Abstract

Sensorineural hearing loss (SNHL) is the most common congenital deficit. As non-genetic contributions congenital cytomegalovirus infection (cCMV) is the most frequent cause for this disease. In 10% - 20% of patients with sensorineural hearing loss intrauterine infection with cytomegalovirus is diagnosed. Hearing impairment due to CMV can be diagnosed at birth; nevertheless 33% - 50% is late-onset loss. Infection of the inner ear seems to lead to a potassium dysregulation in the endolymphatic compartment, thus inducing a secondary degeneration of the sensory structures. An early start with intravenous virostatic therapy seems to be able to prevent SNHL in primary asymptomatic children and improve hearing status in infants born with cCMV and hearing impairment.

ABBREVIATIONS

cCMV: Congenital Cytomegalovirus Infection; CMV: Cytomegalovirus; SNHL: Sensorineural Hearing Loss

INTRODUCTION

Sensorineural hearing loss (SNHL) is the most common congenital deficit in more developed countries, occurring about three times more frequently than Down’s syndrome [1]. Besides the individual burden of this disease, including disabled language acquisition, impaired social development and communication, SNHL is an enormous public health problem. The World Health Organization notes that over 5% of the world’s population has disabling hearing loss, there under 32 million children [2]. In developed countries 1 – 3 newborns per 1,000 live births are born with permanent, bilateral congenital hearing loss [3], the number of children born with unilateral or mild to moderate bilateral SNHL is twice as high [1]. About 50% of congenital hearing loss is inherited; the other 50% can be attributed to environmental causes. Since the introduction of the rubella vaccine, SNHL secondary to congenital rubella syndrome has been greatly decreased [4]. Now congenital cytomegalovirus infection (cCMV) is generally recognized as the most frequent infectious cause of SNHL in newborns [1,5].

EPIDEMIOLOGY OF HEARING LOSS IN CCMV INFECTED CHILDREN

It is now well accepted that Cytomegalovirus is the most common cause of congenital infection. Nevertheless, the oft-cited 1% prevalence of cCMV must be questioned. The prevalence differs between countries and depends on socioeconomic factors, on the serostatus of the mother and on her age [6]. From the known variables influencing the prevalence of cCMV maternal seroprevalence accounted for 29% of the variance in birth prevalence [7]. The risk of primary CMV infection during a full-term pregnancy varies between estimated 1.38 - 3.85 percent due to racial/ethnic and socioeconomic factors [8]. In pregnant women with a primary CMV infection the rate of transmission to the unborn is 32 %, whereas in mothers with secondary infection during pregnancy the rate of transmission is 1.4 % [7]. In the study of Kenneson et al., the overall birth prevalence of cCMV is described to be 0.64% with a considerable variation among different study populations [7]. A retrospective study using polymerase chain reaction to detect CMV on dried blood spots, identified 156 children with cCMV out of a cohort of 31,484 children [8], i.e. a prevalence of 0.5%. Furthermore, maternal serostatus influences the occurrence of symptoms in congenitally infected newborns. In this context one has to be aware that symptomatic congenital CMV infection can occur after a non-primary or recurrent maternal infection [Boppana], so a preexisting positive serostatus to CMV does not protect the unborn from harm. Fowler summarized in her review 2013 [5] that 15% of children with cCMV born to a mother who had primary CMV infection during pregnancy developed SNHL. Of those approximately 50% had severe bilateral hearing loss. In contrast to this 11% of CMV-infected infants born to seroimmune mothers have SNHL, and approximately 25% of them have severe bilateral hearing loss [5]. So, the risk of hearing loss does not vary between primary and non-primary infections. Since non-primary infections usually result in an asymptomatic infection...
at birth, hearing losses are often diagnosed first at school age. Gorderis et al., reported in their review that the overall incidence of hearing loss in cCMV is 12.6%. One third of symptomatic and 1 out of 10 in asymptomatic children will experience loss [9]. In a recent publication Gorderis et al., even reported a 63% incidence of hearing loss in symptomatic cCMV children [10]. One problem of cCMV is the unpredictability of the onset of SNHL, and the degree of damage. Up to 50% of SNHL due to cCMV is late-onset loss [5]. Delayed-onset hearing loss occurs in 10.6% of symptomatic cCMV and in 7.8% asymptomatic cCMV [10]. In symptomatic cCMV children bilateral hearing loss predominates, whereas in asymptomatic cCMV children unilateral hearing loss is more common [9].Thus, hearing impairment is the most likely defect to be found in asymptomatic cCMV children. Although newborn hearing screening is recommended and yet done in many countries [3,4,11], those children with late-onset SNHL will be missed, since in asymptomatic cCMV children late-onset hearing loss occurs at the median age of 44 months, which is 11 months later than in symptomatic cCMV children [5]. Knowing that about 10% of children with hearing impairment were infected congenitally with CMV [12], new strategies are thus necessary to detect these children at risk for SNHL earlier. It is important to inform the parents that universal newborn hearing screening is not an absolute safeguard, since cCMV can be delayed in onset and might progress and fluctuate over varying time frames [9]. A combined newborn hearing and newborn CMV screening program would be recommended. Furthermore asymptomatic cCMV children should be evaluated for hearing function at least annually until 5 – 6 years of age [5]. Thereby earlier intervention could minimize the burden of disease.

