Specials FIAPAS
Number 167, 2018

CODEPEH
COMISIÓN PARA LA DETECCIÓN PRECOZ DE LA HIPOACUSIA
COMMISSION FOR THE EARLY DETECTION OF HEARING LOSS

Update of early detection programmes for pediatric hearing loss: 2018 CODEPEH recommendations (Level 1 Screening)

Actualización de los programas de detección precoz de la sordera infantil: recomendaciones CODEPEH 2018 (Nivel 1 Detección)

Author: CODEPEH
(Faustino Núñez, Carmen Jáudenes, José Miguel Sequí, Ana Vivanco, José Zubicaray)

For bibliographic reference:
CODEPEH (Núñez, F. et al.) (2018): "Update of early detection programmes for pediatric hearing loss: 2018 CODEPEH recommendations (Level 1 Detection)", FIAPAS Journal, 167. Special supplement

ACCESS THE SPANISH EDITION

The present CODEPEH Recommendations 2018 document has been prepared in the context of the project *"Update on the Programs for the Early Detection of Infant Hearing Loss"*, developed by the Spanish Federation of Families of Deaf People (Confederación Española de Familias de Personas Sordas-FIAPAS), in collaboration with the Commission for the Early Detection of Infant Hearing Loss (Comisión para la Detección Precoz de la Sordera Infantil-CODEPEH), and with co-organization by the Royal Patronage for Disability (Real Patronato sobre Discapacidad).

The following are members of the CODEPEH:

Dr. Faustino Núñez-Batalla, Head
ENT Department, Hospital Universitario Central de Asturias-Oviedo
In representation of the Spanish Society of Otolaryngology

Ms. Carmen Jáudenes Casaubón, member,
Director of FIAPAS
In representation of the Spanish Confederation of Families of Deaf People

Dr. José Miguel Sequí Canet, member,
Head of the Pediatrics Department, Hospital Universitario de Gandía-Valencia
In representation of the Spanish Association of Pediatrics

Dr. Ana Vivanco-Allende, member,
Pediatrics Department, Hospital Universitario Central de Asturias-Oviedo
In representation of the Spanish Association of Pediatrics

Dr. José Zubicaray-Ugarteche, member,
Pediatric ENT Department, Navarre Hospital Complex-Pamplona
In representation of the Spanish Society of Otolaryngology

Contact: codepeh@gmail.com

FIAPAS
CONFEDERACIÓN ESPAÑOLA DE FAMILIAS DE PERSONAS SORDAS
SPANISH CONFEDERATION OF FAMILIES OF DEAF PEOPLE

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL
REAL PATRONATO SOBRE DISCAPACIDAD
SPANISH MINISTRY OF HEALTH, CONSUMER AFFAIRS AND SOCIAL WELFARE
ROYAL PATRONAGE FOR DISABILITY

ABSTRACT

Programs for early detection of congenital hearing loss have been successfully established mainly in developed countries, after overcoming some conceptual errors against their implantation or some critics of their efficacy. However, some difficulties and weaknesses are still identified in them: the detection of late-onset hearing loss and the percentage of children who did not pass the screening and did not complete the process of diagnosis and treatment, being cases that are lost in the process.

The purpose of this Document is to analyze these problems to determine areas for improvement and to emphasize one of the basic principles for the success of the programs: the continuous training for the interdisciplinary team.

The result of the review process carried out by CODEPEH is drafted as Recommendations for updating the Programs with the evidences of the last decade, the advances in the screening technology, the impact of the present knowledge on congenital infection by cytomegalovirus, the genetic hearing loss researches and control systems of lost to follow-up cases.

KEY WORDS

Hearing loss, newborn hearing screening, loss to follow-up, congenital cytomegalovirus infection, etiological diagnosis of pediatric hearing loss.

RESUMEN

Los programas de detección precoz de la hipoacusia congénita se han extendido de forma exitosa, especialmente en países desarrollados, superando errores conceptuales argumentados contra su implantación o críticas a su eficacia. No obstante, se identifican algunas dificultades y debilidades en ellos: la detección de la hipoacusia de desarrollo tardío y el porcentaje de niños que no pasaron el cribado y no completan el diagnóstico ni el tratamiento, siendo casos que se pierden en el proceso.

El objetivo del presente Documento es analizar estos problemas para determinar puntos de mejora e incidir en un principio básico del éxito de los programas: la formación continuada del equipo interdisciplinar.

El resultado del trabajo de revisión llevado a cabo por la CODEPEH se plasma en la formulación de unas recomendaciones orientadas a actualizar los programas con las evidencias aparecidas en la última década, abordando los progresos en la tecnología de cribado, el impacto del conocimiento actual sobre la infección congénita por citomegalovirus y los estudios genéticos de la hipoacusia en los programas, así como los sistemas de control de la pérdida de casos en el proceso.

PALABRAS CLAVE

Hipoacusia, cribado neonatal hipoacusia, pérdidas en el seguimiento, infección congénita citomegalovirus, diagnóstico etiológico de la hipoacusia infantil.

Table of contents

1. INTRODUCTION

Eight years have passed since the CODEPEH published the Document of Recommendations highlighting the important role of early detection and early intervention in the learning of spoken language in children with hearing loss, thus providing an important tool for allowing their full inclusion in society (Trinidad *et al.,* 2010: 69-77). The updates on the neonatal screening protocols for hearing loss described in this document were considered to be of reference, and were adopted in many screening programs, assuming the following as established facts: 1. Permanent bilateral congenital hearing loss has an incidence of 1-5 cases per 1000 births. This incidence is higher than that of any of the metabolic diseases which are screened by means of the "heel test" 2. Hearing loss, in the absence of appropriate early treatment, has serious consequences for the child and family, since correct hearing is required during critical childhood periods in order to ensure optimal development 3. Current technologies (automated brainstem evoked potentials and otoacoustic emissions) have been shown to be sufficiently accurate, reliable, objective and cost-effective in their assigned role for the early detection of hearing loss (Nikolopoulos, 2015: 635-7).

A number of studies have confirmed that universal screening shortens the times to both diagnosis and intervention in cases of hearing loss (Wake *et al.,* 2016: 1-10) (Korver *et al.,* 2010: 1701-8) (Kennedy *et al.,* 2005: 660-2) (Kennedy, 1999: 73-5). Compared with the mean age of two years at diagnosis in non-screened cases, it has been shown that neonatal screening is able to confirm the diagnosis of hearing loss before 6 months of life (Wood *et al.,* 2015: 353-8). The consequences of early diagnosis and treatment of hearing loss in terms of language acquisition and reading understanding have been shown to be positive, and there is even evidence of their usefulness beyond the school age (Pimperton *et al.,* 2017: 598-610) (Bruijnzeel *et al.,* 2016: 113-26) (Pimperton *et al.,* 2016: 9-15) (Ching *et al.,* 2013: 535-52) (Kennedy *et al.,* 2006: 2131-41).

The early diagnosis and treatment of hearing loss has been shown to be effective in relation to language acquisition and reading comprehension. The positive effects extend beyond school age

1.1. Updating points

Although programs for the early detection of congenital hearing loss have overcome the conceptual errors that generated initial reluctance to adopt them, and have been successfully and widely introduced (particularly in developed countries), many difficulties and weaknesses persist to the present day. The analysis of such problems makes it possible to identify a number of points on which to act in order to improve these programs.

With the gradual introduction of the programs, the age of the infants at diagnosis of hearing loss has decreased from two years to only a few months of life.

However, it is currently not unusual to find children with profound hearing loss, even requiring cochlear implantation, who had initially passed the neonatal screening test. These children with late-developing hearing loss (in some cases related to congenital cytomegalovirus [CMV] infection or genetic alterations) are in a worse situation than those who did not pass initial screening, since the diagnosis is often delayed because of the false belief that passing the screening test guarantees permanent normal hearing.

