Cognitive and behavioral development of children after human Enterovirus and Parechovirus infection

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ABSTRACT

Both human Enterovirus (EV) and Parechovirus (HPeV) central nervous system (CNS) infection have been reported to cause neuronal damage in several brain areas. This may result in cognitive and behavioural problems, especially in young children with developing brains. There are scanty studies with conflicting results available. This study aimed to determine the impact of EV and HPeV infection on the cognitive and behavioural development of Dutch children aged between 0 and 5 years. We compared the cognitive and behavioural developments of children with EV and HPeV meningitis (case-group) with those of two control groups; those with EV/HPeV elsewhere and those without EV or HPeV infection (healthy peers). Multivariate analyses showed that the cognitive and behavioural development of children with EV and HPeV meningitis did not differ significantly from those of children from the two control groups. However, it showed that a lower verbal intelligence quotient (VIQ) was associated with older age at assessment (β=-0.29) and longer duration of time since diagnosis until psychological testing (β=-0.22). An older age at infection was more associated with internalizing and externalizing problems (respectively, β=0.37 and β=0.34) than a younger age. Children with an EV infection were more prone to externalizing problems (β=-0.32) than those with HPeV. In conclusion, we did not find any difference in cognitive development of children with EV or HPeV meningitis. However, older age was associated with lower VIQ and behavioral problems, especially in children with EV infection.
INTRODUCTION

Human non-polio Enterovirus (EV) and Parechovirus (HPeV) are major causes of viral infection and aseptic meningitis in young children.\textsuperscript{1-4} EV or HPeV central nervous system (CNS) infections have been reported to cause neuronal damage, leptomeningeal enhancement, cortical hyperdensity and edema in the periventricular and subcortical white matter, thalami and corpus callosum.\textsuperscript{4-8} These areas are linked to cognitive and behavioural functioning.\textsuperscript{5} It is plausible that an EV or HPeV CNS infection may lead to cognitive delay and behavioural problems. The similarity in their clinical symptoms suggests that a considerable commonality exists in their effect on the cognitive and behavioural functions. However, no previous studies examined the cognitive or behavioural development in HPeV CNS infected children.

Studies, which have examined the cognitive functioning of EV CNS infected children, reported contrasting results.\textsuperscript{10-15} Some found no\textsuperscript{12,13} or few\textsuperscript{14,15} cognitive developmental delays, others found a lower mean IQ.\textsuperscript{10,11} Two studies evaluated the behavioural development of children with an EV infection. They observed emotional and attention regulation problems, hyperactivity and impulsivity in those with CNS involvement.\textsuperscript{16,17} Most of these previous studies did not include a control group, making it difficult to compare their results with those of healthy peers.\textsuperscript{11,14} Majority of these studies was performed in Asian children, during outbreaks of EV type 71, which rarely occur in Western countries.\textsuperscript{11,14,16-19} There are only a few low-powered studies (n=9; n=19; and n=45, respectively) reporting on non-Asian children.\textsuperscript{10,12,13} These limitations make it difficult to extrapolate these findings to other populations.

There are no known effective antiviral drugs in the management of EV or HPeV CNS infection. The ultimate goal in the management is the prevention of motor, cognitive and behavioural developmental delay. It is important to identify the risk factors involved. This will enable early identification, and provision of interventions to limit severe cognitive and behavioural developmental delays.

The primary objective was to determine the impact of EV and HPeV CNS infection on the cognitive and behavioural development of children aged between 0 and 5 years and to compare these between EV and HPeV. Another objective was identification of the clinical and demographic factors involved.
METHODS

Procedure and patients
As part of a multicenter prospective cohort study evaluating the incidence, clinical features
and prognosis of EV and HPeV infection in children, this study was performed in three
general pediatric wards in the Netherlands. The study enrolment, between March 2008
and September 2011, has been described previously.20,21 Children 0–16 years of age,
who attend any of the study centers with suspected viral infection, were eligible for
inclusion. After obtaining a written informed consent from their caretakers, we collected
nasopharyngeal, blood, urine and feces specimens for EV and HPeV reverse-transcriptase
real time quantitative polymerase chain reaction (RT-qPCR). In addition, viral culture was
performed on fecal and nasopharyngeal specimens. As with routine clinical practice, a lumbar
puncture was performed to collect cerebrospinal fluid (CSF) specimen, only in children
with symptoms of a CNS infection, as judged by the pediatrician on-call. In addition to EV
and HPeV, a CSF PCR RT-qPCR was performed to exclude Herpes Simplex Virus (HSV),
Varicella Zoster Virus (VZV). Both bacterial and viral cultures were also performed on the
CSF specimen.

