When progression was followed by improvement or reverse, it was considered fluctuating.

In this study, the maximum interval between the final vestibular and auditory assessment was 12 months. A patient's final hearing status was determined based on the hearing assessment that was performed closest to the most recent vestibular assessment in case of ventilated middle ears. To determine the evolution of a hearing loss, all hearing assessments were taken into account. Otoscopy and/or tympanometry were performed to evaluate middle-ear function.

2.3.2 Vestibular follow-up

cCMV-infected children were subjected to extensive vestibular follow-up. The first vestibular assessment took place around the age of 6 months and follow-up appointments were scheduled around 1, 2, 3, and 4.5 years of age. Children who were identified with VD received continued follow-up beyond the age of 4.5 years. Vestibular follow-up of children younger than 3 years of age constituted of the video head impulse test (vHIT) of the horizontal SCC's, and the cervical vestibular evoked myogenic potentials (cVEMP). From the age of 3 years, when children generally become more cooperative and have an increased attention span, the protocol was extended with the vHIT of the anterior and posterior SCC's, and the ocular vestibular evoked myogenic potentials (oVEMP). When the patient was 4.5 years old, the caloric test was added. The caloric test was not performed in younger children since it is considered an invasive test that often cannot successfully be performed in children younger than 4 years. Since the start of our study in June 2016, just a few children reached the age 4.5 years and the caloric test was only successfully performed in 10 patients. Therefore, results of the caloric test will not be discussed in this article. This vestibular follow-up protocol ensured that from an early age onwards, both SCC and otolith functioning could be evaluated. More information regarding our centre-specific paediatric vestibular assessment protocol and normative data can be found in Dhondt et al. (2019) and Martens et al. (in preparation), respectively.

Otolith function testing

Cervical vestibular evoked myogenic potential

cVEMP was performed to assess saccular functioning and the integrity of the inferior branch of the vestibular nerve. During this test, children lay down in supine position with the upper body upon a sloping pillow. Their head was supported by the examiner and turned sidewards to the contralateral, non-test side. A visually attractive stimulus was used to maintain head rotation and to ensure adequate contraction of the sternocleidomastoid-muscle. Electromyographic activity was monitored by self-adhesive Ag/AgCl electrodes. The noninverting, inverting, and ground electrode were placed at the midpoint of the left and right sternocleidomastoid-muscles, approximately 1 to 2 cm below the sternoclavicular junction, and on the forehead, respectively. Since middle ear pathologies frequently occur in children (Rosenfeld et al., 2016), bone conduction stimuli were delivered at the mastoid. More specifically, linear 500 Hz tone bursts (1-2-1 ms) were delivered at 59 dB nHL (129 dB FL) with a stimulus repetition rate of 5 Hz. Electromyographic activity was monitored, amplified (5000 times) and bandpass-filtered (10 Hz - 1500 kHz). cVEMP-responses were recorded with a commercial system (Bio-Logic Navigator-Pro platform, Mundelein, IL, USA and Neuro-Audio version 2010, Neurosoft, Ivanovo, Russia). A minimum of 2 trials was obtained with at least 30 sweeps per trial, solely sweeps administered when the electromyographic activity varied between 80 µV and 250 µV were accepted. Absolute P1 and N1 latencies (ms), rectified interpeak amplitude (i.e. the raw peak-to-peak amplitude divided by the averaged electromyographic activity), and asymmetry ratio (%) were determined. A reduced rectified interpeak amplitude (i.e. < 1.3 with the Neuro-Audio system and < 0.3 with the Bio-Logic system) and absent cVEMP-responses were considered a mild and severe saccular dysfunction, respectively.

Ocular vestibular evoked myogenic potential

oVEMP was used to evaluate utricular functioning and the integrity of the superior branch of the vestibular nerve. During this test, children lay down in supine position. An upward gaze of 30° was ensured by showing a video on a screen. Electromyographic activity was administered by self-adhesive Ag/AgCl electrodes. The non-inverting, inverting, and ground electrodes were placed on the right and left musculus obliquus inferior, the right and left nose bridge, and on the forehead, respectively. Bone vibration stimuli, 500 Hz tone bursts (2–2–2 ms), were delivered high at the forehead using a minishaker (type 4810, Brüel & Kjaer, Nærum, Denmark). Tone bursts were presented at an intensity of 140 dB FL with a stimulus repetition rate of 5 Hz. Amplified (20 832 times) and bandpass-filtered (10 to 500 Hz) oVEMP-responses were recorded (Neuro-Audio version 2010, Neurosoft, Ivanovo, Russia). A minimum of 2 trials was obtained with at least 30 sweeps per trial. Absolute N1 and P1 latencies (ms), interpeak amplitude (µV), and asymmetry ratio (%) were established. Patients with an interpeak amplitude < 10µV or absent oVEMP-responses were diagnosed with a mild or severe utricular dysfunction, respectively.

Semi-circular canal function testing

Video head impulse test

The function of the high-frequency SCC's and the superior and inferior branch of the vestibular nerve was evaluated through the vHIT. This test allows separate testing of the horizontal and vertical canals. Younger children were seated on their parent's lap and older children on a chair in front of a remote vHIT-device, a stand-alone infrared camera (Ulmer version III, Synapsys, Marseille, France). A visually attractive stimulus was held behind the vHIT-device by an examiner to ensure fixation of the target. Another examiner stood behind the child and performed the vHIT-manoeuvres with an amplitude of 10° to 20°. Functioning of the horizontal SCC's was assessed by head impulses applied in the horizontal plane. Functioning of the left anterior and right posterior SCC's or the right anterior and left posterior SCC's were evaluated by performing head impulses in the vertical plane with the head turned 45° to the right or left, respectively. The peak velocity was at least 150°/s in the horizontal plane and 120°/s in the vertical plane. A minimum of 10 adequate vHIT-manoeuvres were performed for each

SCC. VOR gain and asymmetry (%) were determined. A gain of < 0.70 and < 0.40 were considered a mild and severe SCC dysfunction, respectively.

Definitions

An abnormal test result, as described above, on at least one test of the vestibular assessment protocol was considered a VD. When a SCC dysfunction occurred in the absence of an otolith dysfunction, and vice versa, it was considered an isolated SCC and otolith VD, respectively. When both a SCC and otolith dysfunction were found, it was categorised a combined VD. When the VD became apparent at the patient's first vestibular assessment or after a period of objectified normal vestibular functioning, it was considered a first assessment VD or delayed-onset VD, respectively. When the VD progressed over time from a partial to a more extensive VD, from a unilateral to a bilateral dysfunction or from a mild to a severe dysfunction, it was considered progressive. Likewise, a reduction of the VD was defined an improvement. The VD was characterised as fluctuating when progression was followed by improvement or reverse.

2.4 Data-analysis

Statistical and descriptive analyses were performed using IBM SPSS Statistics software (IBM SPSS Statistics for Windows, version 28.0 Armonk, NY: IBM Corp.). To determine the occurrence rate of VD within the study population and within subpopulations, and to provide more insight in the characteristics of cCMV-induced VD, descriptive statistics were used. Chi-square and two-tailed Fisher Exact tests were performed to explore the relationship between two categorical variables. Bonferroni correction was applied to the results of the Chi-square and two-tailed Fisher Exact tests. Because there were 10 comparisons, the criterion for statistical significance was set at $p < 0.005$.

3 Results

3.1 Patient characteristics

Table 1 provides an overview of the neonatal characteristics of the study population. Within the study population 31 (16.8%) patients were diagnosed with SNHL at some point during follow-up. At final assessment, the hearing loss was unilateral in 18, and bilateral in 12 children, and in 1 patient initial hearing loss improved to bilateral normal hearing. Within the patients with unilateral SNHL a mild, moderate, severe or profound hearing loss was found in 1, 3, 3, and 11 ears, respectively. Within the patients with bilateral SNHL 1, 3, 1, and 19 ears had a mild, moderate, severe or profound hearing loss, respectively. In 21 patients the hearing loss was congenital and in 10 patients it was delayed in onset. Moreover, patients with a delayed-onset SNHL were diagnosed between 2 and 36 months of age (mean: 12.9, SD: 11). The hearing loss was stable in 18 of the patients, and progressed, fluctuated, or improved in 9, 1, and 2 of the hearing-impaired children, respectively. In 1 patient the evolution could not be determined because the patient had no auditory assessment after diagnosis of the SNHL. Within our study population 8 patients underwent unilateral and 6 patients underwent bilateral cochlear implantation.

Table 1: Neonatal characteristics of the study population.

	Number of patients (%)
Gender	
Boy	90 (48,6%)
Girl	95 (51,4%)
Trimester of seroconversion	
First trimester	58 (31,4%)
Second trimester	38 (20,5%)
Third trimester	17 (9,2%)
Unknown	72 (38,9%)
Severity of the cCMV-infection	
Asymptomatic	102 (55,1%)
Symptomatic, mild	12 (6,5%)
Symptomatic, moderate	11 (5,9%)
Symptomatic, severe	60 (32,4%)
Hearing status at birth	
Normal hearing	164 (88,6%)
Congenital hearing loss	21 (11,4%)
Brain imaging	
Normal	96 (51,9%)
Abnormal	82 (44,3%)
Unknown	7 (3,8%)
Physical examinations	
Normal	182 (98,4%)
Abnormal	3 (1,6%)
Laboratory tests	
Normal	153 (82,7%)
Abnormal	11 (5,9%)
Unknown	21 (11,4%)
Fundoscopy	
Normal	179 (96,8%)
Abnormal	2 (1,1%)
Unknown	4 (2,2%)
(Val)ganciclovir treatment	
No treatment	123 (66,5%)
Treatment	62 (33,5%)

cCMV: congenital cytomegalovirus

3.2 Vestibular follow-up

All patients had 1 to 8 vestibular follow-up examinations (mean: 3.2, SD: 1.48) and were followed longitudinally for 0 to 60 months (mean: 20.8 months, SD: 16.31). More specifically, 22 (11.9%), 49 (26.5%), 37 (20.0%), 39 (21.1%), 31 (16.8%), 3 (1.6%), 2 (1.1%), and 2 (1.1%) patients received 1, 2, 3, 4, 5, 6, 7, and 8 assessments, respectively. The mean ages at first and last assessment were 7 (SD 3.0, range: 5 – 24 months) and 28 months (SD: 16.7, range: 5 – 68 months), respectively.

3.3 Prevalence and characteristics of cCMV-induced vestibular dysfunction

Within the study population 155 (83.8%) patients showed normal vestibular function on the vestibular test battery and 30 patients (16.2%) were identified with VD at some point during follow-up. The VD was unilateral in 70.0% (21/30) and bilateral in 23.3% (7/30) of the cases, and improved to bilateral normal vestibular function in 6.7% (2/30) of the patients at final evaluation. Details about vestibular characteristics, and neonatal characteristics as well as hearing status of the 30 vestibular-impaired patients are displayed in Appendices 1 and 2, respectively.

Table 2: Age at diagnosis of the vestibular dysfunction.

	Age at diagnosis (months)
Mean (SD)	16.6 (10.80)
Minimum	6.0
25th percentile	6.0
50th percentile	12.0
75th percentile	24.3
Maximum	45.0

SD: standard deviation

In 66.7% (20/30) of the vestibular-impaired patients, the dysfunction was diagnosed at the first vestibular assessment. In 18 patients the diagnosis at first assessment was made by means of the cVEMP and/or horizontal vHIT at a mean age of 11.1 months (SD: 5.99, range: 6 – 23 months), and in 2 patients the first assessment VD was detected by means of the oVEMP and/or vertical vHIT at a mean age of 35.5 months (SD: 9.41, range: 35 – 36 months). In 33.3% (10/30) of the cases, the VD was delayed in onset and was diagnosed at a mean age of 22.8 months (SD: 11.21, range: 12 – 45 months). Table 2 shows more information on the age at diagnosis of the VD. Additionally, the evolution of vestibular status was analysed. As illustrated in Figure 1, the dysfunction was stable in 33.3% (10/30) and unstable (i.e. fluctuating, progressive or improving) in 60.0% (18/30) of the vestibular-impaired patients. In 2 patients the evolution could not be determined because they did not yet receive additional vestibular follow-up after diagnosis of the VD. Nine vestibular-impaired patients (12 vestibular-impaired ears) underwent cochlear implantation. In 3 (25.0%) out of the 12 vestibular-impaired implanted ears, the dysfunction occurred after implantation [patient 3 (right ear), 13 (left ear), and 14 (right ear), Appendix 2], in 9 (75.0%) ears the VD was diagnosed before implantation [patient 1 (left ear), 7 (right and left ear), 9 (left ear), 10 (right ear), 13 (right ear), 17 (right and left ear), and 23 (right ear), Appendix 2].