Another major weakness of these programs is the number of children that do not pass screening but in whom the diagnostic process is not completed - this situation resulting in a lack of needed early treatment. The percentage of children who do not pass the screening test and is lost to follow-up is alarming (reaching 20-50%), and this threatens the objectives of the program. It has been shown that this problem is largely related to parent attitude towards the process and to the socioeconomic conditions of the family, which are factors upon which action can be taken (Bush *et al.,* 2017: S1-13). However, other factors may play a role.

Continuous training of the professionals conforming the interdisciplinary team of early detection and diagnosis programs is crucial for success

Although screening, diagnosis and early treatment programs for infant hearing loss have a long history, it is important to remember and update the basic principles that can ensure their success, through ongoing training of the professionals in the interdisciplinary team, as the cornerstone elements of these programs. The CODEPEH therefore considers it necessary to establish new recommendations that can contribute to update hearing screening programs on the basis of the evidence that has emerged in the last decade. These recommendations contemplate the advances related to the first level in the application of these programs: detection. The topics include screening protocols and technology, the impact of current knowledge on CMV and the genetics of hearing loss upon the programs, as well as the systems for the control of case losses in the process. Future publications will continue to revise the other levels and processes of the programs (diagnosis, treatment and monitoring).

2. SCREENING TECHNIQUES

Normal hearing requires correct functioning of the entire hearing system. Most cases of hearing loss are due to lesions from the external ear to the external hair cells found in the cochlea. When evaluating hearing in the newborn infant, a series of tests are available for assessing the integrity of the system.

Tests with aOAE and aAEP remain the recommended techniques for neonatal hearing screening.

Two tests are currently used in our setting at the time of birth: otoacoustic emissions with automatic equipment (aOAEs) and automatic auditory evoked potentials (aAEPs).

● Otoacoustic emissions

Otoacoustic emissions are a response of the normal functioning of the external hair cells. They represent a mechanical response of the inner ear, and are considered to be a pre-neural phenomenon, because they are present even if the auditory nerve is sectioned, and they moreover reverse their polarity together with the stimulus.

Since most cases of hearing loss are characterized by lesions from the external or middle ear or cochlea to the external hair cells, otoacoustic emissions (OAEs) are absent or reduced in these cases. Although there is a small percentage of retrocochlear lesions that cannot be diagnosed by this method, OAEs remain useful and help us to establish the topography of the hearing lesion (Zubicaray *et al.,* 2014: 1-15).

Otoacoustic emissions of clinical usefulness are evoked emissions, whether transient or products of distortion. They are present in 98% of all normally hearing individuals, and disappear when the threshold is higher than 30 dB (Bonfils *et al.,* 1990: 186-9).

Transient otoacoustic emissions (TOAEs) are the most commonly used in neonatal screening protocols. Their advantages include low cost, rapid performance and high sensitivity. However, TOAEs pose some inconveniences, such as the inability to identify lesions posterior to the external or outer hair cells. As a result, they are unable to detect hearing loss of retrocochlear origin, and moreover yield higher false-positive rates than aAEPs - particularly in the first days of life (Boudewyns *et al.,* 2016: 993-1000) (Morant *et al.,* 2014: 119-27).

At present, aOAE equipment that eliminates subjectivity in the interpretation of the results is used for neonatal screening.

- **Auditory evoked potentials**

In order to identify correct hearing, aAEPs are based on a mathematical algorithm that eliminates the subjectivity of the explorer (Keohane *et al.,* 2004: 112-6). These potentials have very high specificity and sensitivity (close to 100%). The advantage of this test is that it is more sensitive, since it detects hearing loss secondary to auditory neuropathy (retrocochlear hearing loss)(Duman *et al.,* 2008: 1091-5). It can also be performed on the first day of life, and produces in fewer false-positive results. The inconveniences of the technique are the cost of the disposable materials used, electrical interferences (care therefore being needed when choosing the place to perform the test), the exploratory time, and lesser precision in the diagnosis of low frequencies - with a possible poorer detection of hearing loss secondary to middle ear disorders (Zubicaray *et al.,* 2014: 1-15).

As steady state auditory evoked potentials (SSAEPs), may be used in the screening phase

We can use aOAEs when considering neonatal hearing screening, though taking into account that retrocochlear hearing loss will not be detected. As a result, we also need to perform aAEPs or brainstem auditory evoked potentials (BAEPS) in high risk infants. On the other hand, given the greater incidence of false-positive results with aOAEs, screening must be performed in two steps so as not to needlessly refer children to the diagnostic phase of the program.

Screening based on aAEPs can be done in a single step, and hearing neuropathy moreover can also be diagnosed - though it must be taken into account that low frequency hearing loss may go unnoticed.

In the future, it is expected that other techniques, such as steady state auditory evoked potentials (SSAEPs), may be used in the screening phase (Mijares *et al.,* 2015:8-15).

3. LOSS OF CASES IN THE PROCESS

The main weakness of neonatal hearing screening programs is the existence of an alarming percentage of children who have failed initial screening but are not taken by their parents for subsequent tests or controls. A report published by the Centres for Disease Prevention and Control (CDC) suggests that about half of all screened cases are lost in the process or have incomplete documentation of their situation (Bush *et al.* 2017: S1-13). These high loss rates adversely affect the efficiency of the early detection and treatment of hearing loss. As a general rule, it is accepted that a loss rate of over 20% adversely affects the validity of the results of the program. In a meta-analysis involving 53 studies on case losses in the process (Ravi *et al.,* 2016: 29-36), the overall rates were found to be 20% in single-centre studies and 21% in multicentre studies.

3.1. Causal factors

It is important to understand the factors that contribute to case losses in the monitoring process, since this would help to develop new regulations and improve and modify the protocols in order to increase the effectiveness of the program for the early detection, diagnosis and treatment of congenital hearing loss. The main factor identified in the different studies that have addressed this problem is a lack of knowledge about the importance of completing the diagnostic process in children who do not pass initial screening for hearing loss. The next most important factor is the distance between the home of the patient and the centres where the tests are made. Work obligations and unfavourable attitudes on the part of both the parents and healthcare professionals are also regarded as significant factors.

The data suggest that a large percentage of screened cases are lost in the process or present incomplete documentation of their status

The main cause of case losses in the process is of parental origin. This is paradoxical, taking into account the high satisfaction rates of parents expressed in surveys on neonatal screening programs for hearing loss (Nikolopoulos, 2015: 635-7). However, other factors also exert an influence, such as living in a rural setting, belonging to ethnic minorities, or having limited financial resources (Liu *et al*., 2008: e335-43). Therefore, and although in most programs the referral circuits for patients with hearing loss detected in the etiological and diagnostic procedures are clearly defined, the process is complex and proves difficult to complete for many parents (Des-Georges, 2003: 89-93).

3.2. Elements for improvement

Although some programs for the early detection of hearing loss have attempted to reduce the number of lost cases, there is currently no standardized and evidence-based method or approach. However, lack of adherence to a diagnostic and therapeutic process in other areas of healthcare has been targeted for intervention through so-called "navigation programs" for patients.

The "navigator" is a trained health professional that provides counselling and mitigates the personal or environmental factors implicated in social cognitive theory (Bush et al., 2017: S1-13) in order to promote adherence to diagnostic and therapeutic processes. These professionals attend and guide patients in order to facilitate compliance with visiting appointments and tests in healthcare centres. In the field of Oncology, these navigation programs have been particularly successful in helping patients of low socioeconomic origin, improving compliance with medical appointments and obtaining a diagnosis in a timely manner - this moreover being associated to significant savings in healthcare expenditure.