Study groups
Children were allocated in the following three study groups.

EV or HPeV meningitis (case group): detection of EV or HPeV in the CSF of a symptomatic
patient.

EV or HPeV infection elsewhere (sick control group): detection of EV or HPeV in nasopharyngeal,
blood, urine or feces, but not in CSF specimen of a symptomatic patient.

No pathogen detected (healthy control group): no EV, HPeV or any other pathogen was
detected in any of the specimens.

Detection methods

EV/HPeV RT-qPCR
Isolated viral RNA from any of the body specimens was analyzed for the presence of HPeV or
EV using respectively an HPeV and EV specific RT-qPCR and for genotyping, as previously
described.20,22
Viral culture

Viral culture was performed on confluent layers of tertiary Cynomolgus monkey kidney cells, as previously described.22

Cognitive and behavioral assessments

Study participants aged 0–5 years were invited to participate. They were subjected to cognitive and behavioural tests, using respectively the Dutch version of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-NL)23 and the Child Behaviour Checklist (CBCL).24 The psychologists who conducted the tests were blinded to the clinical diagnosis of the children. During the WPPSI-III-NL test, parents were invited to complete the CBCL questionnaire. Children with abnormal results were referred to the study paediatrician (CCO) for further evaluation and management.

Cognitive development

The WPPSI-III-NL assesses cognitive development.23 It consists of two versions; one for preschool children (2;6 to 3;11 years), and the other for young school-children (4;0 and 7;11).23,25 The WPPSI-III-NL contains core, supplemental or optional subtests. Only the core subtests were used in this study because they provide the best measures of overall cognitive ability. The version for preschool children consists of four core subtests, which combine the full scale intelligence quotient (FSIQ) (Cronbach’s alpha (α) in the current study = 0.91). The ‘receptive vocabulary’ and ‘information’ constitute together the VIQ (α=0.88). The ‘block design’ and ‘object assembly’ represent the performance intelligence quotient (PIQ) (α=0.84). The WPSSI version for young school-children consists of 7 core subtests, which combine the FSIQ (α=0.91), including ‘information’, ‘vocabulary’ and ‘word reasoning’ which form the VIQ (α=0.88). The ‘block design’, ‘object assembly’, ‘picture concepts’ and ‘coding’ form the PIQ (α=0.87). Raw test scores were converted into scaled scores to form composite IQ scores, including FSIQ, VIQ, and PIQ. Composite IQ scores of both age-specific versions were pooled, and ranged from 55 to 145, with an average score of 100 and a standard deviation of 10.26

Behavioural problems

The CBCL questionnaire for children aged 1.5–5 years assesses behavioral problems. A total of 100 items were scored, using three-point Likert scales: 0 (not true), 1 (somewhat or sometimes true), and 2 (very true or often true). By adding up the scores of all individual
items of that scale, these made up 8 behavioral dimensions (raw scores), including ‘emotional reactivity’ (Cronbach’s alpha (α) in the current study = 0.79), ‘anxious/depressed’ (α=0.69), ‘somatic complaints’ (α=0.76), ‘withdrawn’ (α=0.57), ‘sleep problems’ (α=0.76), ‘attention problems’ (α=0.67), ‘aggressive behavior’ (α=0.89), and ‘other problems’ (α=0.79). According to Cohen, an α ≥0.70 is satisfactory.27 Cronbach’s α for the subscale ‘withdrawn’ was too low and was, therefore, left out from further analyses. If more than 50 percent of the items of a dimension were completed, missing item-score values were replaced by the mean scale score. The CBCL also provides a total behavior problem score and two second-order factor scores for internalizing problems (emotionally reactive, anxious/depressed, somatic complaints, withdrawn and sleep problems) and externalizing behavior (attention problems and aggressive behavior). A digital program from Achenbach System of Empirically Based Assessment (ASEBA) was used to convert the behavioural dimensions into normalized T-scores, with an average T-score of 50 and a standard deviation of 10.28 Children were classified as normal (T-score <65), borderline (T-score 65–70), or clinical (T-score >70) range for each behavioral dimension. Finally, the 5 DSM scales were used, by pooling the scores of all individual items of that dimension (raw scores), including ‘affective problems’ (α=0.49), ‘anxiety problems’ (α=0.72), ‘Pervasive developmental disorder (PDD)’ (α=0.76), ‘ADHD’ (α=0.72), and oppositional defiant problems (‘ODD’) (α=0.79). The DSM scale ‘affective problems’ was left out of further analysis because its internal consistency was too low.

