Neurobehavioral Phenotype and Dysexecutive Syndrome of Preterm Children

Subjects: Health Care Sciences & Services | Neurosciences
Contributor: Gire Catherine

The neurodevelopmental outcome of the premature infant is characterized by a set of minor-to-moderate dysfunctions in the developmental fields (language, praxis, executive, behavioral and attention disorders, social interaction disorders, etc.). These dysfunctions tend to cumulate, even to potentiate, which impacts school learning and the daily life of these children and their parents. Executive functions, such as high-level cognitive operations, play a preponderant role in learning and social adaptation via the regulation of children's behavior and emotions. Thus, the notion of executive dysfunctions as an underlying mechanism of neurodevelopmental difficulties in VP children is now well documented. Executive deficit is central to the neurodevelopmental phenotype of preterm infants and their learning difficulties, both from a cognitive and a behavioral or social point of view.

Keywords: extremely pre-term children ; neurocognitive/behavioral disorders ; executive function ; neurodevelopment

1. Prematurity, Mortality, Morbidity and Long-Term Sequelae

1.1. Mortality

Regarding the mortality of children under 5 years old, prematurity is the leading cause of death in this age category for both developing countries (from 10 to 20% of deaths before the age of 5 years) and developed countries (23%) [1]. The overall survival rate of VPs (<32 weeks) has increased in many countries over the course of the past decade [1][2][3][4][5][6]. In the case of extreme prematurity, the results are more mixed (EPICure cohort 1 and EPICure cohort 2 [3]; EPIPAGE 1 cohort and EPIPAGE 2 cohort [4]). The heterogeneity of definitions makes comparisons between studies difficult [3][7]. In a recent, large international cohort of 11 countries focused on VP-born children, mortality declined between 2007 and 2015 and, except for Canada, there was an increase in bronchopulmonary dysplasia in most countries [2][8].

1.2. Cerebral Palsy and Gross Motor Disabilities

The frequency and severity of cerebral palsy (CP) have decreased in recent years due to advances in perinatal medicine, such as corticosteroid therapy, magnesium sulfate, developmental care and nutritional techniques [7]. The drop in the incidence of CP at two years of corrected age from 17% in 1997 (EPIPAGE 1) to 8% in 2011 (EPIPAGE 2) for children born at 25–26 weeks of gestational age (GA) [8] was confirmed at the European level [4][9][10][11]. EPIPAGE 2 or EXPRESS [12][13] studies have shown a severe cognitive deficit at the age of 5–6 years, in 10–15% of extreme GA groups (<27 weeks of GA) [14][15].

1.3. Cognition

Global cognitive deficits

If mortality and so-called severe morbidity have generally decreased, preterm birth, even moderate, remains a risk context for neurodevelopmental sequelae and educational difficulties, which are more frequent with a low birth term and when the child's environment is socio-economically disadvantaged [7]. Various recent studies on VP children have shown a clinically significant difference of 13–15 FSIQ points, or from −0.85 to −1 SD, compared to term children [12][13][14][15]. A moderate cognitive deficit (FSIQ between −1 and 2 SD) was found in a little more than 25% of VP babies when they reached five years of age. This appeared to be true even in children born moderately premature (32–34 weeks of GA) vs. 10% in the control group children born at term in the EPIPAGE 2 study [10]. There are many methodological biases to consider in describing medium- and long-term cognitive outcomes [10][16][17]. Taking the parents' educational level and socio-economic status into account is essential in any cognitive assessment [18][19]. The "classic physiological" neurodevelopment is modified by preterm birth and the neurobehavioral sequelae found in preterm children do not differ radically from the "dys" problems encountered in term births. Their specificities are greater incidence and complexity; intricacy with behavioral disorders and/or coordination acquisition disorders (CADs); and characteristic prevalence of dysexecutive and attentional disorders [20].

Language skills

Language is one of the most affected functions in the preterm infant [21][22]. Language skills were found to be poorer in preterm children than in full-term infants, with a performance of approximately from −0.5 to −1.0 SD in each language domain studied [22]. This finding was supported by functional MRI which confirmed a language circuit dysfunction in premature children during language processing with a predominance of expressive delay [23].