Within the interdisciplinary team of the program, it is important to appoint a family liaison and support professional

Considering the transfer of these experiences to the early detection of hearing loss, a randomized, prospective controlled trial (Bush *et al.,* 2017: S1-13) has demonstrated the efficacy of the intervention in reducing lack of adherence to the diagnostic process after failing to pass the screening tests, compared with the basal situation in which the "navigator" does not intervene.

The functions of the "navigator" should be assumed by a professional belonging to the interdisciplinary team of the program for the screening of hearing loss. This also implies the need for a reliable database in order to know the cases that need to be contacted and recruited. In turn, the "navigator" would serve as the link with the Family Association Movement, providing the support and attention required by the families, and acting where applicable as liaison professional with the social services.

Thus, the most frequently recommended measures for mitigating the many cases lost in the process include the need for a committed interdisciplinary team; public awareness campaigns on the importance of programs for the early detection, diagnosis and treatment of infant hearing loss; and improved maintenance of the necessary documentation systems and databases.

The Family Association Movement must be a point of support throughout the process

4. CONGENITAL CYTOMEGALOVIRUS INFECTION

Congenital cytomegalovirus (cCMV) infection is very common worldwide, with an estimated incidence in developed countries of 0.5-0.7% among all live newborns (Fowler and Boppana, 2018: 149-54) (Moresco *et al.,* 2018: 88-91).

The incidence in developing countries is even higher (1-5% of all births). The economic burden of cCMV is very important, since affected children require special therapeutic and educational management (Marsico *et al.,* 2017: 38).

4.1. Diagnosis of cCMV

The diagnosis of cCMV infection is based on the detection of CMV DNA through polymerase chain reaction (PCR) amplification, which presents high sensitivity and specificity in a broad variety of biological samples such as urine, saliva, blood and others (Guoyu *et al.,* 2017: 376-86) (Gantt *et al.,* 2017: e267) (De Vries *et al.,* 2013: 113-7).

The preferred samples for cCMV screening in infants are urine and saliva, since large amounts of viruses are excreted in them. Indeed, these samples are more useful than blood, where the low viral loads are often low. Urine samples classically have been collected using a bag, with a sensitivity of 100% and specificity of 99%. A single negative sample thus suffices to rule out infection, while a positive test before 21 days of age would confirm infection (Luck *et al.,* 2017: 1205-13). However, urine sampling in a bag has several limitations that can be avoided by performing urine collection from cotton swabs in the diaper (Ross *et al.,* 2015: 903-5).

The most feasible option is to collect a sample of saliva (fresh or dry), but this also has limitations because it is less sensitive, and especially because it may be contaminated as a result of the intake of breast milk, which could be infected with CMV in 0.03-0.14% of the cases. A positive result always should be confirmed with a urine sample (Hilditch *et al.,* 2018: 988-92) (Kummer and Marcrum, 2018: 20-6) (Rawlinson *et al.,* 2017: e177-88) (Cardoso *et al.,* 2015: 206-7) (Gunkel *et al.,* 2014: 61-4) (Boppana *et al.,* 2011: 2111-8) (Lawrence, 2006: 99-107).

If the infant is more than three weeks old, PCR testing in urine, saliva or blood would not be definitive, since infection in such cases could be congenital or acquired, and PCR testing would have to be made in the blotting paper of the metabolic screening test in order to allow confirmation. A positive result would confirm the infection, though a negative result would not discard infection, due to the poorer sensitivity of this method (Moteki *et al.,* 2018: 708-12) (Vives-Oñós *et al.,* 2018: 10.1097/ INF. 0000000000002144 [Epub ahead of print]) (Ross *et al.,* 2017: 57-61) (Koontz *et al.,* 2015: 95-9) (Boppana *et al.,* 2010: 1375-82) (Choi *et al.,* 2009: 1095-8).

This test may be very useful in the retrospective diagnosis of cCMV, and may provide information on the etiology of hearing loss. A retrospective analysis showed that 26% of all patients with idiopathic hearing loss in childhood had detectable CMV in the metabolic screening test (Meyer *et al.,* 2017: 565-70). Cytomegalovirus serology is not considered useful for the diagnosis of congenital infection (Badia, 2014: 356-66).

Recent studies have identified cCMV as one of the most important causes of congenital and also postnatal hearing loss, only behind hearing loss of genetic origin, since it is detected in a large percentage of children with confirmed hearing loss. Some studies have identified cCMV as the cause of approximately 20% of all cases of congenital sensorineural hearing loss - a figure that reaches 25% at four years of age (Kummer and Marcrum, 2018: 20-6) (Nance *et al.,* 2006: 221-5) (Morton *et al.,* 2006: 2151-64).

4.2. Asymptomatic and symptomatic cCMV

Congenital CMV infection is usually classified as symptomatic or asymptomatic at the time of birth. Symptoms in the newborn are diverse, though in practice signs or symptoms of cCMV infection are detected in the routine neonatal examination in only about 13% of the cases. The great majority therefore remain undiagnosed at this age, and are classified as asymptomatic cases (Fowler and Boppana, 2018: 149-54) (Kummer and Marcrum, 2018: 20-6) (Lim and Lyall, 2017: S89-94) (Williams *et al.,* 2015: F501-6).

Recent data show that in the long term, a large percentage of asymptomatic children (25%) will develop hearing loss (Lanzieri *et al.,* 2018: 736-44) (Lanzieri *et al.,* 2017: 875-80). In global numbers, most children with hearing loss due to cCMV (58%) will have been classified as asymptomatic cases (Bartlett *et al.* 2017: e1938) (Lopez *et al.* 2017: e20171517) (Goderis *et al.* 2014: 972-82).

A child is considered to be symptomatic in the presence of typical signs or symptoms in the hematological, ophthalmological, auditory or neurological sphere, among others (Luck *et al.,* 2017: 1205-13).

Diagnostic suspicion requires complementary studies of different kinds. The use of auditory evoked potential (AEP) testing is recommended for the hearing study, since the typical hearing loss of cCMV may be cochlear and/or retrocochlear (Lanzieri *et al.,* 2018: 736-44) (Lim and Lyall, 2017: S89-94) (Luck *et al.,* 2017: 1205-13).

4.3. Hearing loss associated to cCMV

Hearing loss is the most frequent consequence in symptomatic children. A total of 30-65% will have hearing loss that can be detected at birth, though in 18-30% of the cases the disorder manifests later, reaching an incidence of 74% at 18 years of age. Delayed onset hearing loss can be seen in both asymptomatic and symptomatic patients, though in different proportions (9-18%) (Kummer and Marcrum, 2018: 20-6).

In addition, the disorder is often progressive (18-63% of cases), reaching profound hearing loss in 78% of the cases over the first 6 years of life (Goderis *et al.,* 2016: 110-15) (Goderis *et al.,* 2014: 972-82).

Such hearing loss moreover is usually unilateral, particularly in asymptomatic patients (57%), in whom it may be the only manifestation, and is usually severe. Asymmetrical presentations are sometimes observed. Another feature is that hearing loss can be fluctuating (20-24%) in a single ear or at some frequencies (Kim *et al.,* 2018: 1-8).

Hearing loss associated to cCMV will not be detected unless the infection is identified during pregnancy, through the neonatal clinical manifestations, or from more or less systematic CMV screening. Only about 10% of all children with hearing loss at birth related to cCMV are diagnosed from clinical signs of the infection (Kummer and Marcrum, 2018: 20-6).

Congenital cytomegalovi¬rus [CCMV] infection or genetic alterations as one of the most im¬portant causes of congenital and also postnatal hearing loss, only behind hearing loss of genetic origin

A large multicentre study in the United States on the detection of cCMV found that infected children are 7 times more likely to fail hearing screening (Fowler *et al.,* 2017: e20162128).

