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## Impact and benefits of early hearing screening

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## DECIBEL-STUDY: CONGENITAL CYTOMEGALOVIRUS INFECTION IN YOUNG CHILDREN WITH PERMANENT BILATERAL HEARING IMPAIRMENT IN THE NETHERLANDS

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## ABSTRACT

### Background

A significant number of asymptomatic newborns infected with congenital cytomegalovirus (CMV) will present with permanent childhood hearing impairment (PCHI) during childhood.

### Objectives

To investigate the role of congenital CMV infection in causing PCHI in the Netherlands, and assess the efficacy of two different hearing screening strategies and the developmental outcome following each strategy.

### Study design

We included 192 children with PCHI at the age of 3–5 years, who were offered hearing screening in their first year of life. Dried blood spots from 171 children were available for CMV detection using real-time PCR. The results of eight previously tested samples were also available. Clinical baseline characteristics were collected from medical records and the Child Development Inventory was used to investigate the developmental outcome.

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### Results

The rate of congenital CMV among the 179 children was 8% (14/179) and 23% (9/39) among children with profound PCHI. Two of eight CMV-positive children with PCHI at the age of 3–5 years had passed the newborn hearing screening (NHS) test. Developmental outcome measures showed a significantly greater delay in language comprehension in children with both PCHI and congenital CMV infection (the largest in symptomatic children) than in the children with PCHI without congenital CMV infection.

### Conclusions

Congenital CMV infection is important in the etiology of PCHI. Universal NHS is not a guarantee of normal hearing and development in childhood for children with congenital CMV infection. This is a problem which might be solved by universal congenital CMV screening.

## BACKGROUND

The leading non-genetic cause of permanent childhood hearing impairment (PCHI) is congenital cytomegalovirus (CMV) infection.<sup>10</sup> Approximately 85% of infants with congenital CMV infection do not exhibit signs or symptoms at birth, but about 15% of these children will develop permanent sequelae, such as PCHI and general developmental delay, during early childhood.<sup>11-13</sup> Isolated PCHI is the most frequent long-term sequel in children with congenital CMV infection.<sup>57,58</sup> To diagnose congenital CMV later in life, e.g. in children presenting with PCHI, stored dried blood spots from blood drawn within the first week of life can be used for CMV DNA detection. This is a practical and reliable method for diagnosing congenital CMV infection later in life, since dried blood spots can be stored for very long periods without loss of sensitivity.<sup>44</sup> It has been suggested that newborn hearing screening (NHS) may fail to detect children with progressive or delayed-onset hearing loss linked to congenital CMV infection.<sup>59</sup> Since 2002, infant hearing screening using distraction methods has been gradually replaced by universal NHS in the Netherlands. One of the aims of our study was to determine the efficacy of the NHS program in relation to congenital CMV-related hearing loss. Furthermore, little is known about the developmental outcome of children with both PCHI and congenital CMV. Previous studies on the developmental outcome of children with congenital CMV infections show marked heterogeneity.<sup>12</sup>

## OBJECTIVES

The aim of the present study was to investigate the contribution of congenital CMV infection to PCHI in children in the Netherlands. Furthermore, the efficacy of two hearing screening strategies and the developmental outcomes that followed these were determined.

## STUDY DESIGN

The contribution of congenital CMV to causing PCHI, and its consequences for hearing screening strategies and child development were studied within the framework of the DECIBEL study. The current sub-analysis included all children for whom congenital CMV results were available. The DECIBEL study is a pseudo-randomized study investigating the effects of two different hearing screening strategies on the development of children with PCHI. The development of 3-, 4- and 5-year-old children with PCHI, who were offered either the distraction hearing screening strategy (DHS, at 9 months) or the NHS (within 2 weeks of birth), was evaluated.