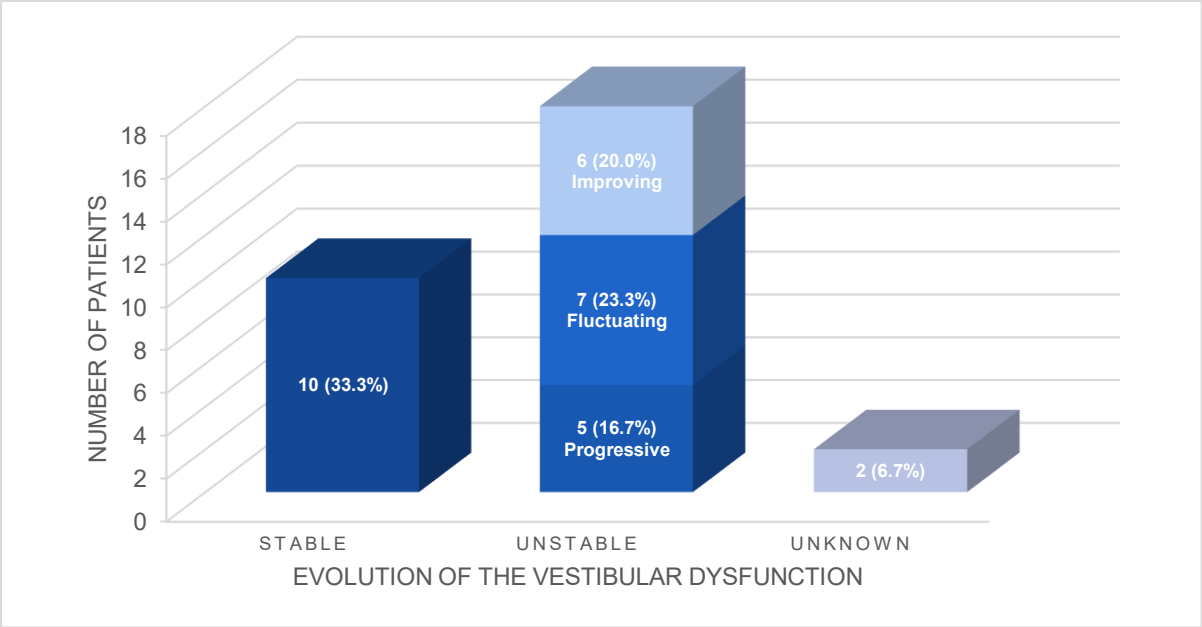

Figure 1: A detailed overview of the evolution of the vestibular dysfunction of the 30 vestibular-impaired patients.

Thirty-nine ears had a confirmed VD on at least one vestibular assessment during the course of follow-up. However, only 35 ears had VD at their final follow-up assessment. More specifically, these 4 ears (i.e. both left and right ear of patients 12, and 30) had an improving or fluctuating VD. A detailed overview of the evolution of the vestibular status of patients 12 and 30 can be found in Figure 2.

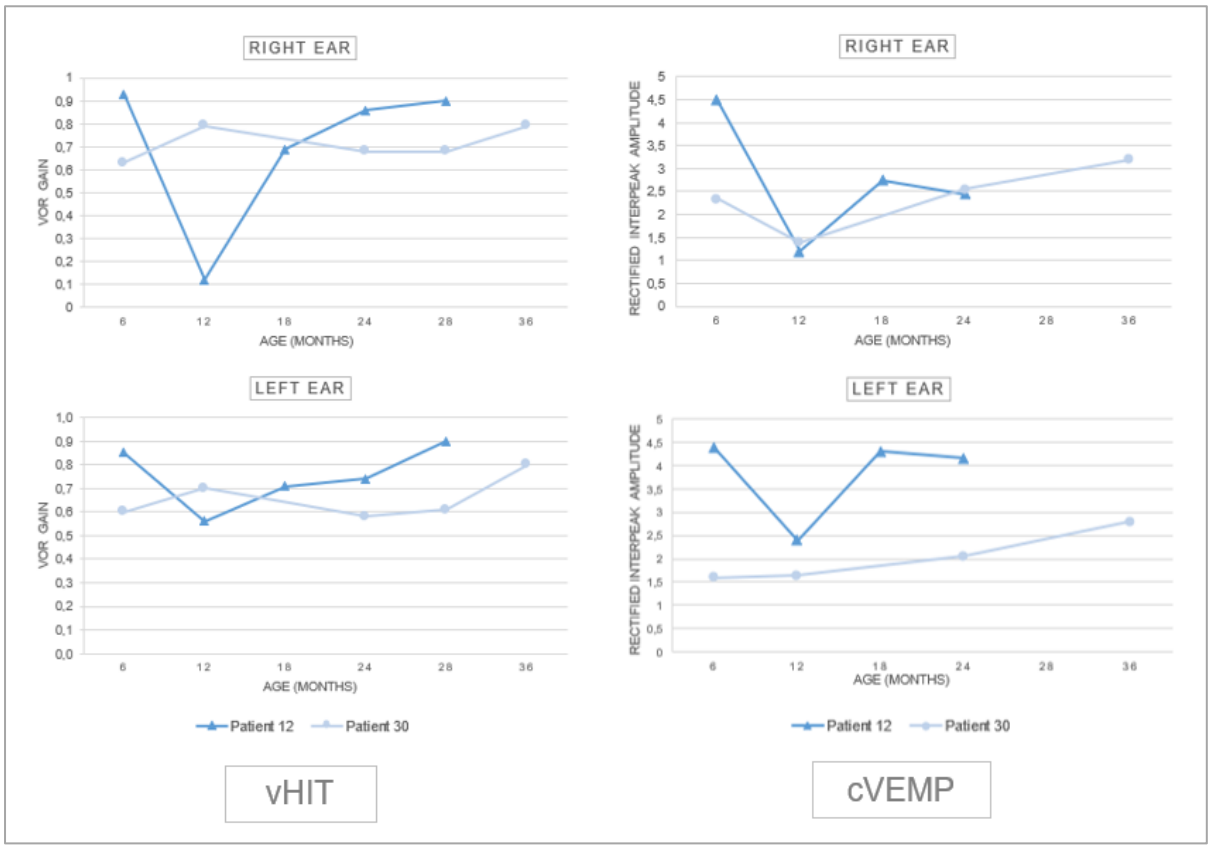

Figure 2: A detailed overview of the results on the video head impulse test (vHIT) and cervical vestibular evoked myogenic potentials (cVEMP) of patients 12 and 30, represented for the right and left ear separately.

Within the 35 ears with VD at final assessment, 85.7% (30/35) had a combined SCC and otolith dysfunction, 5.7% (2/35) had an isolated SCC dysfunction, and 8.6% (3/35) had an isolated otolith dysfunction. The vestibular function of the SCC's was affected in 91.4% (32/35) of the vestibular-impaired ears, while an otolith dysfunction was discovered in 94.3% (33/35). More details about SCC and otolith function are illustrated in Figure 3. It should be noted that in 11 patients the vertical SCC's and utricle could not yet be evaluated because the vertical vHIT and oVEMP are only performed in children aged 3 years or older. A dysfunction of the horizontal, anterior, and posterior SCC was found in 88.6% (31/35), 79.2% (19/24), and 87.5% (21/24) of the vestibular-impaired ears at final assessment, respectively. Additionally, in 74.3% (26/35) and 87.5% (21/24) of the cases, a saccular or utricular dysfunction was established, respectively.

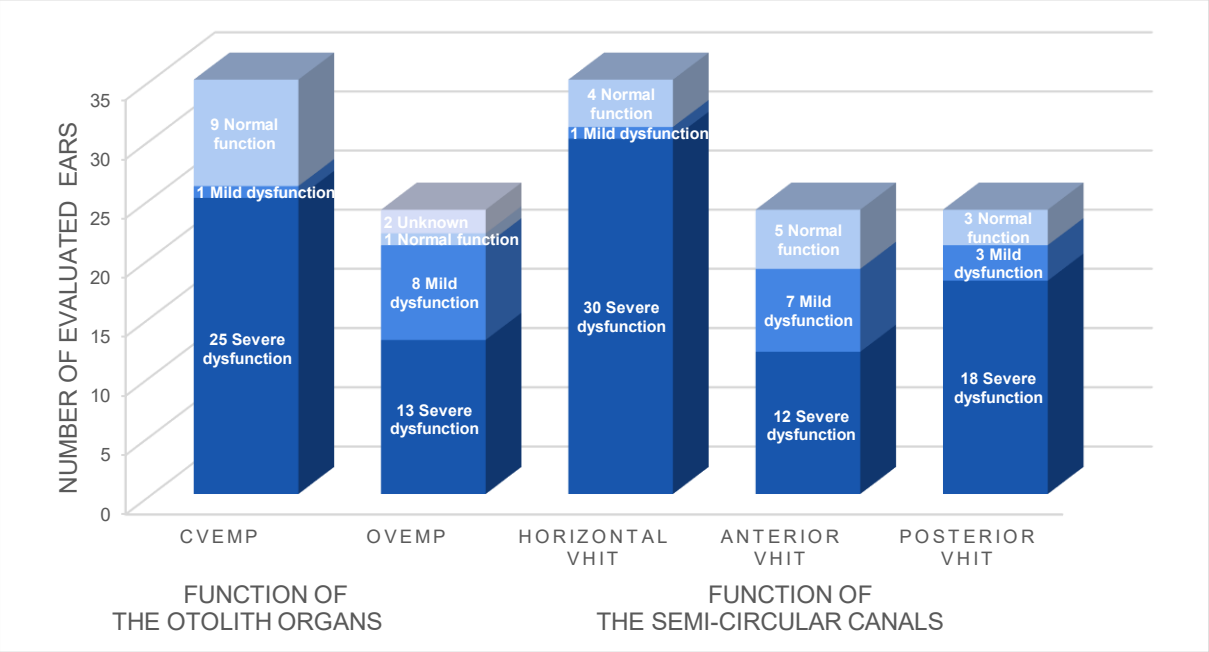

Figure 3: A detailed overview of the results on the vestibular test battery of the ears with a vestibular dysfunction at final assessment. Saccular and utricular function were assessed by means of the cervical vestibular evoked myogenic potentials (cVEMP) and ocular vestibular evoked myogenic potentials (oVEMP), respectively. Horizontal, anterior, and posterior semi-circular canal function was assessed by means of the horizontal, anterior and posterior video head impulse test (vHIT), respectively. The oVEMP, and anterior and posterior vHIT were only performed in 24 ears because these tests are only performed in patients aged 3 years or older. In 2 ears the results on the oVEMP were unknown because the test could not be reliably be performed.

3.4 Risk factors for cCMV-induced vestibular dysfunction

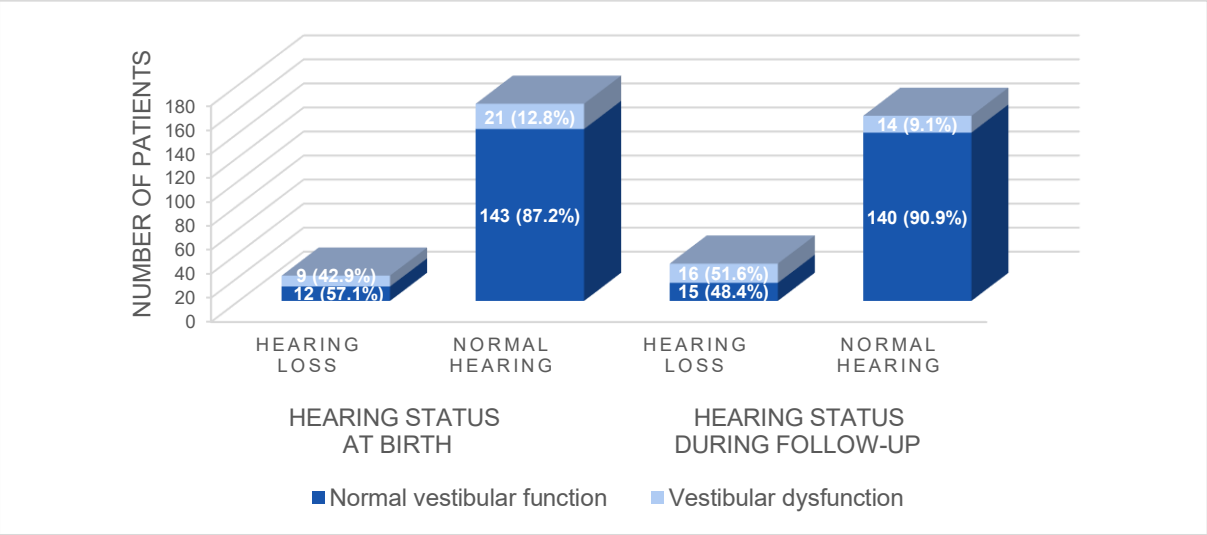

Figure 4: An overview of the vestibular status, represented for hearing-impaired and normal-hearing patients separately.