Fine motor skills and coordination acquisition disorders

Dyspraxia (or CAD, in the international nomenclature) is a disorder in the development of gestural functions in a context of more or less marked deficit of spatial treatments. In VPs, CAD is currently much more frequent than CP. It is present in 18.8% of the VPs born at 24–26 weeks of GA, in 8.5% of the VPs born at 27–31 weeks of GA and in 5% of the VPs born at 32–34 weeks of GA compared with the control population at term, as reported in the EPIPAGE 2 study [10][24]. Furthermore, the VP-born infant has significant dysfunctions in a range of basic cognitive processes, such as working memory (WM), processing speed, visuo-perceptual skills, sensorimotor integration and attention, as compared with term-born infants [25]. Such deficits, due to the impairment of executive functions (EFs), are observed from when they enter school until the time they reach adolescence [26][27]. Several meta-analyses have shown differences in inhibition, WM and planning varying from 0.3 SD to 0.6 SD in premature children as compared with children born at term. This difference is stronger at the youngest GA and worsens over time for WM [14][17][28][29]. Risk factors for VPs' executive deficits can be summarized into four categories, namely, immaturity (weeks of GA), growth restriction, perinatal inflammation/infection and socioeconomic disadvantages [30]. EF deficits are also reported by parents and teachers in preterm infants and appear to persist over time [31][32][33]. Preterm infants at the age of 5 years have shown poorer performance in visual attention than children in full-term control groups, with no differences in other cognitive abilities [34][35]. These visuomotor integration problems persist into childhood and adolescence [36][37].

Behavioral and psychiatric disorders

Preterm birth is associated with a psychopathological risk that can occur in isolation or can be associated with neurocognitive disorders and/or learning disabilities [20]. Although results vary considerably among the rating scales completed by the parents or teachers, the prevalence of psychiatric disorders is three times higher in preterm children than in term-born control groups [38]. A number of studies concerning mid-childhood and adolescence describes a "premature behavioral" phenotype characterized by inattention, anxiety and social difficulties [39]. Three types of behavioral phenotypes are described in the psychiatric disorders observed in VP cohorts, (1) ADHD (symptoms of inattention rather than hyperactivity/impulsivity); (2) emotional disorders (anxiety rather than depression); and (3) ASD, autism spectrum disorder, social interaction and communication problems [26]. Additionally, VP preterm infants have poorer peer relationships and weaker social competence, without major abnormalities in other areas [40]. Elevated autism-spectrum-disorder rates, particularly disorders of facial emotion recognition, have been noted to vary from 5 to 8% in adolescence or adulthood [41]. Recently, in EPIPAGE 2, among 5.5-year-old VP-born children, subgroups could be distinguished with distinct outcome profiles that varied in severity, type and combinations of deficits, with a worsening of neurocomorbidities associated with behavioral disorders [42]. The behavioral disorder characteristic of the child or adolescent born pretermly is the absence of conduct disorders [43]. Academic repercussion for the pretermly birth has a strong economic impact, since lower educational levels in adulthood yield more unemployment, under-qualified work, anxiety disorders and loss of self-esteem [44].

2. Understanding the Neurodevelopment of Prematurity Requires Executive Function Evaluations

EFs define the cognitive operations that allow the individual to adapt their behavior and activities to the demands and fluctuations of the environment. These functions come into play as soon as the individual is faced with a non-routine situation that requires problem solving.

EFs' main mental processes are: (1) planning, i.e., organizing and planning data according to the goal to be achieved and choosing relevant information; (2) inhibition, i.e., inhibiting secondary processes, resisting distractions; (3) working memory (WM), i.e., organizing for memory reuse; (4) flexibility, i.e., implementing treatment operations, inventing new situations and being able to modify them if they deviate from the desired goal [45][46]. It is understood that each of these mental processes ("under executive mental functions") can be evaluated by "specific" tests, but these processes are often entangled and dependent on the attentional mental process (auditory and/or visual). For this reason, their definitions vary significantly from publication to publication [46][47]. FEs are, therefore, "higher" functions that play an important role in cognitive neurodevelopment and social adaptation [48]. The EFs are a set of high-level cognitive processes that guide our actions, regulate behavior and allow us to adapt to our environment to achieve a specific goal.

Cohort descriptions of a premature infant's fate are usually classified according to the severity of the disability based on the full-scale intelligence quotient (FSIQ) score, namely, no disability, mild disability, moderate disability, or severe disability. However, a low intelligence quotient (FSIQ) is the product of social disadvantage, genetic influences, great prematurity and other environmental factors that play a greater role over time. VPs require more discriminative neuropsychological and behavioral analyses to identify all the affected functions [25]. Indeed, an FSIQ threshold above or close to a low mean (Wechsler) is generally considered "normal" in cohorts of premature infants. However, the performance observed is the result of complex processes involving multiple intellectual and non-intellectual characteristics, such as attention, emotions, motivation, movement planning, EFs, etc., which may be in deficit in premature infants. Thus, the FSIQ calculated in premature infants on subtest values, which are most often dissociated, does not reflect the child's cognitive functioning. Rather, it is the analysis of the Wechsler subtest dispersion that should highlight those children that deserve a thorough interpretation, therefore a better brain function assessment. A child born prematurely and viewed with a "normal" FSIQ may also present a dysexecutive syndrome and/or an alteration in behavior that may indirectly disrupt his/her cerebral functioning [49].