In one-half (52%) of all cases of hearing loss associated to cCMV, the hearing problems are present from birth - hence the interest of targeted / selective cCMV screening of infants that fail the hearing tests (Park *et al.,* 2014: 2624-9) (Choi *et al.,* 2009: 1095-8) (Stehel *et al.,* 2008: 970-5). In addition, a large proportion of children with hearing loss infected with cCMV are diagnosed only on the basis of a failed neonatal hearing screening test.

Several studies have concluded that 5-6% of newborns failed hearing screening due to cCMV infection (Rawlinson *et al.,* 2018: 110-5) (Ari-Even Roth *et al.,* 2017: F519-24) (Diener *et al.,* 2017: e20160789) (Fowler *et al.,* 2017: e20162128).

Recent data show that CMV screening in newborns who have failed neonatal hearing screening is cost-effective, resulting in cost savings of over 50% (Vancor *et al.,* 2018: 10.1093/jpids/pix105 [Epub ahead of print]) (Williams *et al.,* 2015: F501-6) (Williams *et al.,* 2014: F230-6) (Kadambari *et al.,* 2013: 928-33).

4.4. Implications in hearing screening and treatment

The diagnosis of congenital infection is of particular interest in children who do not pass the complete hearing screening process before 2-3 weeks of life, because this would start

etiological diagnosis and monitoring in an adequate and timely manner (Luck *et al.,* 2017: 1205-13) (Yamaguchi *et al.,* 2017: e013810).

As mentioned, the time limit for securely diagnosing congenital infection is in the first two to three weeks of life. Cytomegalovirus positivity would thus allow a firm diagnosis of congenital infection (Botet *et al.,* 2015: 69) (Escosa-García *et al.,* 2015: 70-1). This is decisive in hearing loss screening programs that study congenital CMV infection when the newborn infant has altered screening test findings (selective screening), since it obliges us to establish a diagnostic mechanism in that time window. A second screening test is therefore needed (in programs with two steps) at approximately 15 days of life, in order to allow detection of congenital disease and assessment of the start of treatment (if applicable), before one month of age as seems advisable (Rawlinson *et al.,* 2018: 110-5). In this regard, we must remember that positive saliva samples must be confirmed with another urine sample within the mentioned time, and this must be taken into account when designing the changes to be made to the protocols.

On the other hand, it should also be noted that a large multicentre study (Kummer and Marcrum, 2018: 20-6) (Rawlinson *et al.,* 2018: 110-5) has shown that while congenital infection is present in 6% of the children that fail newborn hearing screening, selective screening was only able to identify 57% of the children with cCMV-related hearing loss.

Recent data show that in the long term, a large percentage of asymptomatic children (25%) will develop hearing loss

These limitations of selective screening support the need for universal screening. This would allow the timely recruitment of infected but asymptomatic newborn infants with a normal first hearing test, at risk of developing hearing loss later in time. Universal screening would be justified given the prevalence of the infection and the possibility of improving the prognosis through adequate management, monitoring and treatment (Fowler *et al.,* 2017: e20162128) (Toumpas *et al.,* 2015: 541-4).

A recent study has evidenced that both targeted and universal screening are cost-effective (Fowler *et al.,* 2017: e20162128) (Kadambari *et al.,* 2015: 1117-21) (Kimberlin *et al.,* 2015: 933-43) (Barkai *et al.,* 2014: 361-6) (Cannon *et al.,* 2014: 291-307).

In contrast to congenital CMV disease, acquired infection in the neonate and nursing infant does not appear to be associated with hearing loss or long-term neurodevelopmental disorders - hence the importance of an accurate diagnosis of the time of infection, with PCR detection at birth or in dry blood of the metabolic screening test (Smiechura *et al.,* 2014: 303-7) (Nuñez-Ramos *et al.,* 2013: 93-6) (Botet *et al.,* 2015: 69).

The diagnosis of congenital infection is of particular interest in children who do not pass the complete hearing screening process and are referred to ENT before 2-3 weeks of life, because most studies have concluded that the start of treatment for cCMV could prove effective, particularly in those cases with moderate hearing loss, provided it is started before one month of age and is prolonged for a number of months (at least 6-12 months) (Bilavsky *et al.,* 2016: 433-8) (Kimberlin *et al.,* 2015: 933-43) (Amir *et al.,* 2010: 1061-7) (Kimberlin *et al.,* 2003: 16-25).

In addition to being neonatal, hearing loss caused by cCMV may be of late onset, progressive, fluctuating, unilateral or bilateral, and asymmetric

Treatment with valganciclovir (VGC) is recommended in symptomatic children with proven congenital infection and with involvement of the central nervous system or target organs (bone marrow, liver), provided the condition is severe. In the case of asymptomatic children with isolated hearing loss, it is advisable not to treat, in view of the lack of evidence, though each case should be assessed individually.

The investigation of cCMV infection is also indicated in infants and children with hearing loss as evidenced from samples collected in the neonatal period (e.g., the heel sample).

With regard to the start of treatment in infants with hearing loss due to cCMV and over one month old, the European Society for Pediatric Infectious Diseases (ESPID) (Luck *et al.,* 2017: 1205-13) concluded that treatment is warranted in the presence of progressive hearing impairment (Amir *et al.,* 2014: 444-8) (Del Rosal *et al.,* 2012: 72-4) (Baquero-Artigao *et al.,* 2009: 535-47).

According to the recommendations of the two expert committees that have studied the topic (Rawlinson *et al,* 2017: e177-88) (Luck *et al,* 2017: 1205-13), asymptomatic children should not be treated.

Although drug treatment is the subject of debate, simple knowledge of the infection allows for long-term monitoring of these children and the possibility of an adequate hearing diagnosis in a time frame allowing for the most indicated early hearing therapeutic measures (Hilditch *et al.,* 2018: 988-92). In fact, knowledge of cCMV infection may cause clinicians to change their decision regarding early cochlear implantation, due to the high probability of progression of the disease (Lanzieri *et al.,* 2017: e20162610).

Since CMV hearing loss occurs in symptomatic and asymptomatic children, being of a fluctuating nature and often postnatal, frequent monitoring is recommended during the first two years of life - this being the period of greatest risk

of developing hearing loss associated to cCMV and a critical period for language development. In any case, in general these children should be monitored for at least 6 years, with more frequent controls in the most affected patients.

5. FUTURE PROSPECTS: COMBINED SCREENING

Screening programs currently have limitations for detecting mild or moderate hearing loss (Johnson *et al.,* 2005:663-72), as well as for detecting late onset hearing loss or hearing loss that progresses after birth. Many of these cases originate as infection due to cCMV and/or genetic alterations. As a result, these children will not benefit from the prognostic improvement afforded by early detection and treatment of hearing loss (Young *et al.,* 2011: 230-4).

Knowledge of cCMV affects the decision on the early placement of a cochlear implant

Up to 60% of all cases of congenital or early onset sensorineural hearing loss are due to genetic factors, and usually occur in the absence of a family history of hearing loss (Hilgert *et al.,* 2009:189-96). The most commonly identified alterations correspond to the GJB2 gene (connexin 26), which is the most common variant worldwide, followed by SCL26A4, which is responsible for Pendred syndrome. These mutations are associated with a 3% neonatal hearing loss rate - though this percentage increases significantly over the years and appears to be associated with a dilated vestibular aqueduct (Morton *et al.,* 2006:2151-64) (Prior *et al.,* 2005:159-65). It is also relatively common to find MTRNR1 mitochondrial gene mutations, which can manifest with aminoglycoside-induced hearing loss (Del Castillo *et al.,* 2002: 243-9).