Nine vestibular-impaired patients had a hearing loss at birth, this is shown in Figure 4. Consequently, this means that 42.9% (9/21) of the patients with a congenital hearing loss developed a VD during follow-up in contrast to 12.8% (21/164) of the children with normal hearing at birth. The association between hearing loss at birth and the occurrence of VD was statistically significant ($p = 0.002$).

Similarly, a statistically significant association was found between the trimester of seroconversion and the occurrence of VD ($\chi^2(1) = 12{,}091$, $p < 0.001$). More specifically, VD was more prevalent in patients with a first trimester seroconversion (27.6%, 16/58), whereas patients with a second or third trimester seroconversion were less at risk for VD (5.3%, 2/38 and 0%, 0/17, respectively). It is important to note that the trimester of seroconversion was unknown in 72 (38.9%) of the 185 patients, 16.7% (12/72) of those patients developed VD during follow-up. To verify the effect of trimester of seroconversion independently from the effect of hearing status at birth, the occurrence of cCMV-induced VD in relation to the trimester of seroconversion was determined for normal-hearing and hearing-impaired children, separately. This is detailed in Figure 5. VD tended to be more prevalent among normal-hearing children with a first trimester seroconversion (23.4%, 11/47) compared to normal-hearing children with a second or third trimester seroconversion (5.3%, 2/38 and 0%, 0/17, respectively), this difference was also statistically significant ($\chi^2(1) = 2{,}176$; $p = 0.003$).

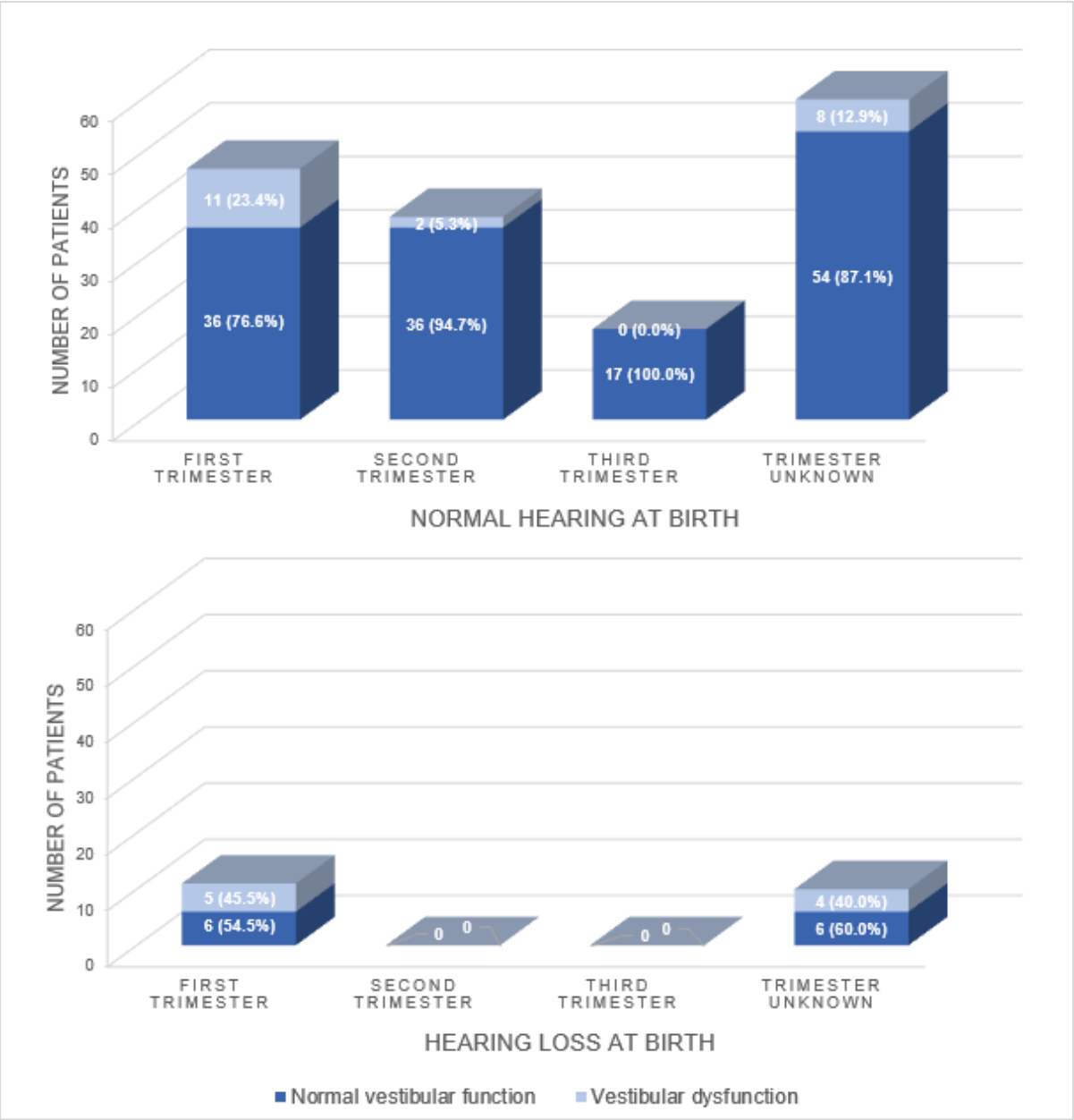

Figure 5: A detailed overview of the vestibular status displayed per trimester of seroconversion for normal-hearing and hearing-impaired children, separately.

VD tended to occur more in symptomatic (24.4%, 20/82) compared to asymptomatic patients (9.7%, 10/103). Similarly, VD appeared to be more prevalent in patients with abnormalities on brain imaging (20.7%, 17/82) compared to patients with normal brain imaging (11.5%, 11/96). However, there was no statistically significant association between either a symptomatic cCMV-infection (p = 0.007) or abnormal results on brain imaging (p = 0.090), and the occurrence of VD at some point during follow-up. It should be kept in mind that because of Bonferroni correction, the criterion for statistical significance was set at $p < 0.005$. When only patients with normal hearing at birth were considered, this trend became less distinct. This is illustrated in Figure 6. 17.7% (11/62) of the normal-hearing, symptomatic patients developed VD during follow-up compared to 9.8% (10/102) of the normal-hearing, asymptomatic patients. A VD was diagnosed in 17.6% (12/68) of the normal-hearing children with abnormalities on brain imaging compared to 8.7% (8/92) of the normal-hearing children with normal brain imaging. These slight differences in prevalence were again not statistically significant (p = 0.140 and p = 0.091, respectively).

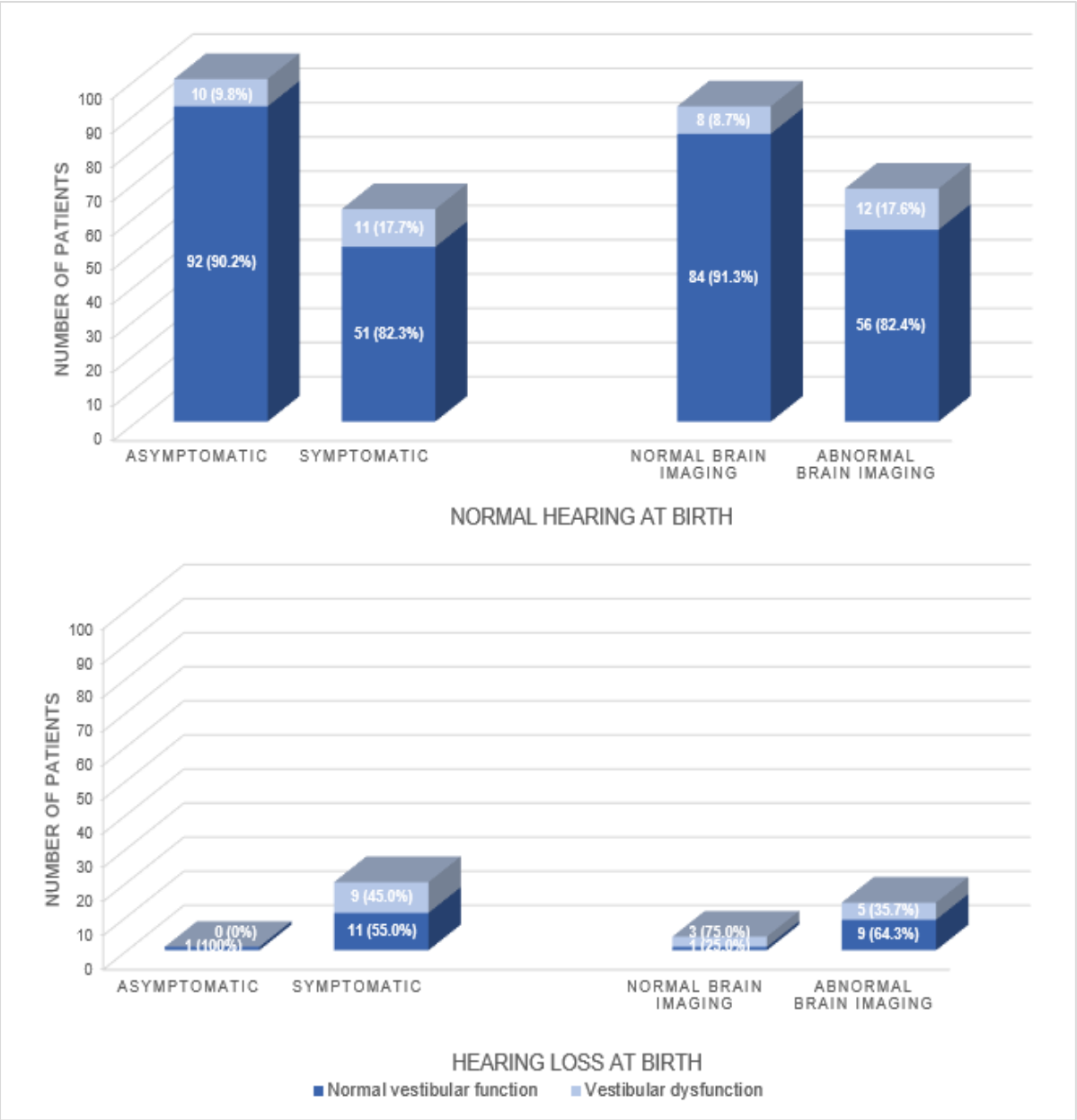

Figure 6: A detailed overview of the vestibular status of hearing-impaired and normal-hearing patients, separately represented for both asymptomatic and symptomatic patients, and for both patients with normal and abnormal brain imaging.

In addition to the analyses of potential neonatal risk factors, the relation between the patients hearing status during follow-up and vestibular status was explored. As shown in Figure 4, 16 patients developed a hearing loss during follow-up, which implies that 51.6% (16/31) of the patients with a hearing loss showed VD during follow-up compared to 9.1% (14/154) of the normal-hearing children. The association between hearing loss and the occurrence of VD was statistically significant ($\chi^2(1) = 43{,}342$, $p < 0.001$). Within our vestibular-impaired population, the children with SNHL more often had bilateral VD compared to normal-hearing patients. More specifically, in our 16 vestibular-impaired patients with hearing loss during follow-up, the dysfunction at final evaluation was bilateral in 37.5% (6/16) and unilateral in 56.3% (9/16) of the cases. While VD at final evaluation was bilateral in 7.1% (1/14) and unilateral in 85.7% (12/14) of our 14 normal-hearing patients. VD was more prevalent in patients with delayed-onset hearing loss (70.0%, 7/10) in comparison to patients with congenital hearing loss (42.9%, 9/21), and in bilateral hearing losses (66.6%, 8/12) compared to unilateral hearing losses

(44.4%, 8/18). However, onset and laterality of the hearing loss showed no statistically significant association with the occurrence of VD ($p = 0.252$ and $p = 0.105$, respectively). In Figure 7, Figure 8, and Figure 9 the concordance between the laterality, severity, and onset of the hearing status and vestibular status is displayed, respectively.