Demographic and clinical variables
Demographic variables collected were age (months), gender, and parental education level (1 = primary school; 2 = vocational education; 3 = higher vocational education or university degree). Clinical variables included were type of virus (EV or HPeV), age at diagnosis/inclusion (days), duration of hospitalization (days), time between diagnosis and assessment (months).

Since none of the children in the study was admitted to a Paediatric Intensive Care Unit (PICU), we used the combination of duration of hospitalization and different laboratory results (white bloodcell count (WBC) in the CSF, leukocytes in blood and c-reactive protein (CRP)), as a proxy for severity of the infection.

Analyses
Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS, version 22). To compare socio-demographic and clinical characteristics of the three study
groups and of EV or HPeV infection a one-way multivariate analysis of variance (MANOVA) for continuous variables and the Chi-square test for discontinuous variables was used.

To examine differences in cognitive and behavioural development between the groups, all sum and subscales were analysed with MANOVA. Socio-demographic and clinical factors that differed significantly between the study groups, were included as covariates in the multivariate analyses. Study groups served as the independent, and cognitive and behavioural development as the dependent variables. By significant differences, Tukey post-hoc analysis was used to identify which of the three groups differed. The same analyses were performed with type of virus (EV/HPEV/no pathogen) as independent and cognitive and behavioral development as dependent variables.

Lastly, with multiple regression analyses we tested the relationship between clinical characteristics, socio-demographic variables and cognitive and behavioural development in children with EV/HPeV meningitis or EV/HPeV infection elsewhere. Only children with an EV/HPeV infection were included (n=90). Nine with co-infection (EV and HPeV) and those with no pathogen detected (n=45) were excluded. To prevent power-problems, a selection of variables was made based on preliminary univariate analyses. Stevens recommends at least 15 subjects per predictor in a multivariate regression analysis.

Ethical considerations
Before enrolment, eligible patients and their caretakers signed a written informed consent form. The study was approved by the Medical Ethics Committee of each participating center. Study Registration number is NL21361.008.07.

RESULTS
Patient characteristics
A total of 144 children, with complete WPPSI-III-NL and CBCL results, were included. Their baseline characteristics are described in Table 7.1. At inclusion, children in the case group were significantly younger than those in the other two groups (39 days versus 208 and 199, respectively). Children with an EV/HPeV infection had a shorter duration of hospitalization than those in other groups (p=0.032). There were no differences in the presence of pleocytosis, WBC and CRP level. The mean time between clinical diagnosis and assessment was 40 months. This large time frame was due to the fact that a majority
of the study children (n=124, 86%) were <1 year of age at the time of diagnosis, while the minimum age for psychological assessment was 2;6 years. Children with any EV infection were younger at assessment (p=0.001), and had a longer duration of hospitalization (p=0.020) (data not shown) than those with HPeV infection.
Cognitive and behavioral development based on location of viral infection

Children in the case group showed a higher FSIQ than those in the healthy control group (p=0.046), which however, disappeared after correcting for 'age at diagnosis' and 'duration of hospitalization'. There were no differences in behavioral development between the three study groups and they were all within the normal ranges. There was a significant relationship between a longer duration of hospitalization and the presence of externalizing problems (p=0.031), total problems (p=0.033), and ODD (p=0.019) (Table 7.2).