2.1. Executive Functions and Learning in Premature Infants

EFs oversee lower-level cognitive processes, hence the term "top-down"; thus, they are at the center of overall cognitive functioning, such as a true "orchestra conductor"; they notably play a preponderant role in academic achievements [48][50][51][52][53][54]. The better EFs are in young children, the better are their results in mathematics [47][55][56][57][58]. Similarly, a higher level of reading comprehension in young children is associated with elevated EFs [59][60]. A timely assessment of EFs, from early childhood, is predictive of school performance [61][62][63]. EFs (especially WM) are more predictive of academic success than FSIQs [64][65] and reflect the child's degree of educational investment [66]. EFs are not only involved in cognitive and learning mechanisms, but also in the regulation of behavior and of emotions. A direct link has been suggested between EFs and QOL in children [67][68]. This EF centrality to cognitive development not only has a persistent impact on adulthood and career success [69] but also on behavior and emotional well-being [70].

2.2. Executive Functions, Behavior and Attention Disorders

A meta-analysis of behavioral profiles of school-aged and adolescent VP children, as compared with those children born at term (2004 premature versus 1238 controls), showed that behavioral profiles, according to their severity, are specific and associated with cognitive and/or neurological comorbidities [71][72]. The research proposed, for the first time, the concept of "behavioral phenotype of premature infants", characterized by attention deficit/hyperactivity disorder, social and emotional difficulties and introversion [20][71][72][73]. Burnett confirmed this association with worsening behavioral disorders when associated with neurological comorbidities [26]. A cluster analysis identified four behavioral profiles in five-year-old VP children, i.e., (1) children with a typical development similar to that of the general population; (2) children at "risk", with neurodevelopmental scores and psychiatric profiles slightly disturbed, but close to the mean; (3) children with moderately severe to severe executive disorders and symptoms of ADHD and/or ASD; and (4) children in inattentive/hyperactive groups with cognitive and linguistic scores close to the deficit [74].

2.3. Executive Functions and Holistic Neurodevelopment

Hutchinson [75] and Anderson [25] hypothesized the impairment of original primary cognitive functions. For example, a WM deficit and/or attention and/or processing speed impacting other mental processes would be the cause of later deficits such as language delays or dysexecutive disorders [76][77]. A lexical stock study of prematurely born infants in the EPIPAGE 2 cohort showed a strong association between language skills and performance in other areas of development when they reached a corrected age of 24 months and confirmed that the neurodevelopment of the premature infant should be considered with a holistic approach during infancy [78]. The child's language implicitly develops on pre-linguistic sensorimotor skills. Sensorimotor constraints affecting oral and facial praxis, auditory and tactile discrimination, visual attention and modality transfers are observed in premature children with phonological disorders [79]. A cluster-based fate analysis approach illustrated the holistic neurodevelopment of VLBW infants from birth to 18 months. The majority of children were cognitively normal, but gathered into three different groups, that is, (1) 17% with cognitive and language results above the standards of the tests used; the majority of children (54%) in the middle range for cognition, expression and reception of language; (2) 21% with an average score for cognition and language reception, but with a notable delay in language expression; and (3) 8.5% with poor performance in all areas of cognitive and language development. This classification made it possible to raise the hypothesis of an attentional problem at the origin of these disorders and to consider surveillance for all groups except for those in Group 1. In the event of a disadvantaged socio-economic environment, reinforced surveillance, when they achieve school age, is essential [80]. Delays in the development of oral language are common in both expression and reception in VP infants. These language difficulties seem to increase as the language becomes more complex, i.e., from age 3 to 12. Language plays a special role in learning abilities and its achievement is based on intellectual functions allowing the child to achieve non-verbal communication and requiring a high level of sensoriality, perception, attention and fine motor skills. It is a necessary function for the construction of cognitive development and social relationships [78].

2.4. Neurobehavior, Executive Functions and Hypoconnectivity

Executive functions are localized in the fronto-striatal and fronto-parietal circuits. They are affected by ADHD and ASD and by very preterm births [81]. The neurobehavioral disorder of prematurity is linked to a lesion and/or environmental mechanism affecting the development of the brain and corresponding to common neuroanatomical lesions [82][83][84][85].

Following the analysis of 100 MRI scans, Inder described the general “pattern” of non-cystic brain lesions of VP infants with both white matter and grey matter (GM) abnormalities, which included white matter atrophy, ventriculomegaly, delayed gyration and enlargement of the brain spaces under the arachnoid. The perinatal risk factors identified for these lesions included weeks of GA, infectious episodes, neonatal hemodynamic disorders and cerebral ultrasound lesions (Hemorragia intra ventricular (HIV) and periventricular leucomalacia [86]. Volpe emphasized that the observed lesions of white matter in VP infants were associated with diffuse neuronal and axonal abnormalities of the white matter but also of the cortical grey matter, thalami and basal ganglia, as well as the cerebellum. He suggested the term “premature encephalopathy”, witness to initial lesions and secondary developmental alterations leading to dysmature evolution of the brain of a child born prematurely [84][85].

