Neurological condition assessed with the Hempel examination and cognition and behaviour at 4 years

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A R T I C L E  I N F O

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A B S T R A C T

Aim: To investigate associations between neurological condition, assessed with the Hempel examination, in terms of minor neurological dysfunction (MND) and neurological optimality, and cognition and behaviour at 4 years.

Study design: Cross-sectional analyses within a prospective, assessor-blinded follow-up study.

Subjects: Four-year-old singletons born to subfertile parents (n = 235; 120 boys).

Outcome measures: Outcome parameters were complex minor neurological dysfunction (complex MND) and the neurological optimality score (NOS). Cognitive outcome was evaluated with the Kaufman Assessment Battery for Children, resulting in a total intelligence quotient (IQ). Behavioural outcome was evaluated with the Child Behavior Checklist, resulting in a total problem T-score.

Results: Fifty-seven (24.3%) children had complex MND. None of the children showed fine motor dysfunction, suggesting a ceiling effect of the Hempel assessment. Complex MND was not correlated with IQ or total problem T-score. Nevertheless, a higher NOS was correlated with a higher IQ and a lower total problem T-score (adjusted mean estimate [95% confidence interval]: cognition: 0.445 [0.026; 0.865], p = 0.038; behaviour: −0.458 [−0.830; −0.087], p = 0.016).

Interpretation: At age 4, complex MND assessed with the Hempel assessment was not associated with cognition and behaviour, presumably due to a ceiling effect in the Hempel domain of fine motor function. A more optimal neurological condition was associated with higher IQ and better behaviour.

1. Introduction

In school-aged children the association between minor neurological dysfunction (MND) and developmental disorders, such as learning and behavioural difficulties has been well established \cite{1}. MND is defined as neurological dysfunction in the absence of evident neurological pathology, such as cerebral palsy (CP) \cite{2}. Two forms of MND may be distinguished: simple MND, representing a non-optimal but normal form of brain function (minor neurological difference), and complex MND, representing the clinically relevant form of MND, as it is clearly associated with perinatal adversities, and a substantial increase of learning and behavioural problems \cite{2}. However, little is known about the association between neurological condition and cognition and behaviour in preschool-age children.

The nervous system of a child substantially differs from that of an adult, owing to the continuous functional and structural changes in the developing, young brain \cite{3,4}. The age-specific brain of the child determines the way in which neural dysfunction is assessed and expressed. Children can only display (minor) deviations in functions which belong to their age-specific abilities. Consequently, the technique and interpretation of the paediatric neurological examination must be adapted to the age-specific characteristics of the nervous system of the child. From school-age onwards, the neurological examination mainly consists of a structured evaluation of muscle tone and power, reactions and reflexes, cranial nerve function and specific tasks to test coordination and fine manipulative abilities. To assess MND at preschool-age, i.e. from 18 months up until 4 years, a less structured examination has been developed, the Hempel assessment \cite{5–7}. This assessment consists for a large part of standardized free play, allowing for the assessment of the quality of gross and fine motor behaviour. The evaluation of the quality of spontaneous motility is a sensitive way to detect MND at preschool-age.

Previous studies revealed that MND at school-age is associated with impaired motor performance \cite{8,9}. In school-aged children and adolescents, MND is also associated with learning disabilities, including limited spelling, reading and writing limited arithmetic skills \cite{10–13}.
and autism spectrum disorders [14]. MND is also, but less strongly, associated with behavioural problems, such as attention problems, social problems and internalizing and externalizing behaviour [15–18]. However, little is known about the association between MND and cognition and behaviour at preschool-age.

The data of the Groningen Assisted Reproductive Technique (ART) cohort study allowed us to study associations between MND and cognition and behaviour at preschool-age. The Groningen ART cohort consists of three groups of children, all born to subfertile couples who underwent fertility treatment (conventional controlled ovarian hyperstimulation in vitro fertilization (IVF) or modified natural cycle (MFC) or who conceived naturally. Neurological, cognitive and behavioural outcome of the three groups was similar up to 4 years of age [19–23]. Neurodevelopmental outcome at 2 and 4 years showed however a negative association with the severity of subfertility, in terms of time to pregnancy (TTP) [22–24].

The primary aim of this study was to investigate the relationship between neurological condition - in clinical terms of complex MND - and cognition, in terms of intelligence quotient (IQ) in 4-year-old children. We hypothesize that the presence of MND, especially of complex MND, is associated with a lower IQ score in preschool-aged children. Neurological condition may be expressed in terms of MND, it may also be expressed in a quantitative measure of neurological condition, the so called neurological optimality score (NOS) [25]. Therefore, the secondary aim of the study was the assessment of the relationship between the NOS, and IQ and the associations between complex MND and NOS and behaviour. We hypothesize that a better neurological condition is associated with a higher IQ and less behavioural problems. We choose cognitive outcome as our primary outcome parameter as cognition has a stronger neurobiological basis than behaviour – the latter being more affected by social environmental factors than the former [15,26].

