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Functional outcome at school age of preterm-born children treated with high-dose dexamethasone

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ABSTRACT

Background: Postnatal dexamethasone (DXM) treatment is associated with adverse motor outcome. It is largely unknown as to what extent functional outcome at school age is affected.
Aims: Our first aim was to determine motor, cognitive, and behavioural outcome at school age of preterm-born children treated with high-dose DXM for pulmonary problems. Our second aim was to identify DXM-related risk factors for adverse outcome.
Study design: In this cohort study, we included 53 very preterm-born children treated with DXM (starting dose 0.5 mg/kg/d) after the first week of life. At the median age of 9 years, we performed a detailed neuropsychological assessment.
Results: Compared to the norm population, DXM-treated children scored worse on the Movement-ABC (abnormal fine motor, ball skills and balance: 59%, 47% and 30%, respectively). They more often had total (36%), verbal (32%) and performance IQs (55%) below 85 ($P < .001$, $P = .002$, $P < .001$, respectively). On each of the remaining measures, DXM-treated children scored worse than the norm population, except for verbal long-term memory and verbal recognition memory. DXM-related risk factors were associated with poorer performance.
Conclusions: At school age, multiple domains of functional outcome were affected in DXM-treated children. Risk factors related to the use of DXM should be considered as serious potentiaters of adverse outcome in children treated with high-dose DXM.

1. Introduction

In preterm infants, bronchopulmonary dysplasia (BPD) is still one of the most challenging complications with a reported overall incidence of 25% [1]. Since the 1990s, preterm infants at risk for BPD were treated with dexamethasone (DXM), commonly in high doses (starting dose of ≥0.5 mg/kg/d). The number of children worldwide that have been treated with this high-dose regimen is now estimated to be around 1 million.

A systematic review reported that high-dose DXM after the first week of life facilitated extubation, reduced the rate of BPD, and reduced neonatal mortality [2]. Evidence also hints at DXM having detrimental effects on the developing central nervous system as illustrated by reduced brain growth [3], and an increased risk of cerebral palsy (CP) [4]. Regarding cognition and behavior, outcome studies of DXM-treated children are sparse and report predominantly on pre-school age outcome [5,6]. The focus of most of these studies is primarily on broad outcome measures, such as motor outcome and intelligence, while information about the neuropsychological functioning, which underlies higher cognitive functioning, is lacking.

Apart from DXM, other variables such as ventilator duration, periventricular leukomalacia and seizures are suggested as possible risk factors for adverse outcome in DXM-treated children [7]. It remains largely unclear, however, if and to what extent functional outcome at school age is affected in children treated with high-dose DXM. Therefore, the first aim of this study was to determine the motor, cognitive, and behavioural outcome at school age of children treated with high-dose DXM. Our second aim was to identify DXM-related risk factors for adverse outcome in these children.

2. Methods

2.1. Patients

We selected all very preterm-born children (<32 weeks' gestation) from our NICU patient database who had been admitted between

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1999 and 2001, and treated with DXM at a starting dose of 0.5 mg/kg/d. Treatment indication was ventilator dependency after the seventh day of life in infants who were considered to be at risk for development of BPD with signs of BPD on chest X-ray, in whom weaning was stagnating despite optimal supportive therapy. We chose not to include DXM-treated children born after 2001 as they received lower starting doses of DXM following international recommendations [8]. We excluded children with major congenital anomalies. We reviewed the medical charts for neonatal characteristics and cumulative doses of DXM. Head circumference (HC) at birth and at follow-up was expressed in z-scores using appropriate reference data [9,10]. Presence of BPD was defined as treatment with supplemental oxygen or continuous positive airway pressure (CPAP) at 36 weeks postmenstrual age. Cerebral pathology was determined using cranial ultrasound [11,12]. DXM was administered following our treatment protocol. In the first three days all infants received DXM at a dose of 0.5 mg/kg/d. On the fourth day, the attending neonatologist decided whether to continue with either a short (10 days) or long (42 days) tapering course of DXM. Depending on the clinical course of the individual infant, the tapering course was sometimes shortened or prolonged.

Our design was an observational cohort study. We considered a case–control study, but refrained from doing so. Preterm control infants would have differed on many neonatal characteristics, and not only on whether or not they were treated with DXM. If we would have matched our cases with children having BPD without DXM treatment, the groups would be different regarding disease severity of the BPD, as the most severely ill infants would have received DXM therapy. In such a design it is difficult to disentangle the effect of treatment with DXM and the effect of BPD on neuropsychological measures. Therefore, we compared our findings with existing literature on outcome in preterm-born children.