The NHS program for healthy newborns, fully implemented in 2006, has a national coverage of approximately 98%, and is a three step screening program. The first step uses oto-acoustic emission testing. In the case of absent emissions in one or both ears this procedure is repeated once. This is followed by automated auditory brain stem response (A-ABR) testing when an abnormal result persists. Referral for extensive audiological diagnostic evaluation follows when these three steps fail to produce a normal screening result. Early hearing screening for infants admitted to a neonatal intensive care unit is carried out using three-step A-ABR testing. Since NHS has gradually replaced DHS in the Netherlands from 2002 onwards, approximately half of the children available for participation in the DECIBEL study have been tested by NHS and the other half by DHS. Diagnostic investigations for congenital CMV infection took place in the workup to determine the etiology of the PCHI in children in the DECIBEL study.

### STUDY POPULATION

The study population consisted of children born in the Netherlands between January 2003 and December 2005, who were offered hearing screening in the first year of life and were known to have PCHI at the age of 3, 4 or 5 years at any of the Dutch Audiological Centers. PCHI was defined as a hearing loss of  $\geq 40$  dB in the better ear. The children were identified at the participating Audiological Centers. To date, 192 children eligible for participation have taken part in the developmental and etiological assessments of the DECIBEL study, of whom 188 gave informed consent for congenital CMV detection using their dried blood spots. These were not available for 17 children, but it was known that 8 of these had previously been tested for congenital CMV by other institutions. This resulted in 171 dried blood spot cards available for testing, and a total of 179 available results.

Participating children were classified as symptomatic for congenital CMV infection when one of the following conditions was present at birth: intrauterine growth retardation, microcephaly, prolonged hyperbilirubinemia, thrombocytopenia, petechiae or hepatosplenomegaly.

### STUDY SPECIMENS AND SPECIMEN PROCESSING

In the Netherlands a blood sample is routinely taken from all newborns during the first week of life for screening for metabolic, endocrine and other disorders. The remaining blood is stored for 5 years as dried blood spots on Guthrie cards by the National Institute for Public Health and Environment (RIVM). The Guthrie cards from the children participating in the DECIBEL study could be recalled with written parental permission. Medical and audiological files, including hearing screening strategies, and correspondence from medical specialists, were used to characterize the study population. DNA extraction from dried blood spots was performed according to the method described by Barbi et al.<sup>60</sup> using one 3.2mm punch, as evaluated by de Vries et al.<sup>61</sup>

Extraction was performed in 96-well plates, and was followed by amplification of a 126-bp fragment from the CMV immediate-early antigen region by means of an internally controlled quantitative real-time polymerase chain reaction as described previously by Kalpoe et al.<sup>62</sup> Each sample was tested in triplicate with a negative control punch between each sample. The results of the triplicates were interpreted using the algorithm described by Barbi et al.<sup>63</sup> The parents of the participants, and their family doctors, were personally informed about the results of the CMV DNA detection.

## ASSESSMENT OF DEVELOPMENT

The Minnesota Child Development Inventory was translated, according to the rules formulated by Guillemin et al., into the Dutch language and adjusted for sign language (CDI-NL).<sup>64</sup> This parental questionnaire consisted of 270 yes or no statements on child behavior and development, and was sent to parents of participating children by mail or e-mail. The developmental items were grouped to form scales including social development, self-help, gross and fine motor development, expressive language and language comprehension. The general development score was a summary score that provided an overall index of development. The developmental quotients (GDQ, general development quotient; ELC, expressive language quotient; LCQ, language comprehension quotient) were derived using the developmental age divided by the chronological age, and multiplying the result by 100.

## DATA ANALYSIS

The prevalence of congenital CMV among children with PCHI was calculated. Statistical tests were carried out using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA), with the significance level set at  $P < 0.05$ . The  $\chi^2$ -test was used to compare the differences in baseline characteristics. Linear regression modeling was used to analyze the developmental outcome based on the CDI-NL. Adjustment was made for age at examination and severity of hearing loss.