Cognitive and behavioral development based on type of viral infection

There were no differences in cognitive development between children with EV or HPeV infection. Children with an EV infection showed more behavioural problems, particularly

![Table 7.2](image)

Note: EV = Enterovirus; HPeV = Human Parechovirus; CNS = central nervous system; FSIQ = full scale IQ; VIQ = verbal IQ; PIQ = performance IQ; PDD = pervasive developmental problems; ADHD = attention deficit and hyperactivity problems; ODD = oppositional defiant problems. * P-value after adjustment for age at diagnoses. The subscale ‘withdrawn’ and the DSM scale Affective problems were left out of the analyses because of α<0.70.
aggressive behaviour (p<0.0001) and ODD (p=0.001). This difference remained unchanged after correcting for ‘location of the infection’ (meningitis or elsewhere), ‘age at assessment’ and ‘duration of hospitalization’. These behavioural abnormalities were, however, not within clinically relevant ranges. An older age at assessment was related to externalizing problems (p=0.002), total behavioural problems (p=0.015), ADHD (p=0.017) and ODD (p=0.003) (Table 7.3).

### Variables related to cognitive development

Univariate analyses showed that ‘age at assessment’, ‘location of infection’ (CNS vs elsewhere), ‘age at diagnosis’, and ‘time from diagnosis to assessment’ were significantly related to cognitive development (data not shown). These variables were included in the multivariate analyses. ‘Education level of father’ was additionally selected based on the literature. Results

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**Table 7.3 Comparison of cognitive and behavioural developments between children with an EV or HPeV infection, and no infection**

<table>
<thead>
<tr>
<th></th>
<th>EV (n=62) M (SD)</th>
<th>HPeV (n=24) M (SD)</th>
<th>No infection (n=44) M (SD)</th>
<th>p-value virus type</th>
<th>p-value group x covariates*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive functioning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSIQ</td>
<td>107.9 (15.6)</td>
<td>106.3 (13.1)</td>
<td>102.0 (11.9)</td>
<td>0.351</td>
<td>0.930</td>
</tr>
<tr>
<td>VIQ</td>
<td>109.6 (14.6)</td>
<td>106.2 (17.6)</td>
<td>103.7 (13.4)</td>
<td>0.121</td>
<td>0.959</td>
</tr>
<tr>
<td>PIQ</td>
<td>103.1 (14.6)</td>
<td>103.5 (10.7)</td>
<td>99.8 (10.9)</td>
<td>0.102</td>
<td>0.860</td>
</tr>
<tr>
<td><strong>Behavioral problems</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sum scales (t-scores)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Total problems</td>
<td>42.2 (7.9)*</td>
<td>36.7 (5.6)*</td>
<td>39.4 (6.9)</td>
<td>0.007*</td>
<td>0.027*</td>
</tr>
<tr>
<td>Internalizing problems</td>
<td>45.5 (11.3)</td>
<td>41.8 (9.4)</td>
<td>43.6 (9.4)</td>
<td>0.310</td>
<td>0.417</td>
</tr>
<tr>
<td>Externalizing problems</td>
<td>50.1 (10.1)*</td>
<td>41.9 (6.9)*</td>
<td>45.9 (8.6)</td>
<td>0.001*</td>
<td>0.056</td>
</tr>
<tr>
<td><strong>Subscales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotionally reactive</td>
<td>2.5 (2.7)</td>
<td>1.5 (1.8)</td>
<td>2.4 (2.9)</td>
<td>0.252</td>
<td>0.231</td>
</tr>
<tr>
<td>Anxious depressed</td>
<td>1.8 (2.1)</td>
<td>1.2 (1.3)</td>
<td>1.4 (1.9)</td>
<td>0.451</td>
<td>0.524</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>2.4 (3.2)</td>
<td>1.7 (2.1)</td>
<td>1.6 (1.7)</td>
<td>0.256</td>
<td>0.631</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>2.0 (2.4)</td>
<td>1.6 (2.1)</td>
<td>1.9 (2.3)</td>
<td>0.831</td>
<td>0.632</td>
</tr>
<tr>
<td>Attention problems</td>
<td>2.5 (2.0)</td>
<td>1.7 (1.6)</td>
<td>1.8 (1.7)</td>
<td>0.097</td>
<td>0.160</td>
</tr>
<tr>
<td>Aggressive behaviour</td>
<td>10.5 (6.7)*</td>
<td>5.0 (3.1)*</td>
<td>7.8 (5.1)</td>
<td>0.000*</td>
<td>0.001*</td>
</tr>
<tr>
<td>Other problems</td>
<td>6.9 (5.3)</td>
<td>4.6 (4.1)</td>
<td>6.4 (5.2)</td>
<td>0.162</td>
<td>0.171</td>
</tr>
<tr>
<td><strong>DSM-IV scales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety problems</td>
<td>2.4 (2.7)</td>
<td>2.1 (2.1)</td>
<td>2.2 (2.5)</td>
<td>0.830</td>
<td>0.683</td>
</tr>
<tr>
<td>PDD</td>
<td>3.0 (2.6)</td>
<td>1.9 (1.9)</td>
<td>3.0 (3.6)</td>
<td>0.280</td>
<td>0.458</td>
</tr>
<tr>
<td>ADHD</td>
<td>4.2 (2.5)</td>
<td>3.3 (2.4)</td>
<td>3.6 (2.2)</td>
<td>0.250</td>
<td>0.500</td>
</tr>
<tr>
<td>ODD</td>
<td>4.3 (2.7)*</td>
<td>2.1 (1.6)*</td>
<td>3.4 (2.1)*</td>
<td>0.001*</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Note: 9 children with both viruses were excluded. PDD = pervasive developmental problems; ADHD = attention deficit and hyperactivity problems; ODD = oppositional defiant problems. * P<0.05 for pairwise comparisons. 

