Care of the Extremely Low Gestational Age Newborns after NICU discharge

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Abstract

Extremely low gestational age newborns, born before 28 weeks of gestation, have a significant risk for medical complications and developmental disabilities, stressing the need to closely follow their health and development. In Belgium, the neurodevelopmental follow-up of these infants is organized according to a RIZIV-INAMI Convention. On the order hand, the general pediatrician also has an essential role in the prevention and diagnosis of complications and in supporting the families. This article provides an overview of the short- and long-term complications these children can present with.

Highlights

- The increasing survival rate in extremely preterms underlines the importance for a close multi-disciplinary follow-up even up until adolescence.
- About 7% develops CP, one fifth has a motor delay at 2 years corrected age, increasing up to one third exhibiting motor skills deficits at preschool age accompanied with a greater risk for DCD
- Cognitive problems are often accompanied by shortcomings in executive functioning and/or behavioral problems.
- Retinopathy and cerebral visual impairment are common visual problems and can further impact their development.
- A three to four-fold increase in psychiatric problems, especially ADD and ASD with a phenotype characteristic for preterms marked by inattention, anxiety and social difficulties
- Parental mental health is crucial for attachment and later cognitive and behavioral development

Introduction

Improvements in neonatal intensive care have been associated with increased survival rate of extremely low gestational age newborns (ELGANs), who are born before 28 weeks of gestation. Nevertheless, about half of those children will present chronic health disorders or complex neurodevelopmental impairments (NDI) in a way that largely exceeds the occurrence of those impairments in term newborns. Moreover, most children do not present an isolated medical problem but a range of physical, neurological and /or emotional difficulties. Those difficulties do not only impact the child, but also the family well-being.

The general pediatrician plays an important role in coordinating primary care, medical subspecialties and neurodevelopmental follow-up (1). Improvements in mortality and morbidity have been made possible thanks to proactive treatment of those babies during Neonatal Intensive Care Unit (NICU) stay and probably the same in follow-up will help them too. This article focuses on following developmental outcomes of ELGAN: growth, feeding behavior, motor outcomes, cognitive, learning and language disabilities, neurovisual disorders, behavioral and psychiatric disorders and parental mental health. Those aspects can have cumulative effects on the development of the child. Early, accurate diagnosis and treatment is important to improve outcome in the sense that injured or compensatory neural networks can develop over time.

Developmental care and family integrated care in neonatal units

Recent research has highlighted the role of the NICU environment and individualized care to influence short- and long-term outcome of ELGANs. Neonatal units evolve into units based on Developmental Care, Family Centered Care and coupled Care while still offering high level of medical assistance. Following this principle, the Neonatal Individualized Developmental Care and Assessment Program (NIDCAP) was established in Belgium since the 1980s. NIDCAP aims to promote the development of premature babies by including and supporting parents in understanding their child's behavior while avoiding separation between mother (also the father) and child, reducing stress related to environmental factors and adapting care procedures.

It is widely accepted that parental mental health is an important factor affecting child development. For human newborns direct skin-to-skin contact from birth, which leads to emotional connection, is essential for developing secure attachment. Maternal-neonate separation prevents these critical processes for secure attachment from taking place (2). Safe, stable, and nurturing relationships during childhood are important protective factors in child development. The support of an adult who helps to make the child feel safe, as a co-regulator in early development and as a sensitive, responsive parent later on, is an effective protective factor that may build resilience. This attitude begins from the NICU admission (3).

Medical care after discharge

After discharge from a NICU, close medical attention is recommended during the first years of life, especially when the infant is leaving the hospital with nutritional or respiratory support. In any case, *growth and development* should be assessed to detect and address possible feeding difficulties, respiratory problems, and severe NDI. Regular (medical) check-ups are

highly appreciated by the families, especially when the general pediatrician can easily appeal on a multidisciplinary support team. As the infant grows up, the need for respiratory and feeding support decreases (1). Moreover, in Belgium, a RIZIV-INAMI Convention proposes 4 neurodevelopmental evaluations on fixed time points of 4, 12 and 24 months corrected age and 5 years in order to detect NDI and organize support and treatment. Content of the RIZIV-INAMI Follow-up convention is listed in figure 1 and table 1.