## RESULTS

CMV DNA was detected in 10 of the 171 dried blood spots tested during this study. When the eight children who had been tested previously, but who could not be retested because of missing dried blood spots (four positive and four negative) were added, the total contribution of congenital CMV infection in young children with PCHI was 8% (14/179). Twenty-three percent (9/39) of all cases of profound PCHI (hearing loss > 90 dB) in this sample were attributable to congenital CMV infection. The baseline characteristics of the children with congenital CMV,

and those without congenital CMV are presented in Table 1. No significant differences were found between the two groups in the baseline characteristics of gender, ethnicity, gestational age, type of hearing screening strategy and parity of the mother. The degree of hearing loss was more severe, and progression of hearing loss was significantly more frequent in children with congenital CMV infection than in children without congenital CMV. Additionally, children with congenital CMV infection had received cochlear implants significantly more frequently than children without congenital CMV infection.

		PCHI WITH CONGENITAL CMV n = 14 (%)	PCHI WITHOUT CONGENITAL CMV n = 165 (%)
Gender	Male	5 (35.7)	100 (60.6)
	Female	9 (64.3)	65 (39.4)
Ethnicity	Caucasian	13 (92.9)	139 (84.2)
	Mediterranean/African/ Asian	0	10 (6.1)
	Mixed	1 (7.1)	12 (7.3)
	Unknown	0	4 (2.4)
Gestational age	25-30 weeks	0	11 (6.6)
	31-37 weeks	2 (14.3)	30 (18.2)
	≥ 38 weeks	12 (85.7)	122 (74.0)
	Unknown	0	2 (1.2)
Parity	Primi-para	2 (14.3)	53 (32.2)
	Multi-para	12 (85.7)	102 (61.8)
	Unknown	0	10 (6.0)
Type of hearing screening strategy	Distraction hearing screening	4 (28.6)	44 (26.7)
	Newborn hearing screening	8 (57.1)	109 (66.0)
	Audiological examination on indication	0	7 (4.3)
	No hearing screening	2 (14.3)	4 (2.4)
	Unknown	0	1 (0.6)
Severity of hearing loss *	Moderate ( 40-60dB)	3 (21.4)	90 (54.5)
	Severe (61- 90 dB)	2 (14.3)	44 (26.7)
	Profound (>90dB)	9 (64.3)	30 (18.2)
	Unknown	0	1 (0.6)
Progression of hearing loss*		6 (43.0)	33 (20.0)
Type of amplification*	Hearing aid	5 (35.7)	117 (70.9)
	Bone-anchored hearing aid	0	9 (5.5)
	Cochlear Implant	8 (57.1)	33 (20.0)
	No hearing aid	1 (7.2)	5 (3.0)
	Unknown	0	1(0.6)

\*  $p < 0.05$ .

**Table 1** Baseline characteristics of the study population: children with permanent childhood hearing impairment with and without a congenital cytomegalovirus infection.



The hearing screening history and the long-term characteristics of children with congenital CMV infection are shown in Table 2. Four children had been screened by DHS, of whom two passed. Two children born in a region where DHS was offered did not take part in the hearing screening program. Eight children had been screened by NHS, of whom two (symptomatic children) passed. These children presented for audiological evaluation at 27 and 51 months, respectively, because of parental concern. One of them presented with profound hearing loss. Six children had symptomatic disease, of whom two were recognized at birth as having congenital CMV infection. These two children both had a referral at hearing screening and were treated for their symptoms. One received antiviral therapy (ganciclovir 12 mg/kg/day intravenously for 5 weeks and 1 week oral therapy). All children with symptomatic disease at birth had profound PCHI at the age of 3–5 years.

Cerebral imaging had been previously performed in eight children; in three because of multidisciplinary workup to determine the cause of PCHI, in one because of cochlear implant candidacy, and in four because of the suspicion of congenital infection in childhood. Abnormalities that could be interpreted as being caused by congenital CMV infection were seen in six children.

Developmental outcome (CDI-NL result) was available from 158 children with PCHI (Table 3). The presence of congenital CMV infection was accompanied by lower raw mean developmental quotients. These scores were even lower for children with symptomatic infection.