5.1. Etiology and incidence

Although there are variations among the different populations, large-scale studies evidence repetition of the etiologies and incidences. This is the case of a recent study of 142,417 newborn infants in China, where the most commonly identified hearing loss-related allele was 235delC of the GJB2 gene. In total, 4289 newborn infants (3.01%) had alterations in at least one allele of some of the studied genes (Hao *et al.,* 2018: e0195740). Since genetic causes produce a high percentage of sensorineural hearing loss, and many of them cannot be detected through universal auditory screening, some studies combine conventional hearing screening with genetic screening in newborn infants, targeted to the most common mutations causing hearing loss. Wang *et al.* performed genetic screening combined with conventional screening (using OAE and aAEP) to determine the three genes most commonly associated with hearing loss in over 14,000 newborn infants. The authors concluded that adding genetic screening could improve the detection of patients with hearing disorders (Wang *et al.,* 2011: 535-42).

Genetic screening, along with hearing screening in newborn infants, not only improves the detection rate of children at risk, but allows early identification and prevention of hearing loss caused by ototoxic drugs

Recently, Wu *et al.* reported a 1.6% incidence of these genetic alterations in their study population of 5173 newborn infants. The most notable finding was the fact that 56.1% had passed conventional hearing screening (Wu *et al.* 2017: 6-12). In another study also carried out in China, conventional screening was combined with the determination of 20 mutations in the four genes most commonly associated to sensorineural hearing loss, based on heel blood samples obtained to screen for endocrine-metabolic diseases. The data confirmed the aforementioned results: a total of 129 children (1.38%) presented hearing loss detected from OAE testing. Genetic screening determined that 348 individuals (3.74%) had at least one mutation in one of the alleles. An overwhelming majority of newborn infants with these genetic alterations had passed hearing screening with OAE, but were at risk of suffering late hearing loss (Peng *et al.,* 2016: 603-8).

5.2. Usefulness of combined screening

The usefulness of combined screening has also been demonstrated by another recent study (Sun *et al.,* 2015: 766-70) on the detection rate of hearing loss through hearing, genetic or combined screening in 11,046 newborn infants. The authors found that combined hearing and genetic testing detected 5.29% of cases, while hearing testing alone identified 0.81% and isolated genetic testing 4.64%. Genetic studies are contemplated to detect gene mutations related to congenital hearing loss in pregnant women, which could facilitate early detection (Fang *et al.,* 2017: 1452-5).

Thus, the use of genetic screening, together with hearing screening in newborn infants, can improve the detec-

tion rate of children at risk, as well as favour early identification before the language development phase is reached. The development of hearing loss could also be prevented by avoiding the use of aminoglycosides in patients carrying mutations to these drugs, and all the information obtained could be used for genetic counselling.

In the future, cCMV screening may be integrated with genetic study, in addition to hearing screening, as a hearing loss diagnostic panel. This approach would allow us to overcome the current limitations of neonatal hearing screening, and would detect all children with present or future hearing risk. It should be remembered that CMV infection does not rule out the possibility of simultaneous genetic alterations related to hearing loss, as some studies have shown (Teek *et al.,* 2013: 419-28) (Lim *et al.,* 2013: 209-15) (Karltorp *et al.,* 2012: e357-62) (Schimmenti *et al.,* 2011: 1006-10).

Specifically, Lu *et al.* conducted a prospective analysis of 1716 newborns, in which genetic screening proved positive in 20 cases (1.2%) and CMV screening in three (0.2%). Interestingly, 12 of the 20 newborn infants with positive genetic screening (60%), and all three with positive CMV screening (100%), passed hearing screening at birth. At three months, hearing loss was confirmed in 6 of the 20 patients with positive genetic test results (30%). This study confirms that hearing, genetic and CMV screening helps detect cases that would not be identified by standard auditory screening programs alone (Lu *et al.,* 2018: 144-50). Thus, integrated and complete screening with hearing, genetic and cCMV infection tests, is feasible and good results are obtained - though further cost-effectiveness studies are needed.

In future, cCMV screening can be integrated with genetic testing, in addition to hearing screening. This combined approach would overcome current limitations in the detection of all children at hearing risk, both present and future

The described combined genetic screening strategy would allow adequate monitoring and early audiological and/or pharmacological treatment of the affected children. In turn, in the near future, if we are able to establish early identification of the genetic defects involved, and precise genetic counselling is provided, we may be able to correct the problem through techniques such as CRISP-Cas9. Studies already show that this is possible in relation to hearing loss in animals. This approach therefore will surely improve the final prognosis of children with hearing loss (Zou *et al.,* 2015: 102-8) (Gao *et al.,* 2018: 217-21).

6. CODEPEH RECOMMENDATIONS 2018

The widespread implementation of programs for the screening of hearing loss in newborn infants could cause us to believe that negative testing at the time will mean that the children will not have problems later in the course of their development. This is a false belief that can seriously harm the future of these children, since postnatal factors that are not uncommon can lead to hearing loss. The prevalence could rise from 2.52 per thousand at birth (any type and degree of hearing loss) to 3.64 per thousand in the primary education stage (Watkin and Baldwin, 2012: 519-28) (Watkin and Baldwin, 2011: 62-6).

It has been found that even in very sensitive neonatal screenings, such tests only identify 56-59% of all school-age children with hearing loss. Thus, up to one in 10 children with hearing loss would be detected by postnatal controls, despite the existence of well established screening protocols. The overall prevalence of late-onset hearing loss is 10% of all cases of childhood hearing loss - a figure that may reach 20% (Benito, 2013: 330-42) (Georgalas *et al.,* 2008: 1299-304). All this suggests the need for diagnostic protocols to identify cases of post-neonatal hearing loss.

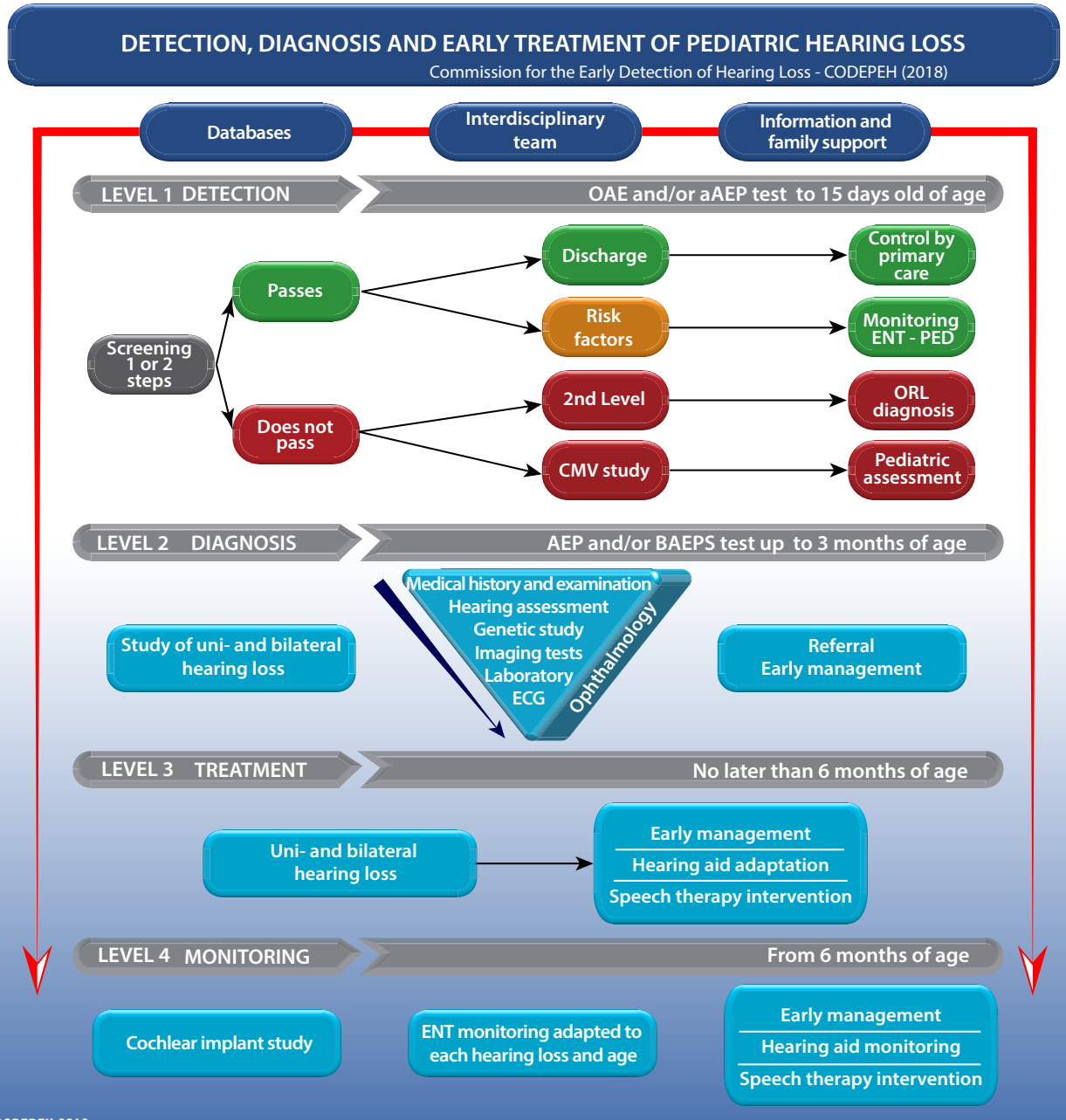
A large proportion of cases of hearing loss manifesting late in childhood appear to be due to genetic defects, congenital cytomegalovirus (cCMV) infection or vestibular aqueduct disorders - thus requiring genetic study, the exclusion of cytomegalovirus (CMV) infection, and the conduction of complementary imaging studies (Alford, 2014: 347-55).

