Seminars in Fetal & Neonatal Medicine 19 (2014) 90–96

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Review

Neuropsychological outcomes of children born very preterm

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Keywords:
Attention
Cognition
Development
Neuropsychology
Very low birth weight
Very preterm

S U M M A R Y

Considerable research has investigated the consequences of being born very preterm (VP; <32 weeks of gestation), especially in relation to cognitive functioning. While numerous cognitive and neuropsychological outcome studies have been published, it is important to consider methodological issues when reviewing this research, as the generalizability of the studies varies greatly. This article describes the nature of cognitive difficulties confronting VP children, both in terms of the frequency and severity of deficits. The breadth of cognitive difficulties reported in this population implies a generalized cognitive impairment; however, the presence of selective or primary cognitive deficits is discussed. It is concluded that whereas mortality and neonatal morbidity rates have decreased significantly in VP infants in recent decades, these children continue to be at significant risk for cognitive impairments and need to be closely monitored throughout childhood.

1. Introduction

This review article describes the nature of the cognitive impairments exhibited by very preterm (VP) children. As well as examining general outcomes such as IQ and academic achievement, functioning in specific cognitive domains are reviewed, including processing speed, attention, visual–spatial abilities, language, memory and learning, and executive function.

2. Methodological considerations

The quality of VP outcomes studies varies greatly and study design requires careful consideration when reviewing the cognitive outcome literature. Before the 1990s, the inclusion criteria for outcome studies tended to be based on birth weight [e.g. very low birth weight (VLBW), <1500 g; extremely low birth weight (ELBW), <1000 g] rather than on gestational age due to the lack of certainty of obstetric estimation. Whereas birth weight and gestational age are related, they are not interchangeable measures, with birth weight-selected cohorts having a proportion of children born later in gestation who are small for gestational age (SGA). Selection criteria for studies may include the entire VP population (<32 weeks of gestation) or may restrict selection to a subgroup such as extremely low gestational age infants (ELGA; <26 weeks of gestation). In addition to expecting the severity of deficits to be greater with increasing immaturity, it is reasonable to speculate that the ELGA infants exhibit a unique profile of cognitive impairments. A variety of exclusion criteria are implemented by studies, some of which can influence the generalizability of the findings. For example, excluding children with cranial ultrasound abnormality [e.g. grade 3/4 intraventricular haemorrhage (IVH), cystic periventricular leukomalacia (PVL)] or with IQ <80 may be appropriate for specific research questions, but the findings are likely to underestimate the population's true level of impairment.

Marked improvement in survival rates was observed between the 1970s and the 2000s with advancements in perinatal medicine [1]. This reduction in mortality has been predominantly observed in the most immature, tiniest and sickest infants [1], which are also those infants considered at highest risk for later cognitive problems. Accordingly, caution is needed when comparing outcomes across eras. For instance, although it may be disheartening to see little change in cognitive outcomes for VP children born in the mid-2000s compared with those born in the early 1990s, one may argue that this really represents an improvement in outcome since the mid-2000s population includes a higher proportion of high-risk infants.

Sample composition is another important consideration when reviewing the VP literature. Prospective geographic cohorts which recruit all infants born in a specific region is the preferred approach, although studies reporting regional samples are rare and tend to focus on broader cognitive and academic outcomes [2,3]. Hospital-based or network cohorts are regularly reported, but are less

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http://dx.doi.org/10.1016/j.siny.2013.11.012

representative due to possible ascertainment bias and local management policies (Smith et al., this issue, Chapter 1). Samples recruited using other strategies such as attendees to follow-up clinics have questionable generalizability. Participation rate and follow-up attrition are also important as non-participation is not random but is more common in socially disadvantaged families and for children with impairments [4]. Therefore, studies with low participation rates are likely to under-report the severity of cognitive deficits in VP children.

VP outcome studies need a baseline to judge the level of functioning. Relying on test norms is less than ideal as the sociodemographic characteristics of the standardization sample will differ from that of the VP cohort. Compounding this issue is the Flynn effect (phenomena in which normative mean scores for cognitive measures such as IQ increase with time) [5], which can mask to some extent the severity of impairments. Numerous studies have demonstrated that the rate of impairment is greatly underestimated if judged according to test norms rather than a locally matched control group [6–8]. Whereas numerous approaches have been used to recruit a local control group, a matched comparison group is preferable.

Early outcome studies tended to focus on IQ. Over the past 20 years more studies have applied a neuropsychological approach in order to better characterize the cognitive profiles of VP children, which is critical for informing surveillance and intervention programs. Neuropsychological studies have tended to focus on a specific cognitive domain (e.g. attention), and in many cases have relied on hospital-based or follow-up clinic samples. Prospective longitudinal neuropsychological studies are lacking.