PATHOPHYSIOLOGY OF HEARING LOSS IN CCMV INFECTED CHILDREN

The inner ear has a complex structure containing the organ of hearing, the cochlea and the organ of balance, the vestibular labyrinth. An excellent short review on the inner ear function is included in the paper of Gabrielli et al., [13]. Briefly: Most important is the well-balanced ionic composition of perilymph in the scala tympani and the scala vestibule, and endolymph in the scala media. The endolymph which is high in potassium and low in sodium and calcium has a positive potential, the endocochlear potential. This is maintained by potassium recycling regulated by the striavascularis. Potassium is essential for the activation of the mechanosensation of sound waves. Immunohistochemical studies in cCMV infected have shown lesions due to CMV infection predominated in the striavascularis [13,14]. As the name implies the striavascularis is one of the most highly vascularized epithelia found in mammals. This makes it vulnerable for the hematologic spread of CMV and the consequent infection of the marginal epithelial cells of the striavascularis, which are prime targets of CMV. Lesions in this structure may lead to a dysregulation of potassium flow and an impairment of cochlear homeostasis resulting in a progressive degeneration of sensory neurone cell hair [15]. In contrast to the striavascularis sensorineural cells seem to be less sensitive to CMV infection [14].

Beside the destruction of the striavascularis epithelial cells by the cytopathic effect of CMV and the consequences of inflammation, there is a cautious hypothesis that CMV could lead to SNHL by inducing mutations in certain genes [15]. This hypothesis is based on the association of mutations in a gene called GJB2, accounting for roughly half of hereditary cases of SNHL [1] and the observation that CMV causes an increase in the number of breaks in chromosome 1 of cultured fibroblasts [16]. There are a number of genes within the fragile loci 1q42 and 1q21 that are associated with SNHL. One of the encoded proteins is connexin 26 which is part of the gap-junction system which might be involved in potassium circulation [1]. Further investigations are necessary, however, to elucidate these interactions.

THERAPY OF HEARING LOSS IN CCMV INFECTED CHILDREN

Virostatic therapy for congenitally CMV infected children has been used since the beginning of the 90ies. There are four licensed drugs for the systemic treatment of CMV infection including ganciclovir, its prodrug valganciclovir, foscarnet and cidofovir. Nevertheless, except for some case reports on foscarnet, ganciclovir and valganciclovir are the only two medications which have been employed in the treatment of cCMV to date [6]. There are few large randomized studies, one of the latest was published by Kimberlin et al., 2015 [17]. In contrast to previous studies [18,19] the duration of therapy was prolonged from 6 weeks to 6 months, and treatment was done with valganciclovir. This prodrug was shown to be as clinically effective as ganciclovir, is well tolerated, but in contrast to ganciclovir, which can only be administered intravenously, the oral syrup is appropriate for a prolonged post-discharge therapy avoiding the discomfort of hospitalization [20]. Results of this study confirmed previous findings showing that antiviral treatment of symptomatic cCMV has a beneficial effect on the improvement of hearing impairment, at least virostatic therapy seems to stop progression [17,18, 22,25]. For the evaluation of antiviral treatment of asymptomatic cCMV infected neonates only one small study has been conducted. Although only a few children were included results presume a positive effect on the prevention of late-onset SNHL [23].

DISCUSSION & CONCLUSION

SNHL after cCMV infection means a great burden for the affected child, resulting in delayed spoken language development. As cCMV is the most common nonhereditary cause of SNHL, prevention should also be of socioeconomic interest. Insight into the pathophysiology of SNHL due to cCMV elucidates the underlying mechanisms of this progressive disease and allow hypothesis on the cause of late-onset SNHL. Most promising are the results of clinical trials investigating the effect of antiviral therapy on the progression of symptomatic cCMV infected neonates. It could be shown that therapy with ganciclovir or valganciclovir has an improving or even curative effect on SNHL. Thereby a longer duration of therapy seems to be seems to be imperative.

Summarizing the latest publications, great effort has been made in understanding the pathophysiological mechanisms of SNHL in cCMV infected children. Furthermore, results of the clinical studies are promising. Nevertheless prevention of cCMV is of the utmost importance. Therefore information on the prevention of transmission is extremely important.
As Demmler-Harrison in the keynote address at the 2nd International Congenital Cytomegalovirus Conference 2008 said: "...baby's congenitally acquired CMV disease could have been potentially prevented by an ounce of CMV awareness and three simple hygienic precautions: do not kiss toddlers on the mouth or face, do not share food, drinks or utensils, and wash hands carefully after changing diapers and wiping away saliva or nasal secretions" [24]. Although it was stated eight years ago, it is still valid today: Informing pregnant women about these simple preventive measures can reduce harm to the children. It is the duty of physicians and public health and government officials to increase awareness. More than 100 years after the first description of the cytomegalovirus [25] it is time to stop ignoring this endemic problem of congenital CMV infection and disease.

REFERENCES


Cite this article