2. Methods

2.1. Participants

Two hundred and thirty-five singletons were included in the current study, all born to subfertile couples that either underwent assisted conception (n = 156) or conceived naturally (n = 79). Pooling the groups is legitimate as the neurological condition, cognition and behaviour did not differ between the groups [20–24]. For details of the follow-up at 4 years of age see Schendelaar et al. [22,23].

The Medical Ethical Commission of the University Medical Center Groningen approved the study design. Parents provided written informed consent for their child’s study participation.

2.2. Measurements

We assessed neurological condition with the standardized and age-specific neurological examination according to Hempel [5]. The Hempel assessment is the neurological tool to assess MND at preschool-age, i.e., from 18 months up until the age of 4 years. It may be considered as the preschool-age equivalent of the Examination of the Child with Minor Neurological Dysfunction (MND-assessment), which is the age-specific tool to assess MND from 4 years onwards [1]. We did not select the MND-assessment, as some test items do not allow for the assessment of minor signs at age 4, as they are too difficult, e.g., the finger opposition test.

The Hempel examination assesses five domains of functions that can be scored as typical or deviant: fine motor function, gross motor function, posture and muscle tone, reflexes and visuomotor function. Children were classified as being neurologically normal, having simple MND or complex MND, or as having a clear neurological disorder, such as CP. Neurologically normal implies the absence of neurological dysfunction, i.e., none of the domains meets the criteria for deviancy, or only the domain of reflexes meets the criteria. Simple MND indicates the presence of one deviant domain (except the domain of reflexes).

Complex MND indicates the presence of more than one domain of dysfunction. Neurological condition was also expressed in a neurological optimality score (NOS), reflecting the integrity of the child’s brain. The NOS consists of 56 items (range 0–56) of which the sum reflects the total score. Higher scores represent better performance. It must be emphasized that optimality is not similar to normality, as the range for optimal behaviour is narrower than for normal behaviour. Moreover, reduced optimality does not necessarily imply abnormality [25]. The inter-rater reliability of the Hempel assessment is satisfactory (κ = 0.62–1.00 [mean 0.93]) and its construct validity is good [5,7]. The latter is illustrated by the finding that higher prevalences of MND and lower NOS values are associated with preterm birth [6,27], perinatal asphyxia [28], neonatal hyperbilirubinaemia [29,30], severity of subfertility [22,23], dysmorphic features [31], prenatal and neonatal fatty acid status [32,33], prenatal exposure to polychlorinated biphenyls and dioxins [34] and abnormal general movements at 3 months corrected age [35].

Cognition was evaluated using the Kaufman Assessment Battery for Children, second edition (K-ABC-II) [36]. This individually administered standardized instrument measures cognitive and processing abilities in children aged 3 to 18 years. Cognitive and processing abilities are expressed in a total intelligence quotient (IQ, i.e., Fluid-Crystallized Index) score and four IQ scale scores: 1) a sequential processing IQ, reflecting short-term memory, 2) a simultaneous processing IQ, reflecting spatial aptitude, 3) a learning ability IQ, reflecting long-term memory capacity and 4) a knowledge IQ, reflecting general knowledge. Raw test scores are normalized into global scores (mean: 100, standard deviation [sd]: 15). The K-ABC-II has been used for children with different social backgrounds or ethnic differences without critical effects on test-scores. Reliability and validity of the K-ABC-II are good [36]. The original American norms were applied as Dutch norms are lacking.

Behaviour was evaluated using the validated Dutch version of the Child Behavior Checklist (CBCL) [37,38]. The CBCL is a parental questionnaire which is used to identify emotional and behavioural problems in children aged 1.5 to 5 years. The questions on the CBCL are classified into the following problem scales: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive behaviour. The first four scales together form the internalizing scale; the latter two scales form the externalizing scale. The sum of all questions results in the total problem scale. Raw test scores are normalized into T-scores with a mean of 50 (sd 10). Higher T-scores represent more problematic behaviour: T-scores < 60 are in the normal range of behaviour, T-scores between 60 and 63 represent borderline behaviour, and T-scores > 63 are in the clinically abnormal range of behaviour. In the present paper, the T-scores were used in the analyses. The reliability and validity of the CBCL are good [37,38].

All assessments were carried out by trained assessors, supervised by a neurodevelopmental expert (M.H.-A.), between February 2009 and February 2012 at the Institute of Developmental Neurology at the University Medical Center Groningen, The Netherlands. The assessor who performed the neurological exam was also in charge of the evaluation of cognition. The assessors were blinded to the mode of conception, prenatal, perinatal and early developmental history.

2.3. Statistical analysis

The potential relation between the neurological condition and cognition was analysed using univariable and multivariable linear regression analyses. We adjusted for the variables ‘gestational age’, ‘high maternal educational level’ and ‘time to pregnancy (TTP, a proxy for the severity of subfertility)’ on an a priori basis. Adjustment for TTP was based on previous findings in the larger follow-up study: we found that increased TTP was associated with a higher prevalence of complex
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