3. General cognitive ability

The foundation of neuropsychological assessments is an assessment of general cognitive ability (IQ). Numerous IQ measures are reported in the literature, and in recent times there has been a movement towards abbreviated measures, which allows additional time to evaluate specific cognitive domains. However, caution is needed when interpreting IQ scores from abbreviated measures as they are based on fewer tasks and assess fewer abilities. Even more caution is needed when abbreviated scales are based on a personal selection of subtests from established batteries as these composite scores lack validation.

Systematic reviews have been performed evaluating the IQ of preterm children (<37 weeks of gestation). The first review pooled the results of 15 case–control studies, including 1556 preterm and 1720 term children born between 1975 and 1988 [9]. The mean group difference for these studies ranged from 7 to 23 points in favour of the term controls, with a mean difference of 10.9 points [95% confidence interval (CI): 9.2, 12.5]. To put this finding in context, the preterm population had an IQ of 0.7 SD below their term peers. Mean cognitive scores were significantly related to gestational age ($R^2 = 0.49$), but the association with age at assessment was weak, suggesting that this level of deficit remained relatively stable across childhood. As expected, the group difference in IQ for high-quality studies was marginally higher than that for low-quality studies (11.2 vs 9.4).

Given that survival rates and management practices have improved over the past 30 years, it is possible that more contemporary preterm children exhibit better outcome in terms of IQ than previous generations. To address this issue, an updated meta-analysis was recently reported which included case–control studies published between 1980 and 2009 [10]. This review identified 27 eligible studies including 3504 preterm and 3540 term children born between 1975 and 2000. The meta-analysis revealed a mean difference of 11.9 points (95% CI: 10.5, 13.4), with the preterm children performing 0.8 SD below term controls on measures of IQ. As with the Bhutta et al. study [9], IQ was associated with gestational age. For example, the mean difference was 8.4 (95% CI: 6.6, 10.2) for children with a mean gestational age ≥32 weeks, 11.4 (95% CI: 9.7, 13.2) for children with a mean gestational age between 28 and 31 weeks, and 13.9 (95% CI: 11.5, 16.2) for children with gestational age <28 weeks. There was no association with year of birth, suggesting no gain in IQ for preterm children in this 25-year period.

In summary, there is convincing evidence that IQ is reduced in preterm children, and there is no evidence to indicate that this has improved in more contemporary eras or that the gap with term peers reduces with increasing age. There is evidence that impairment severity increases with decreasing gestational age, such that IQ is estimated to decrease 1.5 points per week for those born <33 weeks [11]. Whereas IQ scales provide a reliable assessment of general cognitive ability, they are not ideal for detecting mild deficits, specific cognitive strengths and weaknesses, or subtle brain abnormalities [12]. Specific neuropsychological measures are needed for these purposes.

4. Processing speed

Processing speed refers to the time required to interpret and respond to incoming stimuli or information, and is assessed by measures of reaction time and decision time. Processing speed is an 'elementary' cognitive process [13], as it is critical to the functioning of other cognitive domains. Processing speed develops rapidly in childhood [14], and its developmental trajectory mimics that of working memory and fluid intelligence, leading to speculation that increasing efficiency in information processing is associated with enhanced working memory and intelligence [15].

Slower processing speed has been reported in VP/VLBW children. Rose et al. [16] studied processing speed in preterm infants (<1750 g birth weight) in their first year of life and reported that they needed nearly 30% more inspection time than term infants at 5, 7 and 12 months of age. In middle childhood VLBW children have been found to perform similarly to term children on simple reaction time tasks, but their decision time slowed more steeply than controls with increasing complexity on choice reaction time tasks [13]. These findings are supported by a Dutch study of VP 7-year-olds [17], although they found that slower processing speed was due to a greater proportion of extremely slow responses and not related to lower average processing speed. Thus, it may be speculated that VP children, although capable of exhibiting age-appropriate response times, have difficulty maintaining a high level of efficiency when the complexity of the task increases. Whereas no long-term longitudinal studies have been reported, it seems that reduced processing efficiency persists into adulthood [18,19].

5. Attention

Attention is another core cognitive ability, critical for the acquisition of new skills and knowledge [20]. Attention is a multifaceted construct [21,22], consisting of the capacity to selectively focus (i.e. focus on relevant stimuli and ignore distracting stimuli), sustain (i.e. maintain alert state for extended period), encode (i.e. hold information in temporary store), shift (i.e. fluently transfer focus from one activity to another), and divide attention (i.e. focus on multiple competing stimuli simultaneously) [20,23].

Numerous studies have investigated attention domains in preterm infants and preschoolers, as highlighted in a review by Van de Weijer-Bergsma et al. [24]. The review found that all attention domains are delayed in young preterm children compared with term controls, and that these differences tend to increase with