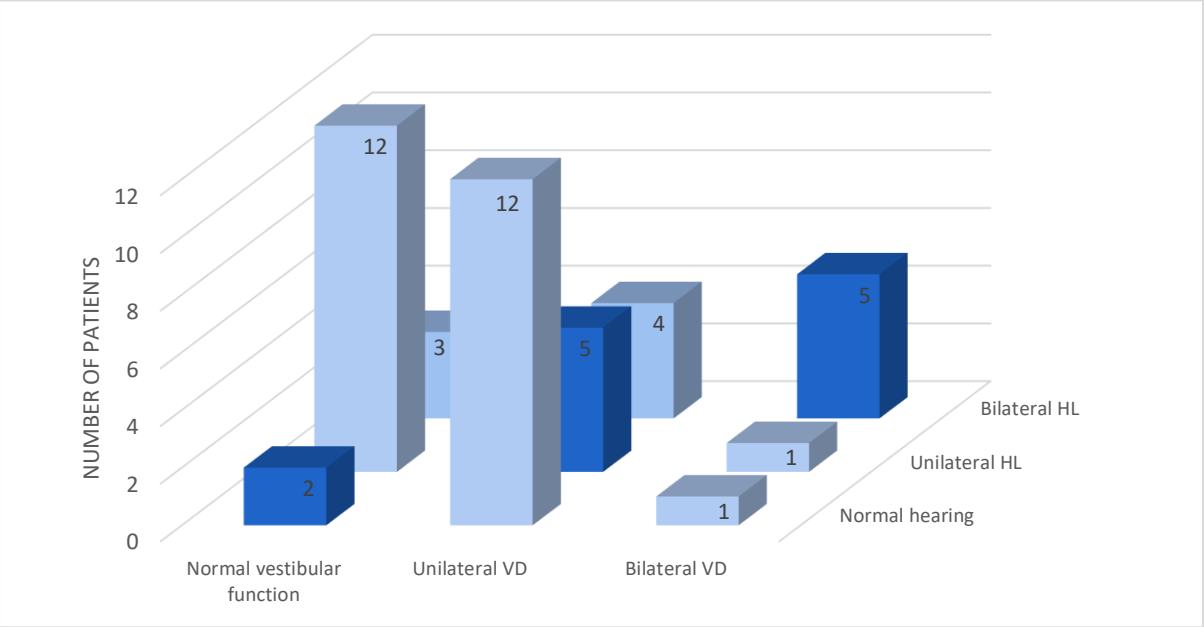

Figure 7: Laterality of the vestibular dysfunction (VD) at final assessment in relation to the laterality of the hearing loss (HL) at final assessment within the group of 45 patients who developed VD and/or HL during follow-up. Dark blue represents concordance between the laterality of the VD and HL. Light blue represents disconcordance between the laterality of the VD and HL.

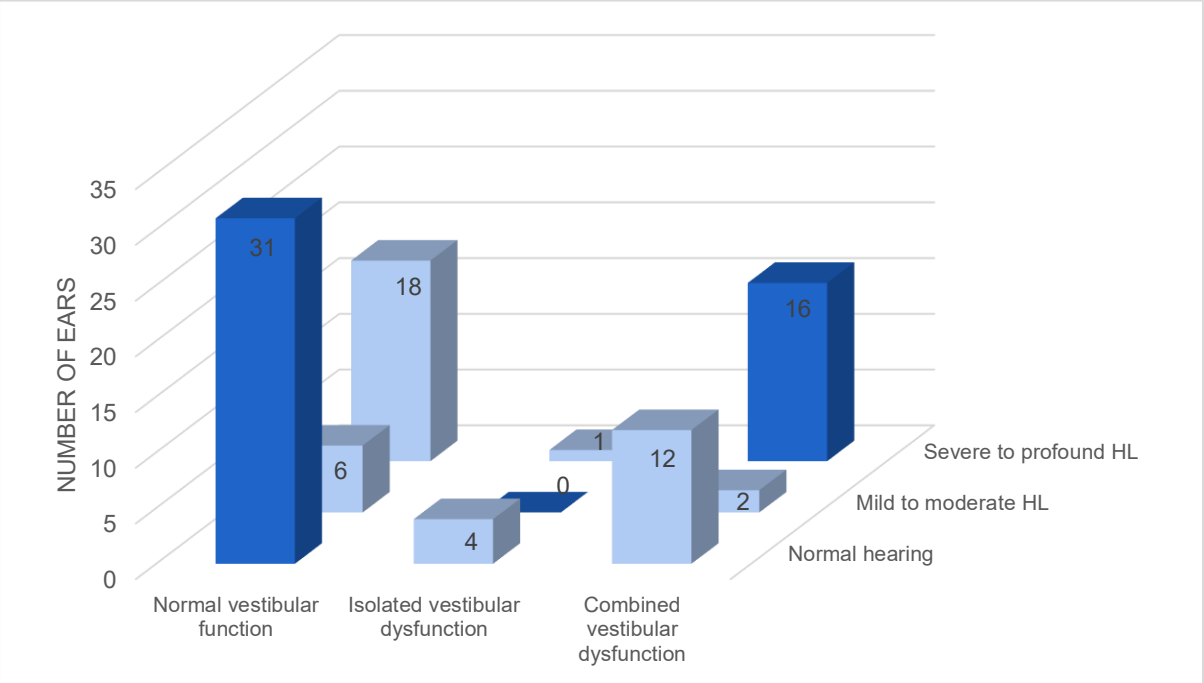

Figure 8: Severity of the vestibular dysfunction (VD) at final assessment in relation to the severity of the hearing loss (HL) at final assessment, represented for each ear separately, within the group of 45 patients who developed VD and/or HL during follow-up. Dark blue represents concordance between the severity of the VD and HL. Light blue represents disconcordance concordance between the severity of the VD and HL.

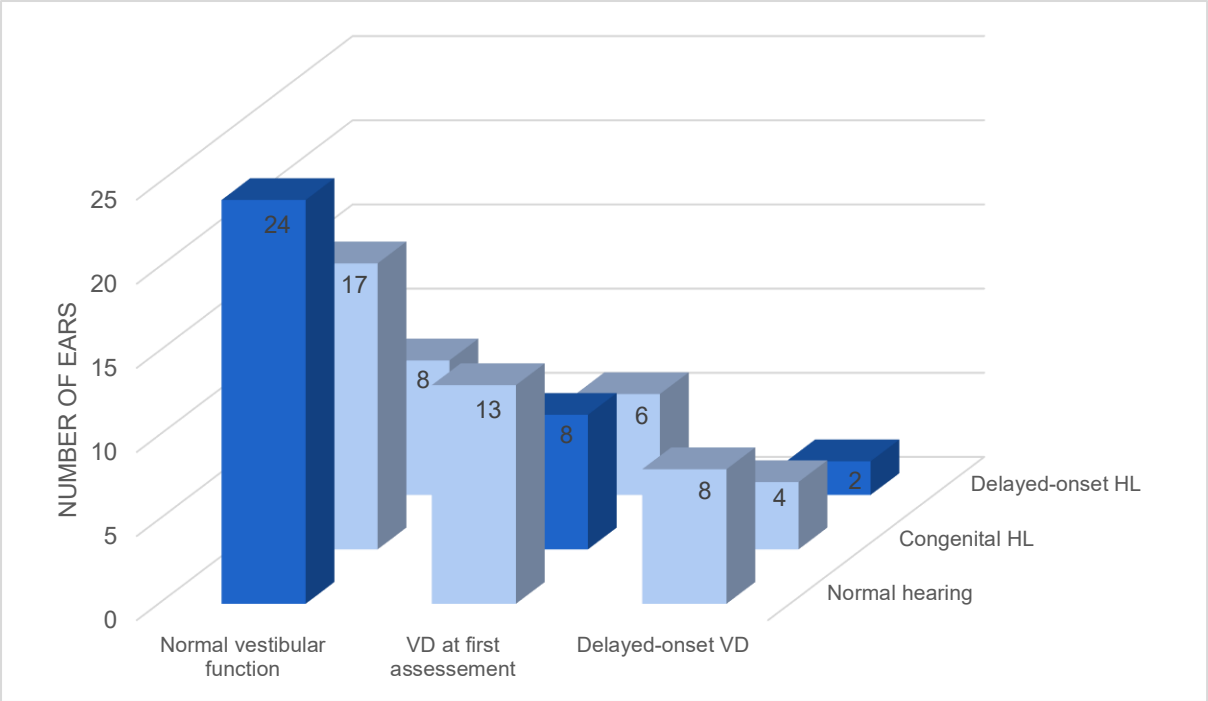

Figure 9: Onset of the vestibular dysfunction (VD) in relation to the onset of the hearing loss (HL), represented for each ear separately, within the group of 45 patients who developed VD and/or HL during follow-up. Dark blue represents concordance between the onset of the VD and HL.

4 Discussion

4.1 Prevalence and characteristics of cCMV-induced VD

4.1.1 Prevalence

16.2% of our patients developed a VD during follow-up. Our occurrence rate is considerably lower than the occurrence rates reported in previous studies (23% - 92%) (Bernard et al., 2015; Karltorp et al., 2014; Maes et al., 2017; Pappas, 1983). These higher occurrence rates could be explained by small test populations and an overrepresentation of severe-to-profound hearing-impaired or symptomatic patients in other studies.

Whitin our study population 55.7% patients had an asymptomatic and 44.3% had a symptomatic cCMV-infection. This differs from the numbers from Goderis et al. (2016) who reported that approximately 66% and 33% of their cCMV patients were asymptomatic and symptomatic, respectively. Therefore, we believe it is plausible that asymptomatic patients were underrepresented in our study population. Additionally, it has been reported in literature that many asymptomatic cCMV patients remain undetected (Fowler & Boppana, 2018; Kenneson & Cannon, 2007). 83.2% of our patients had normal-hearing and 16.8% developed SNHL at some point during follow-up. The occurrence rate of SNHL is slightly higher than the number reported in literature (13%) (Foulon et al., 2019; Goderis et al., 2016), this might be a consequence of a referral bias since our clinic is a reference centre for more severe cases. Therefore, our occurrence rate of cCMV-induced VD of 16.2% could be an overestimation. Conversely, it is also possible that our occurrence rate is an underestimation, as not all patients completed 4.5 years of follow-up, possibly underestimating the number of delayed-onset VD's, and only 17 of our 30 (56.6%) vestibular-impaired patients received extensive vestibular assessment that evaluated all five components of the vestibular system.

Our current occurrence rate of 16.2% is in line with, but slightly higher than, the occurrence rate of 14% reported in our previously published paper based on the intermediate data-analyses of 3 years of follow-up (Dhondt et al., 2020). This difference might be explained by the fact that our current study considered both children with mild and/or severe dysfunctions whereas our previous study only considered patients with a severe vestibular loss. In other words, the higher occurrence rate reported in our current study might be a reflection of the difference in applied criteria for VD. Another possible explanation could be that in our current analysis more patients with a delayed-onset VD could be detected since the patients were followed longitudinally for on average twice as long (i.e. mean follow-up of 20.8 months compared to 10.2 months). Additionally, the previous study only evaluated the function of the saccule and horizontal SCC's, whereas the current analysis also included the utricle and vertical SCC's.

Noteworthy, the occurrence rate of VD (16.2%) is very similar to the occurrence rate of SNHL (16.8%) in our study population, and is in line with the prevalence of cCMV-induced hearing loss reported in literature (13%) (Foulon et al., 2019; Goderis et al., 2016). The vestibular system seems as much at risk for cCMV-induced damage as the cochlear system. Therefore, it seems evident that, just like auditory follow-up of cCMV patients, vestibular follow-up of these patients is important.

4.1.2 Laterality

Unilateral VD (70.0%) was more prevalent than bilateral VD (23.3%). However, different numbers have been reported in previous research. Other authors found that VD was unilateral in 40% to 57% of their vestibular-impaired cCMV patients, and bilateral in 43% to 60% (Dhondt et al., 2020; Karltorp et al., 2014; Maes et al., 2017; Pappas, 1983). Bernard et al. (2015) even reported a prevalence of 23%

and 77% of unilateral and bilateral VD, respectively. This considerable difference between studies could possibly be attributed to selection bias and a higher prevalence of bilateral hearing loss in the populations studied. More in depth analyses of our vestibular-impaired population showed that hearing-impaired patients more often had a bilateral VD (37.5%) compared to normal-hearing patients (7.1%). This leads us to believe that the higher prevalence of bilateral VD reported by other authors could be (partially) explained by the fact that a larger portion of their vestibular-impaired patients did indeed have SNHL.