*P-value after adjustment for age at diagnoses. The subscale ‘withdrawn’ and the DSM scale affective problems were left out of the analyses because of α<0.70.27
showed that older age (β=-0.29) and long time frame from the initial diagnosis to assessment (β=-0.22) were negatively related to VIQ (Table 7.4).

**Variables related to behavioral development**

Univariate analyses showed that ‘age at diagnosis’, ‘duration of hospitalization’, ‘virus type’, and ‘age at assessment’ were significantly related to behavioral functioning (data not shown). These variables, in addition to gender, were included in the multivariate analyses. Gender was included based on the literature.31 An older age was a risk factor for internalizing and externalizing problems (β=0.37 and β=0.34, respectively). EV infection was significantly associated with externalizing behavioral problems (β=-0.32) (Table 7.5).

<table>
<thead>
<tr>
<th>Table 7.4</th>
<th>Relationships between sociodemographics, clinical characteristics and cognitive development of children with an EV or an HPEV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive functioning</td>
<td>FSIQ</td>
</tr>
<tr>
<td>Socio-demographics</td>
<td>β</td>
</tr>
<tr>
<td>Age at assessment</td>
<td>-0.17</td>
</tr>
<tr>
<td>Education level of the father</td>
<td>0.13</td>
</tr>
<tr>
<td>Clinical variables</td>
<td>β</td>
</tr>
<tr>
<td>Group</td>
<td>0.00</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>0.21</td>
</tr>
<tr>
<td>Time frame from diagnosis to assessment</td>
<td>-0.18</td>
</tr>
<tr>
<td>R square</td>
<td>0.16</td>
</tr>
<tr>
<td>Adjusted R square</td>
<td>0.10</td>
</tr>
</tbody>
</table>

* Significant at p<0.05. a All dichotomous variables have binary codings: education level of the father low 0 vs. high 1, group elsewhere 0 vs. CNS 1.

<table>
<thead>
<tr>
<th>Table 7.5</th>
<th>Relationships between sociodemographics, clinical characteristics and behavioural problems of children with EV or HPEV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural problems</td>
<td>Internalising</td>
</tr>
<tr>
<td>Sociodemographic variables</td>
<td>β</td>
</tr>
<tr>
<td>Gender</td>
<td>0.20</td>
</tr>
<tr>
<td>Age at assessment</td>
<td>-0.01</td>
</tr>
<tr>
<td>Clinical variables</td>
<td>β</td>
</tr>
<tr>
<td>Virus type</td>
<td>-0.20</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>-0.05</td>
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<tr>
<td>Age at diagnosis</td>
<td>0.37*</td>
</tr>
<tr>
<td>R square</td>
<td>0.21</td>
</tr>
<tr>
<td>Adjusted R square</td>
<td>0.15</td>
</tr>
</tbody>
</table>

* Significant at p<0.05. a All dichotomous variables have binary codings: boy 0 vs. female 1, EV 0 vs. HPeV 1.
DISCUSSION

In contrast to bacterial CNS infections, there are few studies on the cognitive and behavioral development of children after viral CNS infections. We found no differences in cognitive and behavioral development between children in the case-group (EV or HPeV infection in the CNS) and the sick control group (EV or HPeV infection elsewhere) or the healthy control group (without any detectable pathogen). However, when examining factors involved in cognitive and behavioral development in children with an EV or an HPeV infection (irrespective whether the virus was located in the CNS or elsewhere in the body), we identified that an older age during assessment and a larger time frame between age at diagnosis and assessment were related to lower VIQ, which suggests that verbal skills got impaired with time. This is supported by previous reports of impaired language and speech skills in children with EV infection, and emphasizes the need for future research to focus more on the language developmental skills, preferably in a longitudinal study design. There might be a critical age of postnatal brain development in language skills.