Neurodevelopmental outcome refers to cognitive, neurologic, motor, behavorial and/or sensory outcome. Severe NDI is defined as the presence of one or more of the criteria described in table 2 and can be diagnosed in most cases at the end of the second year of life (1). Nevertheless, individual prognostic value of this assessment is not as predictive as expected. Some children diagnosed as having severe NDI at the age of 2 years, might be classified as having mild impairment at the age of 8 years which can be attributed to early therapy and parental guidance.

Moreover, developmental disabilities are often only diagnosed later in childhood, but may still have a significant impact on the child's participation and quality of life.

Table 3 depicts the necessary parameters to collect at NICU discharge and key points of medical surveillance later in life.

Growth and feeding problems

ELGANs have increased caloric and nutrients requirements compared to term newborns making them at risk for inadequate growth. *Growth impairment* at birth and/or at corrected term age, including poor head growth, has been associated with impaired cognitive and motor performance. On the other side, excessive weight for length exacerbates the risk of metabolic syndrome at adulthood. Breast milk is the best nutritional option, but correct fortification or mixed formula feed is sometimes necessary to assure optimal growth (4). Food diversification is proposed between 4 and 6 months corrected age. Optimal growth curves for ELGANs are still discussed. Nevertheless, using the corrected age until 2 years of age at least is mandatory.

After discharge and through the first years of life, ELGANs have been found to have more *feeding difficulties* than term born babies such as swallowing difficulties, excessive duration of meals, difficult transition to solid food. Such feeding difficulties impact the growth evolution and form a massive stress factor for the parents (1). Prolonged ventilation, feeding gastric tube, nociceptive stimulation of the face can disturb the maturation of suck and swallow rhythms. However, neurologic impairment can also interfere with oral motor function. Hence, children exhibiting oral motor dysfunction need to be referred to a feeding specialist as soon as possible.

Motor disorders and risk of cerebral palsy

Preterm infants often present brain injuries, of which diffuse white matter injury is most common and observed in 50-80% of the cases (5-7). Brain damage makes these infants more vulnerable for NDI, of which *cerebral palsy (CP)* is the most impairing outcome (8). The overall estimated prevalence of CP in preterm infants is 6.8%, but this increases with decreasing gestational age (GA) (9).

As CP is a clinical diagnosis, the detection is mostly based on the combination of clinical and neurological signs, but abnormal neuroimaging can further endorse the diagnosis. Early predictive signs (before 5 months corrected age) are abnormal neonatal neuro-imaging (86-89% sensitivity) and/or motor dysfunction observed with the Prechtl Qualitative Assessment of General Movements (98% sensitivity) and/or Hammersmith Infant Neurological Examination (90% sensitivity)(10). The combined use of these clinical assessments further increases the diagnostic accuracy. After the corrected GA of 5 months, clinical observations including the inability to sit independently by the age of 9 months, hand function asymmetry, or the inability to take weight through the plantar surface (heel and forefoot) of the feet are signs, identified by high-quality evidence, that further standardized investigations for the detection of CP should be initiated. For more information on the current evidence for the early and accurate diagnosis of CP, we refer to the published clinical guidelines (10).

Ninety-four percent of the preterm infants with CP have the spastic form (73% bilateral, 21% unilateral), while only 6 % has predominantly non-spastic characteristics (dyskinesia/ataxia) (11). Due to the ongoing development and maturation of the brain as well as the possibility of plasticity, it is strongly recommended to start as early as possible with early motor interventions in which parental involvement is highly recommended (10). Importantly, children with only a suspected diagnosis of CP should be referred as well for early intervention while refining the diagnostic process (10).

Fortunately, in most cases, prematurely born children will not develop CP. Nevertheless, *deficits in motor skills* remain a common feature. A prevalence of 20.6% of overall motor delay is reported up to 2 years corrected age with mild delays (18%) being more common than moderate-to-severe delays (8.6%) (9). However, these early assessments appear to be poor predictors for motor outcome at preschool age, since the same review reported a higher prevalence of overall motor difficulties in pre-school aged children (36%). This difference is partially due to the fact that a more sensitive test is used at pre-school age requiring more motor control and coordination to perform the tasks successfully. In case motor deficits are persistent and compromise functional independence in daily life, this might be classified as Developmental

Figure 1 : *Inclusion criteria of the RIZIV-INAMI neurodevelopmental follow-up convention*

