MOTOR DEVELOPMENT OF CHILDREN WITH HUMAN PARECHOVIRUS AND ENTEROVIRUS INFECTIONS AT 24 MONTHS OF FOLLOW-UP

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BACKGROUND

- Human Enterovirus (EV) and Parechovirus (HPeV) account for 85-95 % of viral central nervous system (CNS) infections in childhood.
- They may cause damage to the brain and meninges, resulting in functional disorders ranging from cerebral palsy, motor and neurodevelopmental delay to retardation.
- Recent epidemics have been reported from different parts of the globe, including Asia, the USA and Europe.
- Though usually self limiting infections in a majority of children, some subtypes of these viruses (e.g. EV 71 and D68 and HPeV 3) cause epidemics, and have been associated with severe CNS, respiratory and systemic infections leading to intensive care admissions and death. Young children are particularly vulnerable for neurocognitive developmental delay following EV and HPeV infections.
- There are hardly any prospective, cohort studies with enough power, which have addressed the longitudinal motor development of non-Asian Caucasian children, beyond the first few months after infection.

STUDY AIM

- To longitudinally test the motor development of children with EV or HPeV CNS infection up to 24 months after infection, and to compare the results with children without infection.

METHODS

This study was part of an ongoing multicenter prospective study of children 0-16 years visiting three major general hospitals in the Netherlands (St. Elisabeth Hospital Tilburg, Amphia hospital Breda and Tweesteden Hospital Tilburg). The inclusion took place between 2008-2011 and involved only symptomatic children with signs of infection (fever, meningeal irritation, diarrhea, sepsis signs, etc.). Those >16 year or with any other infectious or non-infectious cause of illness or comorbidity, or caretaker refusal to consent were excluded from this study.

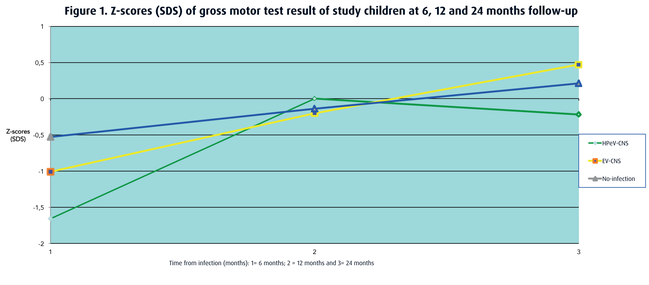
Virological tests : EV and HPeV RT-qPCR in NFA, feces, urine, blood and cerebrospinal fluid (CSF). If the PCR was positive, molecular typing of the virus was performed. Viral culture in feces, NFA and CSF.

Assessments of gross motor function:
- The Alberta Infant Motor Scale (AIMS): children 6 to 15 months
- The Bayley Scales of Infant and Toddler Development (Bayley-3-NL): children 16 – 42.5 months
- The Movement Assessment Battery for Children (M-ABC-2 NL): children > 42.5 months to 16 years
- Results in Z-scores (SD): normal is between SD -1.0 en +1.0
- Statistical analysis (R-statistics; R-version 3.1.3. Austria Vienna)
- Fisher/Chi-square/Independent t-test/Wilcox rank sum test (categorical variables), (multivariate) longitudinal regression analyses with repetitive measures and ANOVA.

RESULTS

- Of 126 included children, 58 (46%) had an EV- and 11 (8.7%) an HPEV CNS infection, in 57 (45.3%) no pathogen was detected.
- In Table 1 are shown the baseline characteristics of the children. Except for the significantly younger age of children with an HPeV CNS infection, there were no differences in gender, hospitalization or parental education.
- Table 2 shows the gross motor scores at 6, 12 and 24 months after infection. At 6 months: children with an HPeV-CNS infection had significant gross motor developmental delay compared to the control group (mean difference Z-score HPeV-CNS-infection versus control: -1.13; 95%CI:-1.96 to -0.30) (Table 2A). Those with EV-CNS also showed delay, but this was not clinically relevant (Table 2B). At 12 & 24 months these differences in developmental delay disappeared in both groups of children.
- Table 3 shows that the interaction of either HPeV and EV CNS infection and time were most closely associated with gross motor development, when compared with age of infection and parental education level.
- Table 4 shows that compared to the control group, HPeV and EV CNS-infected children showed a slower recovery of gross-motor development (HPeV: β=-0.79, 95%CI:-1.59 to 0.01; r2=9.7% en EV: β=-0.48, 95%CI:-0.97 to 0.01).
- During the 24 months follow-up, children with EV-CNS infection showed statistically significant linear catch-up in gross motor development (β=0.47, 95%CI:0.18 to 0.76). Those with HPeV showed a non-linear catch-up.