Furthermore, children with an EV infection had more externalising behavioural problems than those with an HPeV infection, including aggressive behaviour and ODD. Previous studies that also found behavioural problems in children with an EV infection were predominantly internalising of nature. A possible explanation might be the genetic and cultural differences between study populations. Their study involved predominantly Asian children, while ours predominantly involved Caucasian children. It has been shown that under similar stressful situations, Asians tend to express more internalizing problems, whereas Westerners more externalizing problems.

That children with an EV infection had more externalising problems than those with HPeV is an important finding. It is generally assumed that EV and HPeV have the same long term outcomes, based on the mere fact that they share similar pathogenesis and clinical features. There is a possibility that EV and HPeV have predominant affinity for different parts of the brain or affect the CNS in different ways. There are indications that EV predominantly affects the brainstem, pons, and midbrain, whereas HPeV affects the corpus callosum. These brain areas are involved in the behavioural development. It is possible that HPeV infects more renewable cells of the CNS while EV infects more non-renewable cells, such as neurons. Finally, it appeared that children who were diagnosed at an older age reported more behavioural problems. Maybe older children are more aware of being ill and the consequences (feeling sick, worries of the parents, staying in the hospital), suggesting higher impact in older children.
The most important strength of this study is the large patient population and the prospective, cohort multicenter design. It is, to our knowledge, the first study to prospectively describe the cognitive and behavioral outcome of children after HPeV meningitis, which is also compared with children with EV meningitis. Furthermore, children attending three general pediatric wards were included, who are representative of the majority of children with these common viral infections both in the Netherlands and other countries, worldwide. Previous studies included specific patient populations, such as severely ill Asian children admitted to single center PICUs during EV genotype-71 epidemics.\textsuperscript{11,13} One of the major limitations is the relatively low number of patients with HPeV meningitis. This limited the possibility to conduct subgroup analyses. Second, only 6% to 21% of the variance of cognitive and behavioral functioning was explained by the included variables, suggesting that other important unmeasured predictors may also be involved. However, the chance that certain relevant variables are not included is inherent to psychosocial research. A third limitation was a few differences in baseline characteristics of the study groups, including age at diagnosis and duration of hospitalisation.

Children with meningitis in the case-group were younger than children in the two control groups. This is in line with previous studies showing that younger children are more susceptible to CNS viral infection.\textsuperscript{36,37} Remarkably however was that results showed that younger children had higher IQ scores than older children, which resulted in better cognitive functioning of the (younger) children in the case-group. However, controlling for age at diagnosis negated the better IQ scores in the case-group. A possible explanation for the better cognitive functioning of the younger children could be that different age-specific versions of the WPSSI test were administered. The subtest ‘receptive vocabulary’ was only administered to preschool children (this is one of the subsets used to determine VIQ and TIQ), during which strong impulsivity was observed. Maybe these children were able to achieve a high score purely on the basis of gamble chance. Though Wechsler showed the WPPSI-III to be reliable and valid,\textsuperscript{38-40} there could be a ceiling effect of the version for the preschool children in our study. This has been found by previous studies, which concluded that some subtests of the WPPSI were too easy for up to half of their study population.\textsuperscript{41} Another explanation that younger children had better cognitive functioning could be that mild insult to the brain, such as meningitis, at an early age is associated with better outcome, due to young brain plasticity, than at an older age.\textsuperscript{42} Finally, children in the healthy control group had the longest duration of hospitalization, which could be a result of the tendency of paediatricians to keep symptomatic young children, in whom the causative pathogen...
has not been identified, admitted for a longer period than those in whom a viral pathogen has been identified.

In conclusion, we found no cognitive and behavioural functional problems in children with an EV or HPeV meningitis, compared to two control groups. However, children with an EV infection showed more externalizing aggressive behavioural problems and ODD than those with an HPeV infection.

REFERENCES