		CHILDREN n=14	
Type of hearing screening offered and result of screening	Distraction hearing screening	Refer	2 (1)
		Pass	2 (0)
	Newborn hearing screening	Refer	6 (2)
		Pass	2 (2)
	No screening		2 (1)
Reason for audiological evaluation	Refer at hearing screening		7 (4)
	Parental concern #		7 (2)
Reported long-term effects	Motor delay		6 (4)
	Visual impairment		12 (2)
	Cognitive delay		3 (3)

Figures in brackets are children with symptomatic infection at birth. #One of these children refused audiological evaluation after referral following distraction hearing screening, but presented later in childhood because of parental concern.

**Table 2** Characteristics of the children with permanent childhood hearing impairment and congenital cytomegalovirus (CMV) infection.

There was a significant difference in ELQ and LCQ between children with and without congenital CMV infection, in favor of the children with PCHI without congenital CMV infection. Adjustment for age at developmental evaluation or for the severity of hearing loss did not add to the results. Among the children with congenital CMV, a developmental difference, although not significant, was found between asymptomatic children and children with symptoms at birth. In these children, adjustment for age and severity of hearing loss decreased the mean difference. The one child treated with antiviral therapy did not perform better than the untreated CMV-positive children.

	GENERAL DEVELOPMENT QUOTIENT	EXPRESSIVE LANGUAGE QUOTIENT	LANGUAGE COMPREHENSION QUOTIENT
Without congenital CMV infection	77.7	79.3	71.4
With congenital CMV infection	67.4	62.7	56.4
Asymptomatic at birth	69.7	66.2	62.4
Symptomatic at birth	64.3	58.1	48.4
Mean difference between children with and without congenital CMV ( $\beta$ ) (95% CI)	-10.4 (-21.2;0.5)	-16.6 (-32.6;-0.5)*	-15.0 (-29.2;-0.8)*
Mean difference between children with and without congenital CMV ( $\beta$ ) (95% CI) <sup>a</sup>	-9.6 (-20.36;1.16)	-15.0 (-30.68;0.68)	-14.2 (-28.39;-0.01)*
Mean difference between children with symptomatic congenital CMV and children without congenital CMV ( $\beta$ ) (95% CI)	-13.4 (-29.5;2.7)	-21.2 (-45.2;2.77)	-23.1 (-44.3;-1.8)*
Mean difference between children with symptomatic congenital CMV and children without congenital CMV ( $\beta$ ) (95% CI) <sup>a</sup>	-12.7 (-28.8;3.4)	-20.26 (-43.8;3.2)	-22.7 (-43.8;-1.6)*
Mean difference between children with symptomatic congenital CMV and children with asymptomatic congenital CMV ( $\beta$ ) (95% CI)	-5.4 (-30.3;19.6)	-8.1 (-39.1;22.9)	-14.1 (-46.9;18.7)
Mean difference between children with symptomatic congenital CMV and children with asymptomatic congenital CMV ( $\beta$ ) (95% CI) <sup>a</sup>	-2.4 (-26.5;21.7)	-3.0 (-31.0;25.0)	-14.4 (-47.1;18.3)

\*  $p < 0.05$ , <sup>a</sup>Adjustment was made for age and severity of hearing loss.

**Table 3** The mean developmental quotients for children with permanent childhood hearing impairment (PCHI) with or without cytomegalovirus (CMV) infection, and the differences in quotient points between children with PCHI with or without CMV infection (asymptomatic or symptomatic at birth).

## DISCUSSION

The prevalence of congenital CMV infection in young children with PCHI found in this study was 8%. In children with profound PCHI the prevalence of congenital CMV was 23%. Children with congenital CMV infection are at risk for PHCI, even if they have a normal hearing result at NHS, and the developmental outcome of children with PCHI is significantly negatively affected by the presence of congenital CMV infection.