In a considerable portion of the patients, the VD was unilateral. However, currently mainly the effect of bilateral VD on childhood development has been investigated. Infants with bilateral VD are known to have difficulties with balance (De Kegel et al., 2012; Wiener-Vacher et al., 2013) and the acquisition of gross motor milestones (Inoue et al., 2013; Kaga, 1999; Singh et al., 2021). Additionally, an impact on cognition, emotional well-being, and school performance has been suggested (Bigelow et al., 2016; Braswell & Rine, 2006; Grossman & Leigh, 1990; Janky et al., 2022; Lacroix et al., 2020; Lee et al., 2014; Smith et al., 2010; Wiener-Vacher et al., 2013). Future research should aim to elucidate the impact of an unilateral dysfunction on the motor, cognitive, psychosocial, and educational development of these children. In the meantime it seems important to detect both children with unilateral and bilateral VD, to offer them appropriate rehabilitation, and to provide counselling to their parents. During the early development of the child physiotherapy could be provided to stimulate motor development. When the child grows older, vestibular rehabilitation can be offered. Vestibular rehabilitation is an exercise-based treatment that is founded on three important mechanisms: adaptation, substitution and habituation (Whitney et al., 2016). Research in adults with a peripheral VD has shown that both patients with unilateral and bilateral dysfunction can profit from vestibular rehabilitation (Karapolat et al., 2014). Besides, children are considered good candidates for vestibular rehabilitation as promising results regarding amelioration of balance and locomotion have been reported (Fernandes et al., 2015; Melo et al., 2019; Rine, 2018). Additionally, follow-up of patients with unilateral VD seems important because cCMV-induced VD progressed from an unilateral to a bilateral dysfunction in 3 (10%) of our 30 vestibular-impaired patients during follow-up (patients 13, 19 and 23, Appendix 1).

4.1.3 Onset & evolution

It has been well established that a cCMV-infection can cause sequelae later on (Fowler & Boppana, 2018; Kenneson & Cannon, 2007) and that cCMV-induced hearing loss can be progressive or delayed in onset (Goderis et al., 2016). Therefore, it has been assumed that vestibular function in cCMV patients could have an unstable nature as well. Indeed, cCMV-induced VD was delayed in onset in no less than 33.3% of our patients with VD. The actual prevalence of delayed-onset VD might be even higher because not all of our patients received 4.5 years of follow-up, first assessment of the utricle and vertical SCC's was only performed in patients aged 3 years or older, and not all our patients had their first vestibular assessment at the age of 6 months (i.e. patients could be enrolled in the study when they received their first vestibular assessment before the age of 2 years). Additionally, in line with the unpredictable nature of cCMV, the VD was characterized as unstable in the majority (60.0%) of our vestibular-impaired patients. More specifically, 7 (23.3%) patients had a fluctuating VD, 5 (16.7%) patients had a progressive VD, and in 6 (20.0%) children the VD improved during follow-up. It should be pointed out that 12 ears of the 35 ears with VD underwent cochlear implantation, which poses an additional risk for VD (Cushing & Papsin, 2018; Yong et al., 2019). In 3 of these 12 implanted ears, the VD was detected after implantation. Therefore, it remains uncertain whether the dysfunction in these cases was caused by either cochlear implantation or cCMV. Conversely, the vestibular deterioration of our 9 implanted ears with a VD that occurred before implantation and our 22 non-implanted ears, could very likely be attributed to cCMV-sequelae.

The occurrence rate of delayed-onset VD (33.3%) was in line with the findings of our previous research (31%). With regard to the unstable character of cCMV, Bernard et al. (2015) estimated the occurrence of progressive cCMV-induced VD at 50%, which is considerably higher than the 16.7% and 15% reported in our current and previous study, respectively. However, as detailed in Dhondt et al. (2020), Bernard et al. (2015) reported that selection bias was possible.

One in five patients from the vestibular-impaired population showed an improvement at the vestibular test battery. This finding is not unexpected since improvement of the hearing status has been described in the cCMV population (Goderis et al., 2016). However, clinical implications of such improved VD remain unclear and should be elucidated in future research. At final assessment, only 1 (patient 12, Appendix 1) of our 6 patients with improving VD evolved to bilateral normal hearing while in 5 patients (patients 7, 10, 16, 25, and 26, Appendix 1) at least one component of the vestibular system remained affected. Therefore, we believe it is important to also detect these patients through vestibular follow-up so that appropriate rehabilitation can be timely provided to the child.

It is clear that cCMV patients are at risk for delayed-onset occurrence and progression of VD. As much as one in three of our vestibular-impaired patients would be missed if only a single, early vestibular screening would be performed. Furthermore, one screening would be insufficient to provide accurate information of a patient's final vestibular function since in 60% of our vestibular-impaired patients the vestibular status progressed, fluctuated or improved. Consequently, it seems evident that it is strongly recommended to provide regular, longitudinal vestibular follow-up to cCMV patients. We suggest that these patients are scheduled for vestibular assessment around the ages of 6 months, 1 year, and yearly thereafter. Regular follow-up will allow early detection and diagnosis of the VD, which is important to be able to timely rehabilitate the child and counsel the parents.

4.1.4 Age at diagnosis

Half of our patients with VD were diagnosed within the first year of life and in the majority of the patients, the dysfunction was detected before the age of 2 years. The oldest child in whom VD was found in our study population, was 45 months. It should be pointed out that follow-up was generally only provided until the age 54 months, and only 25 out of the 185 (13.5%) patients had reached the age of 54 months (4.5 years) at the end of our data collection. Therefore, it cannot be ruled out that VD can occur after 45 months of age. In rare cases, delayed-onset cCMV-induced hearing loss has been reported in patients up to 15 years of age (Lanzieri et al., 2017). Therefore, it seems possible that, similar to cCMV-induced SNHL, cCMV-induced VD can also be found in older patients. However, this does not imply that prolonged follow-up is necessary. Recently, Lanzieri et al. (2017) and Foulon et al. (2019) provided new insights in the auditory follow-up of cCMV patients. They recommended auditory follow-up until the age of 4 years because in children aged 5 years or older, cCMV patients are equally at risk for hearing loss as children who do not have a cCMV-infection. Therefore, based on our own data and the recent auditory insights, we suggest vestibular follow-up until the age of 4 years.

4.1.5 Involvement of vestibular structures

It has been reported that cCMV can cause virus-induced labyrinthitis, affecting both the cochlea and vestibular system (Davis et al., 1981). In the vestibular end-organs damage has been found predominately in the dark cells which occur in the utricle and SCC's (Gabrielli et al., 2013; Teissier et al., 2016). In agreement with these pathological findings, dysfunctions of the SCC's (91.4%) and utricular dysfunctions (87.5%) seem to occur more often than saccular dysfunctions (74.3%). This is in line with

previous studies that reported that the horizontal SCC's tend to be more frequently affected by the cCMV virus than the saccule (Bernard et al., 2015; Dhondt et al., 2020; Zagólski, 2008).

Overall, in the majority of the ears with cCMV-induced VD at final assessment (85.7%) both SCC and saccular function was impaired, although isolated SCC dysfunctions (5.7%) and isolated otolith dysfunctions (8.6%) did occur. Therefore, vestibular follow-up of cCMV patients by means of a single screening test (e.g. horizontal vHIT or cVEMP) would be insufficient to detect all vestibular-impaired patients. In order to detect all patients with VD, a more extensive vestibular assessment is required. It is recommended to evaluate all five components of the vestibular system (i.e. the saccule, the utricle, and the horizontal, anterior and posterior SCC's). To evaluate functioning of the saccule, the cVEMP can be performed. cVEMP-responses can successfully and reliably be obtained in children, even in 1-month-old new-borns (Janky & Rodriguez, 2018; Maes et al., 2014b; Zhou et al., 2014). Besides, a strong correlation between cVEMP testing and the motor-performance has been found in hearing-impaired children (De Kegel et al., 2012; Ionescu et al., 2020; Maes et al., 2014a). Functioning of the utricle can be evaluated with the oVEMP. However, oVEMP testing should only be routinely completed in children aged three years or older (Dhondt et al., 2019; Janky & Rodriguez, 2018) since it is difficult to ensure an upward gaze in younger children and it has been hypothesized that the pathways that are evaluated through oVEMP testing mature during the first two years of infancy (Wang et al., 2013). To assess horizontal, anterior, and posterior SCC functioning, the vHIT can be carried out. vHIT testing is feasible in infants as young as 3 months of age (Wiener-Vacher & Wiener, 2017). In conclusion, we advise that vestibular follow-up consists of the horizontal vHIT and the cVEMP, and that for children aged 3 years and older the protocol is extended with the vertical vHIT and the oVEMP. We do not advise to standardly perform the rotatory chair test or caloric test for several reasons. Firstly, since both the rotatory chair test and caloric test are considered invasive (e.g. they need to be performed in the dark), it can be challenging to reliably carry out these tests in younger patients (Dhondt et al., 2019; Janky & Rodriguez, 2018). Secondly, as parents and children can consider vestibular testing as demanding, it is not opportune to unnecessarily extend the duration of the vestibular assessment. Thirdly, the vHIT assesses the high-frequency function of the SCC's which correlates more with the physiological stimuli of everyday life than the rotatory chair test and the caloric test that evaluate the midfrequency and low-frequency function of the horizontal SCC's, respectively. Therefore, the rotatory chair test and/or caloric test should only be performed when indicated. For example, in patients whom were diagnosed with a SCC dysfunction by the vHIT, it might be valuable to evaluate the function of the midfrequency and low-frequency horizontal SCC through the rotatory test and caloric test, respectively. Also, patients who present themselves with certain symptoms or concerns that could not be accounted for by the vHIT, cVEMP or oVEMP, should be subjected to an extended vestibular test battery. Additionally, it is recommended to perform motor assessment in cCMV patients that are diagnosed with a confirmed VD to better understand the functional impact on the child. More research on this topic is necessary. Especially since cCMV can cause auditory, vestibular, visual and neurological dysfunctions that each also can, to a larger or lesser degree, complicate motor development.

It should be kept in mind that isolated SCC and otolith dysfunctions were found in our population. To better understand the implications of these results, future studies should investigate the consequences of such isolated dysfunction (e.g. do these patients experience the same complaints, do they have the same rehabilitative needs, etc.).

4.2 Risk factors for cCMV-induced vestibular dysfunction

4.2.1 Hearing status

Since a cCMV-infection can cause histopathological changes in the inner ear that can affect both cochlear and vestibular structures (Gabrielli et al., 2013), it is not surprising that a strong correlation was found between hearing loss and the occurrence of VD. Hearing-impaired patients (51.6%) were more often diagnosed with VD compared to normal-hearing patients (9.1%). These results were in line with our previous findings reported in Dhondt et al. (2020).

VD seemed to occur more often in patients with delayed-onset (70.0%) or bilateral hearing loss (66.6%) compared to patients with congenital (42.9%) or unilateral hearing loss (42.1%), respectively. However, no statistically significant association could be found between the onset and laterality of the hearing loss and the occurrence of VD. Furthermore, as demonstrated in Figure 7 and Figure 8, in a considerable portion of our patients with VD and/or SNHL, laterality and severity of the hearing loss was not concordant with the laterality and severity of VD, respectively. These findings are in agreement with previous research. Although Bernard et al. (2015) did find a significant association between hearing loss and VD regarding their respective laterality and severity, they could not objectify a concordance. In agreement, our intermediate analysis found that the severity and the laterality of hearing loss and VD were not concordant with each other in some of our patients (Dhondt et al., 2020), and Lazar et al. (2021) reported that the auditory and vestibular status were often disconcordant within, and between their five pairs of genetically identical twins with cCMV. Moreover, neither were the onset of SNHL and VD concordant with each other in a considerable number of our patients, this is shown in Figure 9. However, it should be pointed out that the comparison between the onset of SNHL and VD is not straightforward. Since the implementation of the Universal Newborn Hearing Screening Program, it is possible to detect SNHL within the first two months of life, allowing clinicians to distinct a congenital from a delayed-onset hearing loss (JCIH, 2000). However, since in our study the first vestibular assessment did not take place until the age of 6 months, it was not possible to make such distinction in our population. Furthermore, because patients could be enrolled in the study until the age of 24 months and because the utricle and vertical SCC's were only evaluated from the age of 36 months, it was opted to characterise the VD's as first assessment or delayed in onset. Therefore, it seems evident that caution is in order when comparing the onset of SNHL and VD. Nevertheless, these results clearly indicate that although the onset of the SNHL and VD can be in agreement with one another, they frequently did not match in our patients. For example, a congenital hearing loss coincided with a delayed-onset VD in 4 ears.