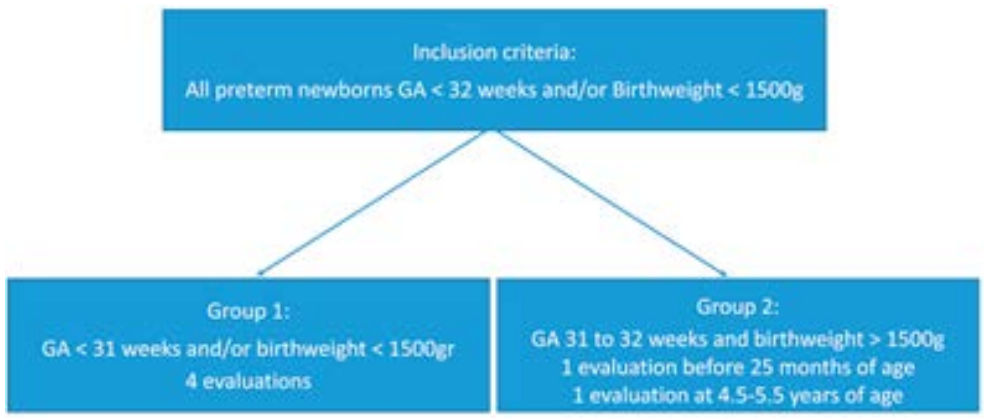

Table 1: schematic overview of the RIZIV-INAMI Follow-up convention

	Time-points of follow-up			
	3-6 months corrected age	**9-13 months corrected age**	**22-25 months corrected age**	**4.5 -5.5 years**
Neuropaediatrician / neonatologist	Collect visual and auditory evaluations	Collect visual and auditory evaluations	Growth Collect sensory evaluations	Growth, Collect sensory evaluation
Physiotherapist	AIMS and BSID-III motor scale	AIMS and BSID-III motor scale	BSID-III motor scale	Beery VMI and M-ABC-2
Psychologist	Parental well being	BSID-III cognitive scale and language scales	BSID-III cognitive scale and language scales	WPPSI IV
Speechtherapist	/	/	/	CELF-Preschool2 NL ELO, N-EEL (Chevrier Muller) or Exalang FR
Social assistant	yes	yes	yes	yes

Abbreviations: AIMS, Alberta Infant Motor Scale; BSID-III, Baley Scales of Infant and Toddler Development third version; VMI, The Beery-Buktenica Developmental Test of Visual-Motor Integration, 6th Edition; M-ABC-2, Movement Assessment Battery For Children second version; CELF, Clinical Evaluation of Language Fundamentals.

Coordination Disorder (DCD). DCD is a neurodevelopmental disorder characterized by 4 criteria: 1) motor skills are delayed and uncoordinated given the child's age and motor experience 2) which persistently interferes with their daily live performance, 3) and cannot be explained by any medical, neurodevelopmental, psychological, or social condition, nor by cultural background, and 4) these symptoms arise early in childhood (10). ELGAN survivors have been reported to have a 3 to 10-fold increase risk for developing DCD compared with the prevalence of of 5%-6% in the general population (12,13). Hence, awareness for the occurrence of this neurodevelopmental disorder in ELGAN children is warranted. For more information on the current clinical guidelines regarding DCD, we refer to the recently published clinical practice recommendations (12)which included a total of 10 293 infants. The pooled prevalence of cognitive and motor delays, evaluated with developmental tests, was estimated at 16.9% (95% confidence interval [CI] 10.4–26.3.

Cognitive, language and learning disabilities

ELGAN children have an increased risk for cognitive and learning disabilities. Within the RIZIV-INAMI Follow-up convention, the *intelligence profile* is only captured during the final assessment at 4.5-5.5 years of age with a proper cognitive test such as the Wechsler Preschool and Primary Scale of Intelligence Test (WPPSI). At the earlier time points, developmental scales with a cognitive subscale, such as the Bayley Scales of Infant and Toddler Development-Version III, are often used to examine the cognitive development. Based on such developmental scales, a meta-analysis has reported an overall cognitive delay of 16.9%, with mild delays being more common (14.3%) than moderate-to-severe delays (8.2%) (9). However, this meta-analysis did not exclusively included infants born before 28 weeks of GA but also included infants born between 28 and 32 weeks of GA. Nevertheless, as in accordance with motor deficits, cognitive and learning disabilities also increase with decreasing GA (9).

Based on cognitive tests at a later age, moderate-to-severe delays occurred in 14.7% of the cases (9). However, this number is based on only two studies, and the occurrence of mild delays could not be calculated by the meta-analysis.