When interpreting the results, some advantages and a few potential weaknesses of this study need to be taken into account. The 5-year storage of dried blood spots in the Netherlands provided us with the opportunity to diagnose congenital CMV retrospectively.<sup>65</sup> Long-term sequelae of congenital CMV, such as PCHI, had time to become apparent in the intervening years. In the absence of systematic hearing screening in the preschool years, moderate hearing losses may have gone unnoticed, leading to underestimation of the prevalence of PHCI, and underestimation of the overall contribution of congenital CMV infection to PCHI in this study.

The sensitivity of CMV DNA detection in dried blood spots is limited, with sensitivities reported ranging from 50% (for dried blood spots with CMV DNA loads of 3–2 log<sub>10</sub> copies/ml) to 100% (for dried blood spots with CMV DNA loads of 5–4 log<sub>10</sub> copies/ml) when using the most sensitive methods.<sup>60,61,66,67</sup> Therefore, the contribution of congenital CMV to PCHI found in this study might be underestimated. The underrepresentation of ethnic minorities (non-whites in the DECIBEL study 15%; in the Netherlands as a whole 20%), in whom congenital CMV infection is found more frequently, might be a bias in our study.<sup>68,69</sup> A second possible bias may have been introduced by the urge of parents to gain insight in the etiology of their child's PCHI, leading to a possible overrepresentation of children with PCHI of unknown cause. Only 54% of parents were aware of an underlying cause of the PCHI at the start of the DECIBEL study. The potential (co-)existence of genetic causes of PCHI in these children is the subject of further study. Finally, the limited sample size of children identified with congenital CMV infection is of importance with respect to the interpretation of the results on developmental outcome.

In our study population, bilateral PCHI was attributable to congenital CMV in 8% of cases, and in 23% of children with profound PCHI. Evidence on the contribution of congenital CMV infection to PCHI has been minutely studied by Grosse et al.<sup>70</sup> Reported figures vary between 15% and 40%<sup>71-74</sup>; the fraction of 23% found in the children with bilateral profound PCHI is in concordance with these studies. The prevalence of congenital CMV in children with PCHI reflects the prevalence of congenital CMV in the country of the study. We expect the prevalence of congenital CMV infection in the Netherlands (0.6–0.7%) to be lower than the estimated overall international prevalence of congenital CMV (0.64%), but the exact prevalence in the Netherlands is unknown to date.<sup>12,65</sup>

Hearing loss caused by congenital CMV might be apparent at birth, but very often it presents during the first years of life.<sup>59</sup> In our study, two children with congenital CMV passed NHS, probably because of delayed-onset or progressive hearing loss. The Joint Committee on Infant Hearing suggests additional hearing evaluations in children with congenital CMV.<sup>15</sup> One should be aware that, lacking universal screening for congenital CMV infection, many congenitally infected children with delayed-onset or progressive hearing loss may be missed by NHS.<sup>75;76</sup> PCHI in children is expected to lead to a delayed developmental outcome.<sup>21;31</sup> Only a limited number of earlier studies have described the developmental outcome in children with congenital CMV infection, who are considered to be at substantial risk of developmental delay, regardless of auditory involvement.<sup>12;77</sup>

The results of our study show that children with PCHI caused by congenital CMV show lower developmental quotients than children with PCHI without congenital CMV. The difference in language development is significant. The raw differences in the language development quotients between children with PCHI with and without congenital CMV infection are large (15 for comprehension and 16.6 for expression). The significant difference in the comprehension quotient persisted when corrected for age and the severity of hearing loss. Further research is necessary to identify possible factors contributing to these results, such as cerebral damage resulting from congenital CMV infection. We recommend that it would be good clinical practice to regularly assess the development of children with congenital CMV, so necessary interventions may be started as soon as possible.

In conclusion, congenital CMV infection is important in the etiology of PCHI. Universal NHS is not a guarantee of normal hearing and development in childhood for children with congenital CMV infection. This is a problem which might be solved by universal congenital CMV screening. Subsequent audiological follow-up of those children with congenital CMV infection could decrease the developmental delay caused by later diagnosis and intervention.

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