Figure 1. Z-scores (SDS) of gross motor test result of study children at 6, 12 and 24 months follow-up



Time from infection (months): 1= 6 months; 2 = 12 months and 3= 24 months

TABLE 1. BASELINE CHARACTERISTICS OF STUDY CHILDREN

Patient characteristics	HPeV CNS-infection	EV CNS infection	No pathogen (control)	P-value HPeV vs control	P-value EV vs control
Number N (%)	11 (8.7)	58 (46.0)	57 (45.3)		
Gender N (%)					
Male	10 (13.3)	33 (44.9)	32 (42.7)	0.03	0.94
Female	1 (2.0)	25 (49.0)	25 (49.0)		
Age at onset in day's					
mean (SD)	38.9 (29.3)	386.3 (878.8)	618.5 (1142.0)	0.01	0.01
min – max	13 – 114	3 – 3784	2 – 4623		
Hospitalization in day's					
mean (SD)	3.6 (0.8)	3.3 (1.1)	2.8 (2.5)	0.78	0.73
min – max	3.0 – 5.0	0.0 – 6.0	0.0 – 11.0		
Education mother N (%)					
Primary school	0 (0.0)	2 (66.7)	1 (33.3)	0.72	0.87
Low	1 (7.1)	6 (42.9)	7 (50.0)		
Middle	6 (15.8)	17 (44.7)	15 (39.5)		
High	3 (5.6)	25 (47.2)	25 (47.2)		
Education father N (%)					
Primary school	0 (0.0)	2 (100.0)	0 (0.0)	0.81	0.69
Low	1 (8.3)	4 (33.3)	7 (58.4)		
Middle	5 (10.9)	23 (50.0)	18 (39.1)		
High	4 (8.3)	21 (43.8)	23 (47.9)		

TABLE 2A. CHILDREN WITH HPEV CNS-INFECTION SHOWED SIGNIFICANT MOTOR DEVELOPMENTAL DELAY AT 6 MONTHS. THIS DISAPPEARED AT 12 & 24 MONTHS.

Average Z-score	HPeV-CNS-infection	No pathogen (control)	Mean difference (95% CI)	P-value
T6 mean (SD)	-1.66 (1.11)	-0.53 (1.07)	-1.13 (-1.96 to -0.30)	S
T12 mean (SD)	0.19 (0.83)	-0.14 (1.34)	0.33 (-0.10 to 1.65)	NS
T24 mean (SD)	-0.22 (1.19)	0.21 (1.00)	-0.44 (-1.21 to 0.34)	NS

TABLE 2B. CHILDREN WITH EV CNS-INFECTION SHOWED SIGNIFICANT MOTOR DEVELOPMENTAL DELAY AT 6 MONTHS. THIS DISAPPEARED AT 12 & 24 MONTHS.

Average Z-score	EV-CNS-infection	No pathogen (control)	Mean difference (95% CI)	P
T6 mean (SD)	-1.01 (1.00)	-0.53 (1.07)	-0.49 (-0.98 to 0.05)	S
T12 mean (SD)	-0.20 (0.86)	-0.14 (1.34)	-0.06 (-0.71 to 0.58)	NS
T24 mean (SD)	0.47 (1.26)	0.21 (1.00)	0.26 (-0.25 to 0.76)	NS

TABLE 3. BIVARIATE ANALYSES SHOWING THE INTERACTION OF RELEVANT VARIABLES ON THE ASSOCIATION HPEV OF EV INFECTION AND GROSS MOTOR DEVELOPMENT

Determinant	Unstandardized β -value (95% CI)	Correlation coefficient
HPeV-CNS-infection vs. control		
Time	0.42 (0.20 to 0.64)	-0.77
HPeV-CNS-infection	-0.72 (-1.25 to 0.05)	-0.41
Age of onset	0.01 (-0.01 to 0.01)	-0.44
Education mother	0.27 (-0.04 to 0.58)	-0.96
Education father	0.32 (-0.01 to 0.65)	-0.96
EV-CNS-infection vs. control		
Time	0.59 (0.43 to 0.75)	-0.68
EV-CNS-infection	-0.15 (-0.50 to 0.20)	-0.74
Age of onset	0.01 (-0.01 to 0.01)	-0.42
Education mother	-0.03 (-0.25 to 0.19)	-0.95
Education father	-0.01 (-0.23 to 0.21)	-0.94

TABLE 4. MULTIVARIATE REGRESSION MODEL SHOWING DIRECT EFFECT OF HPEV OR EV CNS INFECTION ON GROSS MOTOR DEVELOPMENT

Determinant	Unstandardized β -value (95% CI)	Correlation coefficient
HPeV-CNS-infection vs. control		
Intercept	-1.26 (-2.14 to -0.38)	-0.04
Time	0.36 (0.13 to 0.60)	-0.38
HPeV-CNS-infection	-0.79 (-1.59 to 0.01)	-0.31
Age of onset	0.01 (-0.01 to 0.01)	-0.31
Education mother	0.14 (-0.25 to 0.53)	-0.27
Education father	0.14 (-0.27 to 0.55)	-0.40
Interaction HPeV-CNS-infection * time	-0.31 (-0.20 to 0.82)	0.21

Determinant	Unstandardized β -value (95% CI)	Correlation coefficient
EV-CNS-infection vs. control		
Intercept	-0.72 (-1.41 to -0.03)	0.04
Time	0.33 (0.09 to 0.57)	-0.37
EV-CNS-infection	-0.48 (-0.97 to 0.01)	-0.32
Age of onset	0.01 (-0.01 to 0.01)	0.29
Education mother	0.05 (-0.22 to 0.32)	-0.31
Education father	0.11 (-0.16 to 0.38)	-0.44
Interaction EV-CNS-infection * time	0.47 (0.18 to 0.76)	0.26

RESULTS

At 6 months of follow-up: children with an HPeV CNS infection showed clinically significant gross motor developmental delay compared to controls. Though those with EV-CNS also showed a similar delay, this was not clinically relevant. At 12 & 24 months of follow-up, these differences in motor developmental delay disappeared in both groups. During the 24 months of follow-up, children with EV-CNS infection showed statistically significant linear catch-up in gross motor development. Those with HPeV showed a non-linear catch-up.

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