2.2. Follow-up

We determined the presence of CP following Bax' criteria [13]. In the case of CP, gross motor functioning was scored using the Gross Motor Function Classification System (GMFCS) [14]. Only children without CP or with a GMFCS ≤ 2 were invited prospectively to participate in an extension of the routine follow-up program. We assessed motor skills, intelligence, attention, verbal memory, visual perception, visuomotor integration, executive functioning, and behaviour at the age of 6 to 12 years. Children who were lost to follow-up were excluded from the analyses. Parents gave their written informed consent prior to participation in the follow-up program. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen.

2.3. Motor outcome

Motor outcome was assessed using the Movement Assessment Battery for Children (Movement-ABC) [15].

2.4. Cognitive outcome

Total, verbal, and performance intelligence were assessed using a shortened form of the Wechsler Intelligence Scale for Children, third edition, Dutch version (WISC-III) [16]. We assessed central visual perception and visuomotor integration with the subtests Geometric Puzzles and Design Copying of the NEPSY-II-NL (Neuropsychological Assessment, second edition), respectively [17]. Verbal memory was assessed using a standardized Dutch version of Rey's Auditory Verbal Learning Test (AVLT) [18] testing immediate recall of words (learning capacity), delayed recall (long-term memory), and a delayed recognition trial. We assessed selective attention and attentional control with the subtests Map Mission and Opposite Worlds of the Test of Everyday Attention for Children (TEA-Ch), respectively [19]. We obtained information on children's executive functioning in daily life using the parental version of the Behavior Rating Inventory of Executive Function (BRIEF) [20]. Test scores obtained when a child was inattentive or too tired, as assessed by the trained experimenter, were excluded.

2.5. Behavioral outcome

We obtained information on children's behavioural and emotional competencies and problems using the parental version of the Child Behavior Checklist (CBCL) [21], and attentional functioning in daily life using the Attention Deficit Hyperactivity Disorder (ADHD) questionnaire [22].

2.6. Statistical analyses

We classified the intelligence quotients (IQs) into 'normal' (IQ $\geq$ 85), 'borderline' (IQ 70–84) and 'abnormal' (IQ $<$ 70). We used the percentiles on the standardization samples of the Movement-ABC and cognitive tests to classify raw scores into 'normal' ($\geq$P15), 'borderline' (P5–P14) and 'abnormal' ($<$P5). For the ADHD questionnaire, BRIEF, and CBCL, we used a similar classification following the criteria in the manuals. To compare the outcome of the study group with the norm scores of the general population, we used the one sample Chi-square test. We used the Mann–Whitney U test to relate motor, cognitive, and behavioural outcomes to DXM-related risk factors. $P < .05$ was considered to be statistically significant. We used SPSS 20.0 software (SPSS Inc, Chicago, IL) for the analyses.

3. Results

Between 1999 and 2001, 1824 patients had been admitted to our NICU, of whom 77 had been treated with DXM. Nine (12%) died in the neonatal period; two had major congenital anomalies that became apparent during the first year of life. Of the remaining 66 children, 13 children could not be included for various reasons (Fig. 1). Eventually,

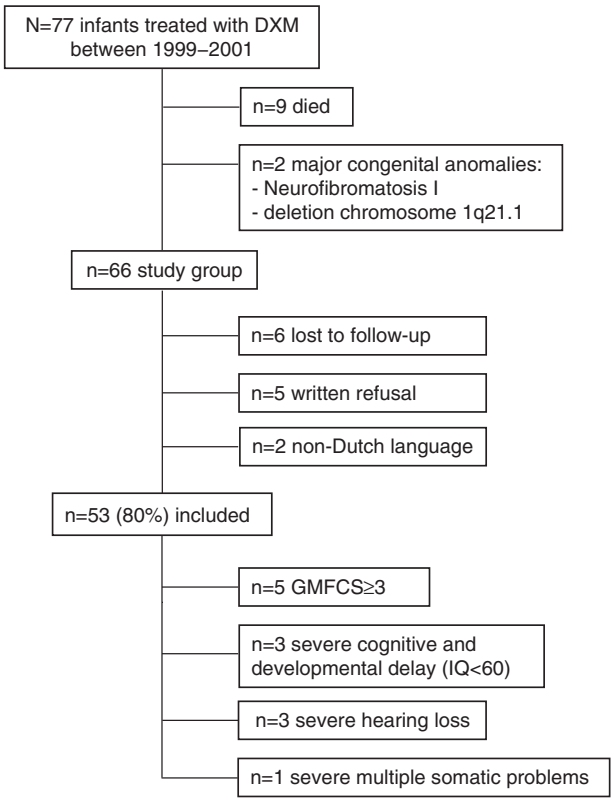

Fig. 1. Flow chart of DXM-treated children who were included for follow-up at school age.