3. Support for the Development of EFs and Neurobehavioral Functions in Children Born Premature

Apart from those who present serious sequelae specific to their type of CP or cognitive impairment, the neurodevelopmental outcome of the VP infant is characterized by a set of minor-to-moderate dysfunctions in the developmental fields (language, praxis, executive, behavioral and attention disorders, social interaction disorders, etc.). These dysfunctions tend to cumulate, even to potentiate, which impacts school learning and the daily life of these children and their parents [12][13][14][44][87][88][89][90]. Executive functions, such as high-level cognitive operations, play a preponderant role in learning and social adaptation via the regulation of children’s behavior and emotions [48][91][92]. Thus, the notion of executive dysfunctions as an underlying mechanism of neurodevelopmental difficulties in VP children is now well documented [14][93][83][94]. Executive deficit is central to the neurodevelopmental phenotype of preterm infants and their learning difficulties, both from a cognitive and a behavioral or social point of view [95][20][96][89][97].

The assessment and development support of EFs, as a whole, seem essential to support the development of prematurely born infants. Early and rapid assessments of EFs are possible, relying on observations of the child’s behavior, via parents or teachers (BRIEF). When premature children have reached school age or adolescence, they need to be able to have a complete evaluation of their neurodevelopment, which includes not only an evaluation of cognitive skills, praxis and executive functions by calibrated behavioral psychology tests, but also an evaluation of their behavior, their level of anxiety, their attentional capacities, their social interactions and their quality of life, via self- and hetero-questionnaires (parents, teachers, etc.).

The possibility of training and strengthening executive functions to optimize overall executive functioning and promote neurodevelopment has been explored in numerous studies, starting at preschool age, but also later, in childhood and adolescence. Very different modalities have been proposed, ranging from generalist interventions in a school environment, to much more specific and targeted interventions, such as computerized cognitive training, including the practice of mindfulness, sports or music [50][98][99]. The specific computerized training programs to support executive functioning have mainly focused on WM training with Cogmed© software, or on a general approach to training all EFs with BrainGame Brian© software. The results of these programs are currently disappointing in premature infants [28][83][100][101][102], even if they can improve one or more executive functions transitorily. Therefore, these should not be used as a standalone and can perhaps have a role in a comprehensive care package for EF support. Focusing on specific EF training was shown to be less effective in children aged from 4 to 12 than programs that integrated emotional and social components (Montessori-type school programs or “Tools of the Mind” in North America), including psychomotor components such as yoga or martial arts [98]. The way to stimulate EFs is to take into account all the components of the child, including emotional, social and physical components [99]. This is certainly even truer for the specific population of VP infants for whom it is the entire neurodevelopment, in all its cognitive, behavioral and social components, that is impacted by premature birth [95][103]. A 2020 meta-analysis of cognitive training of young children to optimize their EFs which covered 30 studies published between 2009 and 2019 on children aged 3–6 years confirmed this trend [104]. The benefit of cognitive EF group training, such as the school-based type, is more effective than individual training. Motivation among peers and interaction with other children is a particularly significant support. In addition, in this same study, the non-computerized nature of the training brought a greater benefit: the use of card games, global or fine psychomotricity activities at this age seems more effective than the use of a computer. Finally, prior to all the programs offered to premature children, in terms of training, rehabilitation or remediation, there is the question of perinatal prevention strategies for neurodevelopmental disorders in the event of preterm birth. Numerous medical and technical advances in the perinatal care of these children have already been employed, such as inborn birth strategy, antenatal corticosteroid therapy and magnesium sulfate, optimal respiratory and nutritional support, and postnatal monitoring; other advances are certainly to come, such as the neuroprotective erythropoietin approach, for example [105][106], or caffeine as further neuroprotection [107]. Another essential avenue of prevention is the set of developmental care strategies applied in the neonatal period, such as skin-to-skin practice, the kangaroo method and the Newborn Individualized Developmental Care and Assessment (NIDCAP) program. Scientific data on the neurodevelopmental benefits of these developmental care techniques and programs bear witness to this [108][109][110]. Parents, considered as the main support for the neurodevelopment of the child in these programs, are put at the center of care. It can postulate that the parent–child bonds (attachment and bonding) created during this neonatal period [111][112][113] make therefore possible special attention and support to the neurobehavior of these very premature children throughout their early childhood.

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