Taking everything in to account, hearing loss constitutes an important risk factor for cCMV-induced VD. However, targeting only hearing-impaired cCMV patients for vestibular testing, would be insufficient to detect all vestibular dysfunctions. As can be seen in Figure 4, 21 (70.0%) and 14 (46.6%) of our 30 vestibular-impaired patients would have been missed if only cCMV patients with hearing loss at birth or hearing loss during follow-up would have received vestibular follow-up, respectively. Therefore, it would be valuable to determine additional risk factors for cCMV-induced VD that allow to predict VD in the large group of normal-hearing cCMV patients. Since vestibular follow-up of all cCMV patients is often not feasible in clinical practice, and the hearing status of the child is an important predictive factor that allows clinicians to better estimate the risk for cCMV-induced VD and to provide counselling to the child's parents, we advise that at least cCMV patients with a hearing loss should receive regular, longitudinal follow-up. Given that the characteristics of the SNHL are frequently not concordant with the characteristics of VD, all hearing-impaired cCMV patients, irrespective of the onset, laterality and severity of the hearing loss, should be enrolled in a vestibular follow-up protocol.

4.2.2 Trimester of seroconversion

Seroconversion during the first trimester of pregnancy is well known to increase the risk of cCMV-induced morbidity (Manicklal et al., 2013). Moreover, a clear relation could be established between the time of seroconversion and the occurrence of hearing loss as children with a first trimester seroconversion are more at risk to develop SNHL (Craeghs et al., 2020; Foulon et al., 2019). In line with these findings, VD was significantly more prevalent in our patients where the cCMV-infection occurred during the first trimester of pregnancy (27.6%) compared to the second and third trimester (5.3% and 0%, respectively). When only patients with normal hearing at birth were considered, the difference between the occurrence of cCMV-induced VD in patients with a first trimester seroconversion (23.4%) and a second or third trimester seroconversion (5.3% and 0%, respectively) remained statistically significant. In agreement, both Dhondt et al. (2020) and Maes et al. (2017) found that all vestibular-impaired patients of whom the timing of seroconversion was known, were infected during the first trimester of pregnancy. Therefore, seroconversion during the first trimester of pregnancy could be considered a risk factor for cCMV-induced VD. However, in clinical practice timing of seroconversion is often unknown. Indeed, this was the case in a considerable portion of our population (72/185, 38.9%). In addition, it is important to note that VD did occur in 2 (5.3%) of our 38 patients with a second trimester seroconversion. Notwithstanding, trimester of seroconversion is a valuable parameter to consider in the risk estimation of cCMV-induced VD and the counselling of parents.

As mentioned above, it is recommended to at least perform vestibular assessment in hearing-impaired cCMV patients. However, we believe that the trimester of seroconversion is an important additional parameter to consider when deciding which cCMV patients should be followed more closely. As demonstrated in Figure 5, 11 (36.6%) additional children of our 30 vestibular-impaired children would be identified with VD, if in addition to children with congenital SNHL, normal-hearing children with a first trimester seroconversion would be tested. In other words, if only cCMV patients with hearing loss and/or a first trimester seroconversion would have been subjected to vestibular follow-up, 66.6% (20/30) of our patients with VD would have been detected. When the hearing status during follow-up would be considered, the number of identified VD's would go up to approximately 75% (23/30). Therefore, we recommend that not only hearing-impaired cCMV patients but also normal-hearing patients with a first trimester seroconversion should receive regular, longitudinal vestibular follow-up. Additionally, it would be valuable to determine additional predictive factors so that also patients in whom the trimester of seroconversion is unknown can be subjected to a more targeted follow-up protocol.

4.2.3 Symptoms at birth

Previous research has reported that VD seems to be more prevalent in symptomatic than in asymptomatic patients. Although adequate comparison of these studies is difficult due to the use of varying definitions of symptomatic cCMV-infection, a clear trend could be observed. Maes et al. (2017) and Zagólski (2008) reported that saccular dysfunctions were more common in their symptomatic (36% and 60%, respectively) than in their asymptomatic patients (0%). Accordingly, Zagólski (2008) found a dysfunction of the horizontal SCC's in 60% and 12,5% of the symptomatic and asymptomatic population, respectively. Furthermore, our previous study found VD in 22% of the symptomatic patients compared to 8% in the asymptomatic group (Dhondt et al., 2020). Similarly, 24.4% of the symptomatic children in our current study population were vestibular-impaired compared to 9.7% of the asymptomatic children. However, this difference between our symptomatic and asymptomatic patients was not statistically significant. It should be noted that our criteria for statistical significance was set at $p < 0.005$ because of Bonferroni correction.

However, as demonstrated in Figure 6, a more in depth analysis of our data showed that VD occurred more often in hearing-impaired symptomatic (48.0%) and asymptomatic (66.7%) patients

compared to normal-hearing symptomatic (14.0%) and asymptomatic (6.2%) patients. This in line with the findings of Maes et al. (2017) who reported VD in 14% of their normal-hearing and in 57% of their hearing-impaired symptomatic patients. Consequently, it might be questioned to what extend the occurrence of hearing loss contributes to the results found in the symptomatic population as hearing loss at birth is an important reason to label a patient as symptomatic. Indeed, 20 (24.4%) of our 82 symptomatic children were considered symptomatic because they had, sometimes among other symptoms, hearing loss at birth. Besides, when zooming in on the children with normal hearing at birth of our study population, 17.7% of our children with a symptomatic infection had VD compared to 9.8% of our children with an asymptomatic infection, this difference was also not statistically significant. In addition, Pinninti et al. (2021) investigated the occurrence of VD in a study population of asymptomatic patients and found a VD in 45% of their population. The occurrence rate reported by Pinninti et al. (2021) is considerably higher than the occurrence found in our and other studies (Dhondt et al., 2020; Maes et al., 2017; Zagólski, 2008), which may be due to a difference in vestibular test-battery, mean age of the participants or definition of (a-)symptomatic infection. Pinninti et al. (2021) included patients with SNHL which is known to heighten the risk of cCMV-induced VD. All things considered, this leads us to believe that a symptomatic cCMV-infection as such might not be a good predictor for cCMV-induced VD.

4.2.4 Brain imaging

Abnormalities on brain imaging are known to be associated with the development of cCMV-induced SNHL (Craeghs et al., 2020). Although a similar trend of a higher occurrence of cCMV-induced VD in patients with abnormalities on brain imaging (20.7%) compared to patients with normal brain imaging (11.5%) was found in our study population, no statistically significant relation could be established. This trend could possibly be (partially) explained by the hearing status of the child. Since neurological abnormalities are predictive for hearing loss, and hearing loss itself elevates the risk for cCMV-induced VD, the higher occurrence of VD in our patients with abnormalities on brain imaging could reflect their hearing status at birth. Indeed, a more detailed review of our data demonstrated that VD occurred more often in hearing-impaired patients both with and without abnormalities on brain imaging (35.7% and 75.0%, respectively) compared to normal-hearing patients (17.6% and 8.7%, respectively), this is shown in Figure 6. Moreover, when the occurrence of VD was compared between normal-hearing patients with and without abnormalities on brain imaging, the association remained not statistically significant.

However, it should be kept in mind that more in-depth analyses with specific neurocranial parameters, were not performed. It seems possible that more specific abnormalities on either cranial ultra sound or cranial magnetic resonance imaging, could indeed be predictive for vestibular abnormalities. For example, Rivera et al. (2002) have reported that intracerebral calcifications revealed on cranial ultra sound are an early predictor for cCMV-induced SNHL. Such association could perhaps also exist between intracerebral calcifications and cCMV-induced VD, but such analyses were beyond the scope of this study. Nevertheless, future research should provide a more in-depth understanding of the predictive value of neurocranial parameters.

4.2.5 Clinical examinations

Wu et al. (2019) have demonstrated that low gestational age, low birth weight, and prolonged cCMV-infection increase the risk of cCMV-induced hearing loss. Rivera et al. (2002) reported that hearing loss is more prevalent in cCMV patients with petechiae, hepatosplenomegaly, hepatitis, thrombocytopenia, or intrauterine growth retardation. Currently, such associations have not yet been investigated for cCMV-induced VD. Future research should aim to elucidate the predictive value of these parameters.

5 Conclusion

This research aimed to formulate recommendations regarding the vestibular follow-up of cCMV patients based on the results of a large-scale, longitudinal follow-up study. It can be concluded that cCMV-induced VD is characterized by its unstable nature as, the vestibular impairment of children with a cCMV-infection progressed, fluctuated, or improved in 60% of our vestibular-impaired population, and was delayed in onset in no less than 33.3%. Therefore, systematic longitudinal vestibular follow-up of cCMV patients is of utmost importance. This will enable early detection and adequate rehabilitation to improve the developmental outcome of the child. Based on recent insights in auditory follow-up and because in our study population most cases of VD were detected before the age of 24 months, it seems appropriate to provide vestibular follow-up until the age of 4 years. In 88.6%, 79.2%, and 87.5% of our ears with VD, a dysfunction of the horizontal, anterior, and posterior SCC was found, respectively. A saccular dysfunction was found in 74.3% of the cases and an utricular dysfunction in 95.5%. Even though that in the majority of our vestibular-impaired ears both SCC and otolith organs were affected (85.7%), isolated SCC dysfunctions (5.7%) and isolated otolith dysfunctions (8.6%) did occur. Since one single vestibular test would be insufficient to detect all patients with a cCMV-induced VD, extensive vestibular follow-up that evaluates all five components of the vestibular system is recommended. The risk for cCMV-induced VD is significantly higher in hearing-impaired patients and children where seroconversion occurred during the first trimester of pregnancy. Additionally, VD tended to occur more often in symptomatic cCMV patients and patients with abnormalities on brain imaging. However, this trend was not significant and could be a result of the patients hearing status rather than their symptoms at birth or results on brain imaging. Therefore, the predictive value of a symptomatic cCMV-infection and abnormalities on brain imaging remains uncertain. When solely those cCMV patients who present themselves with risk factors (i.e. hearing loss, and first trimester seroconversion) would receive vestibular follow-up, approximately 75% of our vestibular-impaired patients would have been detected. Therefore, it is advised to at least provide appropriate, longitudinal vestibular follow-up to cCMV patients with hearing loss and/or a first trimester seroconversion. To be able to detect all vestibular-impaired patients, ideally all cCMV patients should receive vestibular follow-up. However, this ideal scenario is often not feasible in clinical practice. Nevertheless, we believe it would be valuable to provide information about cCMV-induced VD to all parents of cCMV patients (e.g. by means of an information brochure). Parents should learn how to recognise certain red flags in their child possibly indicating VD (e.g. delay, stagnation or deterioration of the motor development). When they notice such red flags, vestibular assessment should be performed.

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8 Appendix

Appendix 1: details about the vestibular characteristics at last assessment of the 30 patients who developed a vestibular dysfunction during follow-up.

