Long-term neurocognitive outcomes of SGA/IUGR infants

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Abstract

With advances in the management of preterm neonates, the chances of survival have increased even among those who are intrauterine growth restricted (IUGR) or who are born small for gestational age (SGA). However, infants who are IUGR/SGA are considered at higher risk of physical and neurodevelopmental abnormalities, although the reported impacts of IUGR and SGA status at birth on neurodevelopmental outcomes in long-term outcomes studies have varied. In particular, some reports have indicated gradual improvement in neurodevelopmental functions over time in these infants. We have therefore reviewed all the available reports describing neurodevelopmental outcomes of preterm and term SGA infants beyond 5 years of age. Preterm SGA infants are at increased risk of impairment in neuromotor, cognitive, behavioural and scholastic attainments compared with preterm non-SGA infants. On the other hand, term SGA infants had problems in scholastic/vocational attainments compared with term non-SGA infants, while adverse neuromotor, cognitive and behavioural outcomes were not consistently observed at higher rates. Limitations regarding the validity of studies of long-term outcomes of SGA infants are discussed and a potential approach is suggested.

Keywords achievement; cognition; growth restriction; performance; shcolastic; vocation

Introduction

Very low birth weight infants are at increased risk of adverse motor and neurobehavioral outcomes in childhood and adolescence. Similarly, intrauterine growth restriction (IUGR) and small for gestational age (SGA) births are considered at higher risk of developing long-term adverse health consequences, both physical and neurodevelopmental. However, it is unclear whether gestational age (GA) at birth has any influence on these outcomes among IUGR/SGA infants.

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Background

Inadequate *in utero* growth can be caused by a multitude of factors, ranging from maternal, placental, fetal, environmental, nutritional, infective and genetic. Underlying pathological mechanisms for IUGR that have been identified include either inadequate supply of nutrients to the growing fetus or excess utilization of nutritional resources. It is perceived that, in response to so-called under-nutrition, the fetus develops an adaptive response that initiates what is described as a "diving reflex". The blood is diverted to the brain, adrenals and heart, mainly at the cost of the liver, muscles, skin and subcutaneous tissues. This could lead to neuroprotection; however, with persistent insult the brain suffers from a lack of nutrients, potentially affecting its growth and development. The clinical phenotypes of this process are classified into symmetrical and asymmetrical growth restriction. If the insult leading to IUGR occurs before the first trimester, growth of the head and brain is affected to a similar degree to the body, and these infants are classified as symmetrically growth restricted. In contrast, later insult leads to head sparing and results in asymmetrical IUGR, with presumed brain sparing. Head growth is very important in the context of later neurodevelopment, as subnormal head circumference at approximately 1 year of age in infants is associated with lower IQ, poor academic achievement, and poor adaptive behaviour.

Several single-centre and multicentre studies have examined outcomes of IUGR or SGA infants at various postnatal ages ranging from 1 year to 26 years. Some of these studies have identified that childhood and adolescent outcomes improve as age advances even in the same cohort. Additionally, some review articles have implied that SGA or IUGR status per se has very little effect on long-term outcomes.

Several factors affect the long-term outcomes of individuals born SGA (Figure 1). Both proximal (related to this pregnancy) and distal (maternal life-long factors) maternal factors are trigger points for growth restriction *in utero*. This could be aggravated by immediate life-course events such as prolonged hospitalization, complications of prematurity, asphyxia and infections. Long-term life-course events of social, neighbourhood and environmental deprivation play a larger role in the later outcomes. It has been suggested that the outcomes of SGA infants are dependent upon GA, with different influences playing important roles in preterm versus term infants. In this article, we summarize the available literature describing long-term (after 5 years of age) outcomes in the domains of neurological, cognitive, behavioural and academic achievements, for both term and preterm IUGR and/or SGA infants.

Before a detailed description of the outcomes can be entered into, a couple of caveats need to be made. First, the biggest limitation of the available literature is that the different studies have not been consistent in their definition of IUGR/SGA. Some studies have used only intrauterine estimation of fetal weight and attempted prognostication, whereas others have used postnatal growth curves. This may lead to comparison of dissimilar populations. Second, there is a lack of consistency as to when and how population cohorts are evaluated in terms of long-term outcomes. Thus the outcome results from different studies may not be comparable.