The CODEPEH therefore considers it necessary to establish new recommendations to update infant hearing screening programs in relation to the detection phase, adopting the changes described in the present document (Figure 1):

1. Tests with aOAE and aAEP remain the recommended techniques for neonatal hearing screening.
2. Hearing screening programs must remain alert to the percentage of cases that may be lost in the detection, diagnosis and early treatment process, adopting appropriate measures to avoid this problem.
3. The Family Association Movement must be a point of support throughout the process.
4. Screening for CMV based on PCR testing should be performed in all newborn infants that fail to pass bilateral neonatal hearing screening.
5. The diagnosis of cCMV infection must be established before three weeks of life, and treatment (if required) should start before one month of age. The current screening protocols must be adapted for this purpose, and a hearing risk monitoring protocol may be established, adjusted to the peculiarities of CMV (unilateral, progressive, fluctuating, asymmetrical hearing loss, etc.).
6. In addition to ENT monitoring, children with cCMV infection require a complete study by the Departments of Pediatrics and Ophthalmology.
7. Universal screening for cCMV infection should be considered in the near future, since selective study only identifies 57% of all infected infants who will suffer hearing loss in childhood - both strategies being cost-effective.
8. Hearing screening, genetic testing and cytomegalovirus testing should be integrated into one same protocol, where possible, to achieve a complete diagnosis and early treatment of childhood hearing loss.

7. FIGURE

FIGURE 1. ***Update of the infant hearing screening programs Level 1 Detection***



8. REFERENCES

Alford, RL. (2014): "American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss". Genet Med.,16 (4): 347-55

Amir, J. *et ál.* (2014): "Treatment of late-onset hearing loss in infants with congenital cytomegalovirus infection". Clin Pediatr, 53: 444-8

Amir, J. *et ál.* (2010): "Treatment of symptomatic congenital cytomegalovirus infection with intravenous ganciclovir followed by long-term oral valganciclovir". Eur J Pediatr, 169: 1061-7

Ari-Even Roth, D. *et ál.* (2017): "Contribution of targeted saliva screening for congenital CMV-related hearing loss in newborns who fail hearing screening" Arch Dis Child Fetal Neonatal Ed, 102: F519-24

Badia, J. (2014): "Infecciones congénitas". Pediatr Integral, 18: 356-66

Baquero Artigao, F. *et ál.* (2009): "Documento de consenso de la Sociedad Española de Infectologia Pediátrica sobre el diagnóstico y el tratamiento de la infección congénita por citomegalovirus". An Pediatr (Barc), 71: 535-47

Barkai, G. *et ál.* (2014): "Universal neonatal cytomegalovirus screening using saliva. Report of clinical experience". J ClinVirol, 60: 361-6

Bartlett, AW. *et ál.* (2017): "Hearing and neuro develop mental outcomes for children with asymptomatic congenital cytomegalovirus infection: A systematic review". Rev Med Virol, 27: e1938

Benito, JI. (2013): "Hipoacusia: identificación e intervención precoces". Pediatr Integral, 17: 330-342

Bilavsky, E. *et ál.* (2016): "Hearing outcome of infants with congenital cytomegalovirus and hearing impairment". Arch Dis Child, 101: 433-8

Bonfils, P. *et ál.* (1990): "Evoked otoacoustic emissions in newborn hearing screening". Laryngoscope, 100: 186-9

Boppana, SB. *et ál.* (2011): "National Institute on Deafness and Other Communication Disorders CHIMES Study. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns". N Engl J Med, 364: 2111-8

Boppana, SB. *et ál.* (2010): "Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection". JAMA, 303: 1375-82

Botet, F. *et ál.* (2015): "Cribado universal de infección por citomegalovirus en prematuros de menos de 1.500 g". An Pediatr, 83: 69

Boudewyns, A. *et ál.* (2016): "Auditory neuropathy spectrum disorder (ANSD) in referrals from neonatal hearing screening at a well-baby clinic". Eur J Pediatr, 175 (7): 993-1000

Bruijnzeel, H. et ál. (2016): "A systematic review to define the speech and language benefit of early (<12 Months) pediatric cochlear implantation". Audiol Neurotol, 21: 113-26

Bush, *et ál.* (2017): Promotion of early pediatric hearing detection through patient navigation: a randomized controlled clinical trial". Laryngoscope, 127: S1-13

Cannon, MJ. *et ál.* (2014): "Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit?" Rev Med Virol, 24: 291-307

Cardoso, ES. *et ál.* (2015): "The use of saliva as a practical and feasible alternative to urine in large-scale screening for congenital cytomegalovirus infection increases inclusion and detection rates". Rev Soc Bras Med Trop, 48: 206-7

Castillo, I. del *et ál.* (2002): "A deletion involving the connexin 30 gene in nonsyndromic hearing impairment". N Engl J Med, 346 (4): 243-9

Ching, TYC. *et ál.* (2013): "Outcomes of early- and late-identified children at 3 years of age: findings from a prospective population-based study". Ear Hear, 34: 535-52

Choi, KY. *et ál.* (2009): "Detection of cytomegalovirus DNA in dried blood spots of Minnesota infants who do not pass newborn hearing screening". Pediatr Infect Dis J, 28: 1095-8

DesGeorges, J. (2003): "Family perceptions of early hearing, detection, and intervention systems: listening to and learning from families". Ment Retard Dev Disabil Res Rev, 9: 89-93

Diener, ML. *et ál.* (2017): "Outcomes from a hearingtargeted cytomegalovirus screening program". Pediatrics, 139: e20160789

Duman, K. *et ál.* (2008): "Incidence of auditory neuropathy among the deaf school students". Int J Pediatr Otorhinolaryngol, 72 (7): 1091-5

Escosa-García, L. *et ál.* (2015): "Cribado de citomegalovirus en prematuros menores de 1.500 g. Comité Científico del Registro Estatal de Infección Congénita por Citomegalovirus". An Pediatr, 83: 70-1

Fang, Y. *et ál.* (2017):" Application of gene detection technique in the antenatal diagnosis of hereditary hearing loss". Eur Rev Med Pharmacol Sci, 21: 1452-5