	Laterality	*Onset*	*Age at diagnosis Right Ear*	*Age at diagnosis Left Ear*	*Evolution*	*Otolith Dysfunction Right Ear*	*Otolith Function Left Ear*	*SCC Function Right Ear*	*SCC Function Left Ear*	*N° of assessments*	*Duration of FU*
Patient 1	Unilateral	First assessment	NA	6 mo	Stable	N: Utricular function: U Saccular function: N	D: Utricular function: U Saccular function: SD	N: H SCC function: N A SCC function: U P SCC function: U	D: H SCC function: SD A SCC function: U P SCC function: U	4	16 mo
Patient 2	Unilateral	Delayed	45 mo	NA	Fluctuating	D: Utricular function: MD Saccular function: N	N: Utricular function: N Saccular function: N	D: H SCC function: SD A SCC function: MD P SCC function: SD	N: H SCC function: N A SCC function: N P SCC function: N	7	54 mo
Patient 3	Unilateral	Delayed	25 mo	NA	Fluctuating	D: Utricular function: MD Saccular function: N	N: Utricular function: N Saccular function: N	D: H SCC function: SD A SCC function: MD P SCC function: MD	N: H SCC function: N A SCC function: N P SCC function: N	7	51 mo
Patient 4	Unilateral	First assessment	35 mo	NA	Stable	D: Utricular function: MD Saccular function: N	N: Utricular function: N Saccular function: N	N: H SCC function: N A SCC function: N P SCC function: N	N: H SCC function: N A SCC function: N P SCC function: N	5	47 mo
Patient 5	Unilateral	Delayed	12 mo	NA	Fluctuating	D: Utricular function: MD Saccular function: N	N: Utricular function: N Saccular function: N	D: H SCC function: SD A SCC function: MD P SCC function: MD	N: H SCC function: N A SCC function: N P SCC function: N	5	30 mo
Patient 6	Unilateral	First assessment	17 mo	NA	Stable	D: Utricular function: MD Saccular function: SD	N: Utricular function: N Saccular function: N	D: H SCC function: SD A SCC function: SD P SCC function: SD	N: H SCC function: N A SCC function: N P SCC function: N	3	18 mo
Patient 7	Bilateral	First assessment	23 mo	23 mo	Improving	D: Utricular function: SD Saccular function: SD	D: Utricular function: SD Saccular function: SD	D: H SCC function: SD A SCC function: SD P SCC function: SD	D: H SCC function: MD A SCC function: MD P SCC function: SD	6	47 mo
Patient 8	Unilateral	First assessment	NA	6 mo	Progressive	N: Utricular function: U Saccular function: N	D: Utricular function: U Saccular function: SD	N: H SCC function: N A SCC function: U P SCC function: U	D: H SCC function: SD A SCC function: U P SCC function: U	4	18 mo
Patient 9	Bilateral	First assessment	9 mo	9 mo	Stable	D: Utricular function: SD Saccular function: SD	D: Utricular function: SD Saccular function: SD	D: H SCC function: SD A SCC function: SD P SCC function: SD	D: H SCC function: SD A SCC function: SD P SCC function: SD	4	46 mo
Patient 10	Unilateral	First assessment	11 mo	NA	Improving	D: Utricular function: SD Saccular function: SD	N: Utricular function: N Saccular function: N	D: H SCC function: SD A SCC function: MD P SCC function: MD	N: H SCC function: N A SCC function: N P SCC function: N	6	50 mo
Patient 11	Unilateral	Delayed	NA	12 mo	Progressive	N: Utricular function: U Saccular function: N	D: Utricular function: U Saccular function: SD	N: H SCC function: N A SCC function: U P SCC function: U	D: H SCC function: SD A SCC function: U P SCC function: U	4	18 mo
Patient 12	Bilateral normal	Delayed	12 mo	12 mo	Improving	N: Utricular function: U Saccular function: N	N: Utricular function: U Saccular function: N	N: H SCC function: N A SCC function: U P SCC function: U	N: H SCC function: N A SCC function: U P SCC function: U	5	24 mo
Patient 13	Unilateral	First assessment	8 mo	18 mo	Fluctuating	D: Utricular function: SD Saccular function: SD	N: Utricular function: N Saccular function: N	D: H SCC function: SD A SCC function: SD P SCC function: SD	N: H SCC function: N A SCC function: N P SCC function: N	8	46 mo
Patient 14	Bilateral	First assessment	12 mo	12 mo	Stable	D: Utricular function: U Saccular function: SD	D: Utricular function: U Saccular function: SD	D: H SCC function: SD A SCC function: U P SCC function: U	D: H SCC function: SD A SCC function: U P SCC function: U	2	2 mo
Patient 15	Unilateral	Delayed	25 mo	NA	Fluctuating	D: Utricular function: MD Saccular function: N	N: Utricular function: N Saccular function: N	D: H SCC function: SD A SCC function: MD P SCC function: SD	N: H SCC function: N A SCC function: N P SCC function: N	8	60 mo

Patient 16	Unilateral	First assessment	36 mo	36 mo	Improving	D:	Utricular function: MD Saccular function: N	N:	Utricular function: N Saccular function: N	N:	H SCC function: N A SCC function: N P SCC function: N	N:	H SCC function: N A SCC function: N P SCC function: N	5	48 mo
Patient 17	Bilateral	First assessment	10 mo	10 mo	Stable	D:	Utricular function: SD Saccular function: SD	D:	Utricular function: SD Saccular function: SD	D:	H SCC function: SD A SCC function: SD P SCC function: SD	D:	H SCC function: SD A SCC function: SD P SCC function: SD	3	26 mo
Patient 18	Unilateral	Delayed	NA	24 mo	Fluctuating	N:	Utricular function: N Saccular function: N	D:	Utricular function: SD Saccular function: SD	N:	H SCC function: N A SCC function: N P SCC function: N	D:	H SCC function: SD A SCC function: SD P SCC function: SD	6	35 mo
Patient 19	Bilateral	First assessment	23 mo	27 mo	Progressive	D:	Utricular function: SD Saccular function: SD	D:	Utricular function: SD Saccular function: SD	D:	H SCC function: SD A SCC function: SD P SCC function: SD	D:	H SCC function: N A SCC function: N P SCC function: SD	5	31 mo
Patient 20	Unilateral	First assessment	NA	6 mo	Stable	N:	Utricular function: U Saccular function: N	D:	Utricular function: U Saccular function: SD	N:	H SCC function: N A SCC function: U P SCC function: U	D:	H SCC function: SD A SCC function: U P SCC function: U	4	30 mo
Patient 21	Bilateral	First assessment	18 mo	18 mo	Progressive	D:	Utricular function: U Saccular function: SD	D:	Utricular function: U Saccular function: SD	D:	H SCC function: SD A SCC function: SD P SCC function: SD	D:	H SCC function: SD A SCC function: SD P SCC function: SD	3	17 mo
Patient 22	Unilateral	First assessment	NA	6 mo	Unknown	N:	Utricular function: U Saccular function: N	D:	Utricular function: U Saccular function: SD	N:	H SCC function: N A SCC function: U P SCC function: U	D:	H SCC function: SD A SCC function: U P SCC function: U	1	0 mo
Patient 23	Bilateral	First assessment	18 mo	33 mo	Progressive	D:	Utricular function: SD Saccular function: SD	D:	Utricular function: SD Saccular function: SD	D:	H SCC function: SD A SCC function: SD P SCC function: SD	D:	H SCC function: SD A SCC function: N P SCC function: SD	4	50 mo
Patient 24	Unilateral	First assessment	NA	7 mo	Stable	N:	Utricular function: U Saccular function: N	D:	Utricular function: U Saccular function: SD	N:	H SCC function: SD A SCC function: SD P SCC function: SD	D:	H SCC function: SD A SCC function: U P SCC function: U	2	3 mo
Patient 25	Unilateral	First assessment	6 mo	NA	Improving	D:	Utricular function: U Saccular function: MD	N:	Utricular function: U Saccular function: N	D:	H SCC function: SD A SCC function: U P SCC function: U	N:	H SCC function: N A SCC function: U P SCC function: U	2	6 mo
Patient 26	Unilateral	Delayed	26 mo	NA	Improving	D:	Utricular function: MD Saccular function: N	N:	Utricular function: N Saccular function: N	N:	H SCC function: N A SCC function: N P SCC function: N	N:	H SCC function: N A SCC function: N P SCC function: N	5	45 mo
Patient 27	Unilateral	First assessment	7 mo	NA	Stable	N:	Utricular function: U Saccular function: N	N:	Utricular function: U Saccular function: N	D:	H SCC function: SD A SCC function: U P SCC function: U	N:	H SCC function: N A SCC function: U P SCC function: U	2	5 mo
Patient 28	Unilateral	Delayed	NA	12 mo	Stable	N:	Utricular function: U Saccular function: N	N:	Utricular function: U Saccular function: N	N:	H SCC function: N A SCC function: U P SCC function: U	D:	H SCC function: SD A SCC function: U P SCC function: U	4	18 mo
Patient 29	Unilateral	Delayed	35 mo	NA	Unknown	D:	Utricular function: N Saccular function: SD	N:	Utricular function: N Saccular function: N	D:	H SCC function: SD A SCC function: SD P SCC function: SD	N:	H SCC function: N A SCC function: N P SCC function: N	4	29 mo
Patient 30	Bilateral normal	First assessment	7 mo	7 mo	Fluctuating	N:	Utricular function: U Saccular function: N	N:	Utricular function: U Saccular function: N	N:	H SCC function: N A SCC function: N P SCC function: N	N:	H SCC function: N A SCC function: N P SCC function: N	5	28 mo

mo: months, N: normal function, D: dysfunction, U: unknown, MD: mild dysfunction, SD: severe dysfunction, SCC: semi-circular canal, H SCC: horizontal semi-circular canal, A SCC: anterior semi-circular canal, P SCC: posterior semi-circular canal, N° of assessments: total number of vestibular assessments, duration of FU: duration of follow-up, NA: not applicable.
Definitions: onset at first assessment: the vestibular dysfunction is present since the first assessment, delayed-onset: the vestibular dysfunction became apparent after a period of objectified normal vestibular functioning, progressive: the vestibular dysfunction progressed from a partial to a total or a mild to a severe or an unilateral to a bilateral dysfunction, fluctuating: the vestibular dysfunction changed frequently, improving: the vestibular dysfunction transitioned from a total to a partial or a mild to a severe or a bilateral to an unilateral dysfunction, mild saccular dysfunction: reduced rectified interpeak amplitude (i.e. < 1.3 with the Neuro-Audio system or < 0.3 with the Bio-Logic system) on the cervical vestibular evoked myogenic potential test, severe saccular dysfunction: absent responses on the cervical vestibular evoked myogenic potential test, mild utricular dysfunction: interpeak amplitude < 10µV on the ocular vestibular evoked myogenic potential test, severe utricular dysfunction: absent responses on the ocular vestibular evoked myogenic potential test, mild semi-circular canal dysfunction: VOR gain < 0.70 on the video head impulse test, severe semi-circular canal dysfunction: VOR gain < 0.40 on the video head impulse test.

Appendix 2: details about the neonatal characteristics and risk factors, and the hearing status of the 30 patients with a vestibular dysfunction.

	Neonatal characteristics				*Hearing status at last assessment*							
	Trimester of seroconversion	Hearing status at birth	Degree of the cCMV-infection	Brain imaging	HL (laterality)	Onset	Evolution	Degree HL Right Ear	Degree HL Left Ear	CI [age (months)] Right Ear	CI [age (months)] Left Ear	Age at diagnosis (months)
Patient 1	Unknown	NH	Asymptomatic	Normal	HL (B)	Delayed	Progressive	Moderate	Profound	No CI	CI (15)	6
Patient 2	First trimester	HL	Severe	Normal	HL (U)	Congenital	Stable	Profound	NH	No CI	No CI	0
Patient 3	First trimester	HL	Severe	Abnormal	HL (U)	Congenital	Stable	Profound	NH	CI (11)	No CI	0
Patient 4	First trimester	NH	Severe	Abnormal	NH	NA	NA	NH	NH	No CI	No CI	NA
Patient 5	First trimester	NH	Severe	Abnormal	NH	NA	NA	NH	NH	No CI	No CI	NA
Patient 6	Second trimester	NH	Severe	Abnormal	HL (U)	Delayed	Improving	Moderate	NH	No CI	No CI	13
Patient 7	Unknown	NH	Asymptomatic	Unknown	HL (B)	Delayed	Progressive	Profound	Profound	CI (24)	CI (24)	20
Patient 8	First trimester	NH	Severe	Abnormal	HL (B)	Delayed	Progressive	Moderate	Moderate	No CI	No CI	11
Patient 9	Unknown	HL	Severe	Abnormal	HL (B)	Congenital	Stable	Severe	Profound	No CI	CI (10)	0
Patient 10	Unknown	HL	Severe	Abnormal	HL (B)	Congenital	Progressive	Profound	Profound	CI (17)	CI (14)	0
Patient 11	Second trimester	NH	Severe	Abnormal	NH	NA	NA	NH	NH	No CI	No CI	NA
Patient 12	Unknown	HL	Severe	Normal	HL (U)	Congenital	Stable	Severe	NH	No CI	No CI	0
Patient 13	First trimester	NH	Asymptomatic	Normal	HL (B)	Delayed	Progressive	Profound	Profound	CI (13)	CI (9)	2
Patient 14	First trimester	HL	Severe	Abnormal	HL (B)	Congenital	Stable	Profound	Profound	CI (11)	No CI	0
Patient 15	First trimester	NH	Asymptomatic	Normal	NH	NA	NA	NH	NH	No CI	No CI	NA
Patient 16	Unknown	NH	Asymptomatic	Normal	NH	NA	NA	NH	NH	No CI	No CI	NA
Patient 17	First trimester	HL	Severe	Normal	HL (B)	Congenital	Stable	Profound	Profound	CI (11)	CI (11)	0
Patient 18	First trimester	NH	Severe	Abnormal	HL (U)	Delayed	Progressive	Severe	NH	No CI	No CI	2
Patient 19	First trimester	NH	Asymptomatic	Normal	HL (U)	Delayed	Fluctuating	NH	Severe	No CI	No CI	19
Patient 20	Unknown	NH	Severe	Abnormal	NH	NA	NA	NH	NH	No CI	No CI	NA
Patient 21	Unknown	NH	Asymptomatic	Abnormal	NH	NA	NA	NH	NH	No CI	No CI	NA
Patient 22	Unknown	NH	Asymptomatic	Normal	NH	NA	NA	NH	NH	No CI	No CI	NA
Patient 23	First trimester	HL	Severe	Abnormal	HL (B)	Congenital	Progressive	Profound	Profound	CI (22)	No CI	0
Patient 24	Unknown	NH	Asymptomatic	Normal	NH	NA	NA	NH	NH	No CI	No CI	NA
Patient 25	First trimester	NH	Moderate	Abnormal	NH	NA	NA	NH	NH	No CI	No CI	NA
Patient 26	First trimester	NH	Severe	Abnormal	NH	NA	NA	NH	NH	No CI	No CI	NA
Patient 27	Unknown	HL	Severe	Unknown	HL (U)	Congenital	Stable	NH	Profound	No CI	No CI	0
Patient 28	First trimester	NH	Severe	Abnormal	NH	NA	NA	NH	NH	No CI	No CI	NA
Patient 29	First trimester	NH	Severe	Abnormal	NH	NA	NA	NH	NH	No CI	No CI	6
Patient 30	Unknown	NH	Asymptomatic	Normal	NH	NA	NA	NH	NH	No CI	No CI	0