When performing the WPPSI, ELGAN children appear to have greater weaknesses in working memory and perceptual reasoning than verbal comprehension and processing speed abilities. Therefore, it is especially important to realize that, beyond the overall IQ score, it is above all the heterogeneity of the subscales that is highlighted (14). Moreover, their intelligence profile can be highly heterogeneous, underlining the importance to look beyond the overall IQ-score.

Besides intelligence profile, *cognitive development* is also crucial for school performance and executive functioning. It is therefore important that adaptations are made at school to support these patients. The need for individualized support at school increases with lower GA; e.g. 50% at 24 weeks GA, 13% at 26 weeks GA (15). The support needed also varies according to the difficulties presented. For example, mathematics seems to be particularly difficult, which seems in ELGAN-children to be related to underlying difficulties with executive function and working memory, rather than number estimation in term born children. Strategies to optimize learning are related to attentional strategies and favoring sequential information management.

Table 2: Definition of Severe neurodevelopmental impairment (NDI) (1)

At two years of age	- Cognitive delay based on scores on standardized cognitive tests that are 2 standards deviations below the mean.
	- Moderate to severe cerebral palsy, defined as a score of more than 2 on the Gross Motor Function Classification System.
	- Bilateral hearing deficit requiring amplification.
	- Severe visual impairment with visual acuity <20/200 with the best correction, in the better seeing eye.
Later in life:	- No international agreement; severe NDI is based on the same definition than at 2 years or one of the complications noted below **:**
	- Consider severe behavioral disorders: autism spectrum disorders, attention deficit disorders, anxiety
	- Severe learning disabilities
	- Developmental coordination disorder
	- Cerebro-visual-impairment

Specific *language* studies show that ELGANs have lower scores than children born at term and those born between 28 and 36 weeks.

Problems in language acquisition appear in the early childhood period. The RIZIV-INAMI Follow-up convention only involves a language test by a professional speech therapist at around 5 years of age, which is quite late. Children who present language retardation usually have already been diagnosed and oriented to follow speech therapy. However, there is a strong relationship between language deficit and cognitive difficulties. It is therefore important to identify as soon as possible specific language impairments are present (16). Moreover, communication and language skills, and language pragmatics in particular, should be assessed at each appointment between pre-school age and adulthood.

When the deficit is established, difficulties often persist into school-age and adolescence. In the article of Lee, language and reading skills are associated with the degree of prematurity and studied independently of gender, IQ and socioeconomical status in a population of 9-16 years old children. Language analysis was performed with specific tests according to the field studied. The linguistic processing speed, verbal memory

Table 3: Important information at NICU discharge and childhood

	Important points to check at discharge	Long term medical follow-up
Growth parameters	Weight, length, cranial circumference: *Is there growth restriction, pre- or postnatal?*	Need for growth hormone supply Evaluation around 2-3 years
Clinical status	Respiratory rate, heart rate, saturation, blood pressure: *Chronic lung disease? Risk of hypoxia? Risk of pulmonary hypertension?*	Blood pressure Lung function CT-scan Cardiac ultrasound/catheterization to diagnose Pulmonary Hypertension in case of Bronchopulmonary Dysplasia
Nutrition and feeding	Type- volume-frequency-duration of feeding sessions and incidents: *Quality of growth? Risk for aspiration?*	
Biology	Hemoglobin, reticulocyte count, ferritine, Calcium-Phosphorus-alkaline phosphatases: *Need for vitamins or nutrients supplementation?*	
Immunization	Current immunization (3 doses Pneumococcal vaccination) + Influenza immunization after 6 months RSV prophyllaxis	Current immunization
Vision/hearing status	Eye fundus (retinopathy and treatment) Auditory Evoked potentials at discharge	Annual vision assessments Hearing assessment at 1 and 2 years
Neurodevelopmental status	Cranial imaging through ultrasound +/- MRI: *risk for NDI, risk of hydrocephaly.*	According to clinical evolution Cerebral MRI if indicated Genetic investigations
Neurodevelopmental status	Holding/carrying and/or physiotherapy recommendations	Long term neurodevelopmental follow-up beyond 5 years of age Indication for individual support: physiotherapy, speech therapy,…
Sleep safety	Cardiopulmonary Resuscitation training: *risk for Sudden Infant Death Syndrome*	Polysomnography indications
Day care attendance	Avoid during the first winter: *risk of infections and readmissions.*	School attendance + individual support if needed
Family	Concern about family well-being: Postpartum depression- Parental and siblings support groups	Psychological support of parents if indicated.
Administrative	Major familial Allocations – conventions for special care or feedings	