Fowler, KB. y Boppana, SB. (2018): "Congenital cytomegalovirus infection". Semin Perinatol, 42: 149-54

Fowler, KB. *et ál.* (2017): "A targeted approach for congenital cytomegalovirus screening within newborn hearing screening". Pediatrics, 139 (2): e20162128

Gantt, S. *et ál.* (2017): "In reference to should infants who fail their newborn hearing screen undergo cytomegalovirus testing?". Laryngoscope, 128: e267

Gao, X. *et ál.* (2018): "Treatment of autosomal dominant hearing loss by in vivo delivery of genome editing agents". Nature, 553 (7687): 217-21

Georgalas, C. *et ál.* (2008): "Screening for hearingloss and middle-ear effusion in school-age children, using transient evokedoto acoustic emissions: a feasibility study". J Laryngol Otol, 122: 1299-304

Goderis, J. *et ál.* (2016): "Hearing in children with congenital cytomegalovirus infection: results of a longitudinal study". J Pediatr, 172: 110-15. e2

Goderis, J. *et ál.* (2014): "Hearing loss and congenital CMV infection: a systematic review". Pediatrics, 134: 972-82

Gunkel, J. *et ál.* (2014): "Urine is superior to saliva when screening for postnatal CMV infections in preterm infants". J ClinVirol, 61: 61-4

Guoyu, L. *et ál.* (2017): "Detection of congenital cytomegalovirus in newborns using nucleic acid amplification techniques and its public health implications". Virologica Sinica, 32: 376-86

Hao, Z. *et ál.* (2018): "Large scale newborn deafness genetic screening of 142.417 neonates in Wuhan, China". PLoS One, 13 (4): e0195740

Hilditch, C. *et ál.* (2018): "Does screening for congenital cytomegalovirus at birth improve longer term hearing outcomes?". Arch Dis Child, 103: 988-92

Hilgert, N. *et ál.* (2009): "Forty-six genes causing nonsyndromic hearing impairment: which ones should be analyzed in DNA diagnostics?". Mutat Res, 681:189-96

Johnson, JL. *et ál.* (2005): "A multicenter evaluation of how many infants with permanent hearing loss pass a two-stage otoacustic emissions/automated auditory brainstem response newborn hearing protocol". Pediatrics, 116: 663-72

Kadambari, S. *et ál.* (2015): "Evaluating the feasibility of integrating salivary testing for congenital CMV into the Newborn Hearing Screening Programme in the UK". Eur J Pediatr, 174: 1117-21

Kadambari S, *et ál.* (2013): "Clinically targeted screening for congenital CMV. Potential for integration into the National Hearing Screening Programme". Acta Paediatr, 102: 928-33

Karltorp, E. *et ál.* (2012): "Congenital cytomegalovirus infection: a common cause of hearing loss of unknown aetiology". Acta Paediatr, 101 (8): e357-62

Kennedy, CR. *et ál.* (2006): "Language ability after early detection of permanent childhood hearing impairment". N Engl J Med, 354: 2131-41

Kennedy, C. *et ál.* (2005): "Universal newborn screening for permanent childhood hearing impairment: an 8-year follow-up of a controlled trial". Lancet, 366: 660-2

Kennedy, CR. (1999): "Controlled trial of universal neonatal screening for early identification of permanent childhood hearing impairment: coverage, positive predictive value, effect on mothers and incremental yield. Wessex Universal Neonatal Screening Trial Group". Acta Paediatr Suppl, 88 (432): 73-5

Keohane, BM. *et ál.* (2004): "Clinical evaluation of the vector algorithm for neonatal hearing screening using automated auditory brainstem response". J Laryngol Otol, 118 (2): 112-6

Kim, BJ. *et ál.* (2018): "Characterization of detailed audiological features of cytomegalovirus Infection: a composite cohort study from groups with distinct demographics". Biomed Res Int, 5: 1-8

Kimberlin, DW. *et ál.* (2015): "National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Valganciclovir for symptomatic congenital cytomegalovirus disease". N Engl J Med, 372: 933-43

Kimberlin, DW. *et ál.* (2003): "National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial". J Pediatr, 143: 16-25

Koontz, D. *et ál.* (2015): "Evaluation of DNA extraction methods for the detection of Cytomegalovirus in dried blood spots". J ClinVirol, 66: 95-9

Korver, AMH. *et ál.* (2010): "Newborn hearing screening vs later hearing screening and developmental outcomes in children with permanent childhood hearing impairment". JAMA, 304: 1701-8

Kummer, P. y. Marcrum, SC. (2018): "Potential benefit of selective CMV testing after failed newborn hearing screening". Int. J. Neonatal Screen, 4: 20-6

Lanzieri, TM. *et* ál. (2018): "Congenital cytomegalovirus longitudinal study group. hearing trajectory in children with congenital cytomegalovirus infection". Otolaryngol Head Neck Surg, 158: 736-44

Lanzieri, TM. *et* ál. (2017): "Long-term outcomes of children with symptomatic congenital cytomegalovirus disease". J Perinatol, 37:875-80

Lanzieri, TM. *et* ál. (2017): "Hearing loss in children with asymptomatic congenital cytomegalovirus infection. Congenital Cytomegalovirus Longitudinal Study Group". Pediatrics, 139 (3): e20162610

Lawrence, RM. (2006): "Cytomegalovirus in human breast milk: risk to the premature infant". Breastfeed Med, 1: 99-107 Lim, Y y Lyall, H. (2017): "Congenital cytomegalovirus. Who, when, what, with and why to treat?". J Infect, 1: S89-94

Lim, BG. *et* ál. (2013): "Utility of genetic testing for the detection of late-onset hearing loss in neonates". Am J Audiol, 22: 209-15

Liu, CL. *et* ál. (2008): "Evaluating loss to follow-up in newborn hearing screening in Massachusetts". Pediatrics, 121 (2): e335-43

López, AS. *et* ál. (2017): "Congenital cytomegalovirus longitudinal study group. Intelligence and Academic Achievement with Asymptomatic Congenital Cytomegalovirus Infection". Pediatrics, 140 (5): e20171517

Luck, SE. *et* ál. (2017): "Congenital cytomegalovirus: A european expert consensus statement on diagnosis and management". Pediatr Infect Dis J, 36: 1205-13

Lu, CY. *et* ál. (2018): "Concurrent hearing, genetic, and cytomegalovirus screening in newborns, Taiwan". J Pediatr, 199: 144-50

Marsico, C. y Kimberlin, DW. (2017): "Congenital cytomegalovirus infection: advances and challenges in diagnosis, prevention and treatment". Ital J Pediatr, 43: 38

Meyer, L. *et* ál. (2017): "Analysis of archived newborn dried blood spots (DBS) identifies congenital cytomegalovirus as a major cause of unexplained pediatric sensorineural hearing loss". Am J Otolaryngol, 38: 565-70

Mijares, E. *et* ál. (2015): "Hearing screening using auditory steady state responses obtained by simultaneous air- and bone-conduction stimuli". Acta Otorrinolaringol Esp, 66: 8-15

Morant, A. *et* ál. (2014): "Otoemisiones", en Manrique y Marco (coords): Audiología. Ponencia Oficial de la Sociedad Española de Otorrinolaringología y Patología Cérvico-Facial. Madrid: CYAN Proyectos Editoriales S.A.