NH: normal hearing, HL: hearing loss, U: unilateral, B:bilateral NA: not applicable, cCMV: congenital cytomegalovirus, CI: cochlear implant
Definitions: first trimester: 0 – 12 weeks, second trimester: 13 – 27 weeks, third trimester: 28 – 40 weeks, asymptomatic cCMV-infection: there were no clinically apparent symptoms during neonatal examinations, moderate symptomatic cCMV infection: the infection caused multiple (> 2) or persisting (> 2 weeks) symptoms, severe symptomatic infection: the infection affected the central nervous system, caused isolated sensorineural hearing loss, severe single organ damage or multiple organ damage, progressive: the hearing loss progressed from a unilateral to a bilateral hearing loss or from one hearing loss-category to a more severe category, fluctuating: progression was followed by improvement or reverse, improving: the hearing loss transitioned to a better hearing loss-category, normal hearing: hearing thresholds ≤ 25 dB HL, moderate hearing loss: hearing thresholds between 41 and 70 dB HL, severe hearing loss: hearing thresholds between 71 and 90 dB HL, profound hearing loss: hearing thresholds ≥ 91 dB HL.

9 Approval of the local Ethical Committee (BC-03014 E06)

Afz.: Commissie voor Medische Ethiek

Prof. dr. Ingeborg Dhooge
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Ons kenmerk	Uw kenmerk	datum	pagina
BC-03014 E06	NVT	22/03/2021	1/2

Betreft : Advies voor monocentrische studie met als titel:

Titel hoofdstudie: "Audiovestibulair en motorisch onderzoek bij kinderen met een congenitale cytomegalovirus (cCMV) infectie en kinderen met een neurosensorieel gehoorverlies"

Titel thesis: Naar een gerichte vestibulaire opvolging bij kinderen met cCMV: data-analyse van 4.5 jaar audiovestibulaire follow-up. - Scriptie: Emmely Van Acker

B.U.N.: B6702021000253

*Alle goedgekeurde documenten van studie met als referentie BC-03014
*Begeleidende brief dd 2021-2-11
*Adviesaanvraagformulier Versie 2 2021-2-12 (Document E) (Volledig ontvangen dd 04/03/2021)

Advies werd gevraagd door: Prof. dr. Ingeborg Dhooge

BOVENVERMELDE DOCUMENTEN WERDEN DOOR HET ETHISCH COMITÉ BEOORDEELD. ER WERD EEN POSITIEF ADVIES GEGEVEN OVER DIT PROTOCOL OP 18/03/2021 INDIEN DE STUDIE NIET WORDT OPGESTART VOOR 18/03/2022, VERVALT HET ADVIES EN MOET HET PROJECT TERUG INGEDIEND WORDEN.
Vooraleer het onderzoek te starten dient contact te worden genomen met HIRUZ CTU (09/332 05 00).

THE ABOVE MENTIONED DOCUMENTS HAVE BEEN REVIEWED BY THE ETHICS COMMITTEE.A POSITIVE ADVICE WAS GIVEN FOR THIS PROTOCOL ON 18/03/2021 IN CASE THIS STUDY IS NOT STARTED BY 18/03/2022, THIS ADVICE WILL BE NO LONGER VALID AND THE PROJECT MUST BE RESUBMITTED.
Before initiating the study, please contact HIRUZ CTU (09/332 05 00).

DIT ADVIES WORDT OPGENOMEN IN HET VERSLAG VAN DE VERGADERING VAN HET ETHISCH COMITE VAN 20/04/2021.
THIS ADVICE WILL APPEAR IN THE PROCEEDINGS OF THE MEETING OF THE ETHICS COMMITTEE OF 20/04/2021.

* *Het Ethisch Comité werkt volgens 'ICH Good Clinical Practice' - regels*
* *Het Ethisch Comité bekiemtoont dat een gunstig advies niet betekent dat het Comité de verantwoordelijkheid voor het onderzoek op zich neemt. Bovendien dient U er over te waken dat Uw mening als betrokken onderzoeker wordt weergegeven in publicaties, rapporten voor de overheid enz., die het resultaat zijn van dit onderzoek.*
* *In het kader van 'Good Clinical Practice' moet de mogelijkheid bestaan dat het farmaceutisch bedrijf en de autoriteiten inzage krijgen van de originele data. In dit verband dienen de onderzoekers erover te waken dat dit gebeurt zonder schending van de privacy van de proefpersonen.*
* *Het Ethisch Comité benadrukt dat het de promotor is die garant dient te staan voor de conformiteit van de anderstalige informatie- en toestemmingsformulieren met de nederlandstalige documenten.*
* *Geen enkele onderzoeker betrokken bij deze studie is lid van het Ethisch Comité.*
* *Alle leden van het Ethisch Comité hebben dit project beoordeeld. (De ledenlijst is bijgevoegd)*
* *The Ethics Committee is organized and operates according to the 'ICH Good Clinical Practice'*

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rules.
- *The Ethics Committee stresses that approval of a study does not mean that the Committee accepts responsibility for it. Moreover, please keep in mind that your opinion as investigator is presented in the publications, reports to the government, etc., that are a result of this research.*
- *In the framework of 'Good Clinical Practice', the pharmaceutical company and the authorities have the right to inspect the original data. The investigators have to assure that the privacy of the subjects is respected.*
- *The Ethics Committee stresses that it is the responsibility of the promotor to guarantee the conformity of the non-dutch informed consent forms with the dutch documents.*
- *None of the investigators involved in this study is a member of the Ethics Committee.*
- *All members of the Ethics Committee have reviewed this project. (The list of the members is enclosed)*

Namens het Ethisch Comité / On behalf of the Ethics Committee

Prof. dr. P. Deron
Voorzitter / Chairman

CC: UZ Gent – HIRUZ CTU
FACG - Research & Development; Victor Hortaplein 40, postbus 40 1060 Brussel
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Mevr. C. VANCAENEGHEM (patiëntvertegenwoordiger)
Dhr. B. VANDERHAEGEN (UZG - moraaltheoloog, ♂)
Prof.dr. W. VAN BIESEN (UZG – nefroloog, ♂)
Dr. J. VAN ELSEN (huisarts, ♂)
Dr. G. VAN LANCKER (UZG – klinisch farmacoloog, ♀)
Prof.dr. K. VAN LIERDE (UG – logopediste, ♀)
Prof.dr. H. VERSTRAELEN (UZG – Vulva-arts, ♂)

UZ GENT
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Universitair Ziekenhuis Gent
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www.uzgent.be

10 Unilateral Declaration of Confidentiality

UNIVERSITEIT GENT

VERTROUWELIJKHEID & OVERDRACHT VAN RECHT EENZIJDIGE VERKLARING

Deze Verklaring wordt afgelegd ten aanzien van

Universiteit Gent, openbare instelling met rechtspersoonlijkheid, waarvan de bestuurszetel gevestigd is te 9000 Gent, Sint-Pietersnieuwstraat 25, gekend onder ondernemingsnummer 0248.015.142 voor wie optreedt bij delegatie ingevolge het besluit van de Raad van Bestuur, prof. dr. Rik Van de Walle, rector ("UGent")

Door:

Emmely Van Acker – **woonachtig te** Gent

Student, ingeschreven aan UGent in de richting: logopedische en Audiologische wetenschappen - Audiologie

Project: Naar een gerichte vestibulaire opvolging bij kinderen met cCMV: data-analyse van 4,5 jaar audiovestibulaire follow-up

In het kader van zijn/haar opleiding aan UGent, zal ondergetekende kennis krijgen van bepaalde vertrouwelijke informatie toebehorend aan UGent of door derden toevertrouwd aan UGent.

Ondergetekende verbindt er zich toe om de aan hem/haar in het kader van het Project ter beschikking gestelde informatie op geen enkele manier publiek bekend te maken zonder voorafgaande uitdrukkelijke schriftelijke toelating van UGent. Deze verbintenis geldt voor een duur van **tien (10) jaar** te rekenen vanaf de datum van deze Eenzijdige Verklaring.

Ondergetekende draagt eveneens al zijn/haar rechten op onderzoeksresultaten behaald in het kader van het Project over aan UGent.

Deze Eenzijdige Verklaring vervangt alle schriftelijke en mondelinge overeenkomsten die de partijen eerder zijn aangegaan met betrekking tot haar voorwerp en omvat de enige en volledige overeenkomst ter zake tussen de partijen.

Aldus verklaart en tekent voor akkoord:

Naam	Emmely Van Acker
Handtekening	*Voorafgegaan door handgeschreven vermelding "gelezen en goedgekeurd"* Gelezen en goedgekeurd
Datum:	30/09/2020

GHENT UNIVERSITY

VERTROUWELIJKHEID & OVERDRACHT VAN RECHT EENZIJDIGE VERKLARING

NDA-EV

Deze Verklaring wordt afgelegd ten aanzien van

Universiteit Gent, openbare instelling met rechtspersoonlijkheid, waarvan de bestuurszetel gevestigd is te 9000 Gent, Sint-Pietersnieuwstraat 25, gekend onder ondernemingsnummer 0248.015.142 voor wie optreedt bij delegatie ingevolge het besluit van de Raad van Bestuur, prof. dr. Rik Van de Walle, rector ("UGent")

Door:

Emmely Van Acker

Student, ingeschreven aan UGent in de richting: logopedische en audiologische wetenschappen - Audiologie

Project: Omschrijving / titel onderzoeksproject Naar een gerichte vestibulaire opvolging bij kinderen met cCMV : data-analyse van 4,5 jaar audiovestibulaire follow-up.

In het kader van zijn/haar opleiding aan UGent, zal ondergetekende kennis krijgen van bepaalde vertrouwelijke informatie toebehorend aan UGent of door derden toevertrouwd aan UGent.

Ondergetekende verbindt er zich toe om de aan hem/haar in het kader van het Project ter beschikking gestelde informatie op geen enkele manier publiek bekend te maken zonder voorafgaande uitdrukkelijke schriftelijke toelating van UGent. Deze verbintenis geldt voor een duur van **tien (10) jaar** te rekenen vanaf de datum van deze Eenzijdige Verklaring.

Ondergetekende draagt eveneens al zijn/haar rechten op onderzoeksresultaten behaald in het kader van het Project over aan UGent.

Ondergetekende garandeert de mensenrechten te zullen respecteren.

Deze Eenzijdige Verklaring vervangt alle schriftelijke en mondelinge overeenkomsten die de partijen eerder zijn aangegaan met betrekking tot haar voorwerp en omvat de enige en volledige overeenkomst ter zake tussen de partijen.

Aldus verklaart en tekent voor akkoord:

Naam	Emmely Van Acker
Handtekening	*Voorafgegaan door handgeschreven vermelding "gelezen en goedgekeurd"* Gelezen en goedgekeurd 
Datum:	27/09/2021