Neurodevelopmental outcomes are mainly assessed in four domains, as indicated in Table 1. For the purposes of this review, we used a cut-off of 5 years of age for assessment of long-term outcomes, as reports on outcomes prior to 5 years of age are

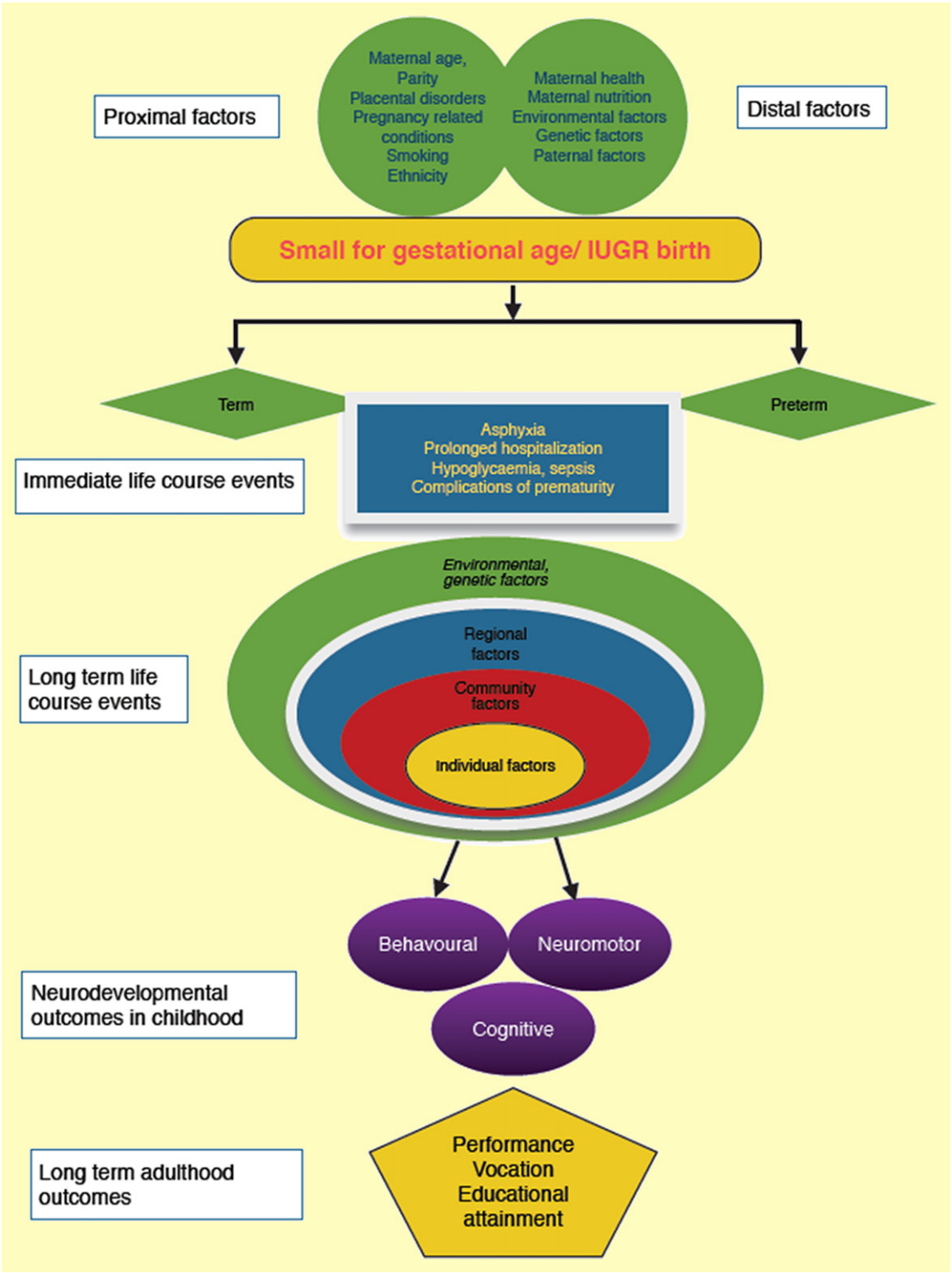

Figure 1 Causes and life time trajectory of SGA/IUGR infants.

subject to debate due to uncertainty regarding correlation of short-term outcomes with long-term outcomes.

Pathophysiological rationale for adverse neurocognitive outcomes in SGA/IUGR infants

The aetiology for SGA/IUGR births is multifactorial, while the primary reason underlying the SGA/IUGR birth may play a significant role in the subsequent pathophysiology of the neurocognitive outcomes. The insult or injury that led to development of fetal growth restriction may directly affect the immature and developing brain, leading to adverse consequences. Animal studies reveal that IUGR animals have reduced brain weight, with volume loss occurring mainly in the cerebellum, hippocampus, and in the cerebral cortex. Delayed migration of