Moresco, BL. *et* ál. (2018): "A quiet disease with loud manifestations". Semin Pediatr Neurol, 26: 88-91

Morton, CC. y Nance, WE. (2006): "Newborn hearing screening. A silent revolution". N Engl J Med, 354: 2151-64

Moteki, H. *et* ál. (2018): "A rational approach to identifying newborns with hearing loss caused by congenital cytomegalovirus infection by dried blood spot screening". Acta Otolaryngol, 138: 708-12

Nance, WE. *et* ál. (2006): "Importance of congenital cytomegalovirus infections as a cause for pre-lingual hearing loss". J. Clin. Virol, 35: 221-25

Nikolopoulos, TP. (2015): "Neonatal hearing screening. What we have achieved and what needs to be improved". Int J Pediatr Otorhinolaryngol, 79: 635-7

Nuñez-Ramos, R. *et* ál. (2013): "Early diagnosis of congenital cytomegalovirus infection: lost opportunities". Enferm Infecc Microbiol Clin, 31: 93-6

Park, AH. *et* ál. (2014): "A diagnostic paradigm including cytomegalovirus testing for idiopathic pediatric sensorineural hearing loss". Laryngoscope, 124: 2624-9

Peng, Q. et ál. (2016): "Concurrent genetic and standard screening for hearing impairment in 9317 southern chinese newborns". Genet Test Mol Biomarkers, 20: 603-8

Pimperton, H. *et* ál. (2017): "Language outcomes in deaf or hard of hearing teenagers who are spoken language users: effects of universal newborn hearing screening and early confirmation". Ear Hear, 38: 598-610

Pimperton, H. *et* ál. (2016): "The impact of universal newborn hearing screening on long-term literacy outcomes: a prospective cohort study". Arch Dis Child, 101: 9-15

Pryor, SP. *et* ál. (2005): "SLC26A4/PDS genotypephenotype correlation in hearing loss with enlargement of the vestibular aqueduct (EVA): evidence that Pendred syndrome and non-syndromic EVA are distinct clinical and genetic entities". J Med Genet, 42: 159-65

Ravi, R. *et* ál. (2016): "Follow-up in newborn hearing screening. A systematic review". Intl J Pediatr Otorhinolaryngol, 90: 29-36

Rawlinson, WD. *et* ál. (2018): "Neonates with congenital cytomegalovirus and hearing loss identified via the universal newborn hearing screening program". J ClinVirol, 102: 110-5

Rawlinson, W.D. *et* ál. (2017): "Congenital cytomegalovirus infection in pregnancy and the neonate: Consensus recommendations for prevention, diagnosis, and therapy". Lancet Infect Dis, 17: e177-88

Rosal, T. del *et* ál. (2012): "Treatment of symptomatic congenital cytomegalovirus infection beyond the neonatal period". J ClinVirol, 55: 72-4

Ross, SA. *et* ál. (2017): "Newborn dried blood spot polymerase chain reaction to identify infants with congenital cytomegalovirus-associated sensorineural hearing loss". J Pediatr, 184: 57-61

Ross, SA. *et* ál. (2015): "National Institute on Deafness and Other Communication Disorders CHIMES Study. Urine collection method for the diagnosis of congenital cytomegalovirus infection". Pediatr Infect Dis, 34: 903-5

Schimmenti, LA. *et* ál. (2011): "Evaluation of newborn screening bloodspot-based genetic testing as second tier screen for bedside newborn hearing screening". Genet Med, 13: 1006-10

Stehel, E.K. *et* ál. (2008): "Newborn hearing screening and detection of congenital cytomegalovirus infection". Pediatrics, 121: 970-5

Smiechura, M, *et* ál. (2014): "Congenital and acquired cytomegalovirus infection and hearing evaluation in children". Otolaryngol Pol, 68: 303-7

Sun, *et* ál. (2015): "Combined hearing and deafness gene mutation screening of 11,046 Chinese newborns". Zhonghua Yi Xue Yi ChuanXueZaZhi, 32 (6): 766-70

Teek, R. *et* ál. (2013): "Hearing impairment in Estonia: an algorithm to investigate genetic causes in pediatric patients". Adv Med Sci, 58: 419-28

Toumpas, CJ. *et* ál. (2015):"Congenital cytomegalovirus infection is a significant cause of moderate to profound sensorineural hearing loss in Queensland children". J Paediatr Child Health, 51: 541-4

Trinidad, G. *et* ál. (2010): "Recomendaciones de la Comisión para la Detección Precoz de la Hipoacusia (CODEPEH) para 2010". Acta Otorrinolaringol Esp, 61: 69-77

Vancor, E. *et* ál. (2018): "Results of a targeted screening program for congenital cytomegalovirus infection in infants who fail newborn hearingscreening". J Pediatric Infect Dis Soc, 10.1093/jpids/pix105 [Epub ahead of print]

Vives-Oñós, I. *et* ál. (2018): "Is Polymerase Chain Reaction in Neonatal Dried Blood Spots Reliable for the Diagnosis of Congenital Cytomegalovirus Infection?". Pediatr Infect Dis J, 10.1097/INF.0000000000002144 [Epub ahead of print]

Vries, JJ. de *et* ál. (2013): "Cytomegalovirus DNA detection in dried blood spots and perilymphatic fluids from pediatric and adult cochlear implant recipients with prelingual deafness". J ClinVirol, 56: 113-7

Wake, M. *et* ál. (2016): "Population Outcomes of Three Approaches to Detection of Congenital Hearing Loss". Pediatrics, 137: 1-10

Wang, QJ. *et ál.* (2011): "Newborn hearing concurrent gene screening can imporve care for hearing loss: a study on 14.913 chinese newborns". Int J Pediatr Otorhinolaryngol, 75: 535-42

Watkin, P. y Baldwin, M. (2012): "The longitudinal follow up of a universal neonatal hearing screen: the implications for confirming deafness in childhood". Int J Audiol, 51: 519-28

Watkin, P. y Baldwin, M. (2011): "Identifying deafness in early childhood: requirements after the newborn hearing screening". Arc Dis Child, 96: 62-6

Williams, EJ. *et ál.* (2015): "First estimates of the potential cost and cost saving of protecting childhood hearing from damage caused by congenital CMV infection". Arch Dis Child Fetal Neonatal Ed, 100 (6): F501-6

Williams, EJ. *et ál.* (2014): "Feasibility and acceptability of targeted screening for congenital CMV-related hearing loss". Arch Dis Child Fetal Neonatal Ed, 99(3): F230-6

Wood, SA. *et ál.* (2015): "Performance and characteristics of the Newborn Hearing Screening Programme in England: The first seven years". Int J Audiol, 54: 353-8

Wu, CC. *et al.* (2017): "Newborn genetic screening for hearing impairment: a population-based longitudinal study". Genet Med, 19 (1): 6-12

Yamaguchi, A. *et ál.* (2017): "Screening for seemingly healthy newborns with congenital cytomegalovirus infection by quantitative real-time polymerase chain reaction using newborn urine: an observational study". BMJ Open, 7: e013810

Young, NM. *et ál.* (2011): "Limitations of universal newborn hearing screening in early identification of pediatric cochlear implant candidates". Arch Otolaryngol Head Neck Surg, 137: 230-4

Zou, B. *et ál.* (2015): The application of genome editing in studying hearing loss. Hear Res, 327: 102-8

Zubicaray, J. *et ál.* (2014): "Sistemática del cribado de la audición en el niño", en Manrique y Marco (coords): Audiología. Ponencia Oficial de la Sociedad Española de Otorrinolaringología y Patología Cérvico-Facial. Madrid: CYAN, Proyectos Editoriales, S.A.

FIAPAS

CONFEDERACIÓN
ESPAÑOLA
DE FAMILIAS
DE PERSONAS SORDAS

SPANISH CONFEDERATION OF FAMILIES OF DEAF PEOPLE

Supplement No. 167 FIAPAS Magazine

This publication is available for download in PDF at the www.bibliotecafiapas.es

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL
SECRETARÍA DE ESTADO DE SERVICIOS SOCIALES

SPANISH MINISTRY OF HEALTH, CONSUMER AFFAIRS AND SOCIAL WELFARE SECRETARY OF STATE FOR SOCIAL RIGHTS

Fundación ONCE

ONCE FOUNDATION