and reading comprehension are directly proportionally associated with the degree of prematurity. For the receptive vocabulary, syntactic comprehension or reading abilities, GA was not a direct predictor. These impairments seem to be associated with white matter injury caused by the prematurity. Diffuse myelination disturbances represent the majority of cases but focal cystic necrotic lesions of periventricular leukomalacia can also be found even if their prevalence is decreasing compared to diffuse lesions (17).

Neurovisual disorders

Annual visual evaluation is important to diagnose strabismus, refractive errors and visual field defects (prevalence: 25-50%). The most frequently described ophthalmological pathology affecting ELGANs is *retinopathy of prematurity*. This condition impairs vision through direct involvement of the eye.

Visual disturbances are most of the time equated with acuity disturbances resulting from peripheral damage. However, lesions affecting the retro-chiasmatic visual pathways or the cerebral visual areas also generate a visual deficit. Brain lesions in ELGAN children may affect the visual functions of the brain resulting in *cerebral visual impairment* (CVI) (18). CVI is therefore defined as a verifiable visual dysfunction which cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment (19,20). Transmission of the visual information from the retina to the occipital visual cortex is carried out by the optical radiations. These fibers run along the occipital horn of the lateral ventricle within the cerebral white matter, making them prone to damage in case of leukomalacia. The further neural processing of vision occurs via two pathways: the dorsal and ventral stream. The dorsal stream runs from the occipital lobe to the parietal lobe. This stream processes the object's spatial location ('where'-pathway) and is the more vulnerable part (21). The ventral stream goes from the occipital lobe to the temporal lobe and is involved in visual recognition ('what'-stream).

CVI is subdivided into 3 non-independent categories: low level visual deficit, oculomotor disorders (fixation, pursuit, visual capture), and higher level visual perceptual deficits (alteration of the stages of analysis and integration of visual information) (22). Neurovisual disorders have multiple impacts on daily life, school learning and social relationships (23). They are e.g., involved in postural and gestural control, the construction of spatial representations allowing displacements, in object recognition and the learning academic skills such as reading, writing and mathematics. As such, recognition of its early signs before the age of 3 is paramount.

Behavioral problems and psychiatric disorders

Preterm birth is identified as a significant risk factor for *mental health disorders* with a 3- to 4-fold increased risk for mental health issues reported. Attention Deficit Hyperactivity disorder (ADHD) and Autism Spectrum Disorders (ASD) are the most prevalent at school age and adolescence.

A spectrum of *"preterm behavioral phenotype"*, characterized by inattention, anxiety and social difficulties, is often described with presentation ranging from subclinical symptomatology, which is frequent, to overt psychiatric disorder. The association with other comorbidities, particularly cognitive impairment, is mostly present (24). Altered brain development due to biological vulnerability and environmental influences, such as neonatal pain and stress, and non-optimal parental strategies are thought to explain the link between preterm birth and those socio-emotional and mental health problems (25).

ADHD is diagnosed in 17-20% of ELGANs comparing to 5-10% in term peers. Some differences are noticed. The child shows signs of internalizing behavior, is withdrawn or shy. Inattentive behavior is more frequent than hyperactivity. The gender ratio is about 1. It is characterized by the low association with conduct disorders, the weaker association with socio-familial risk, close correlation with medical variables revealing inflammatory processes in the

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EEN STRIKT GECONTROLEERD WATER.
Interview met Arnaud Collignon, Water Ressources Manager bij SPA®, die uitleg geeft over de beschermingsmaatregelen in de stroomgebieden in de Venen en over de uitgevoerde controles om zuiver, zwak gemineraliseerd water met een constante samenstelling te garanderen.

EEN STROOMGEBIED VRIJ VAN MENSELIJKE ACTIVITEIT

AC: *Het beschermingsgebied van het mineraalwater van Spa is meer dan 13.000 hectare groot. Binnen deze perimeter is er geen enkele industriële activiteit, geen landbouw en geen pesticiden, om de zeer hoge zuiverheid van het water te garanderen. Van de bron tot de fles blijft het water in een gesloten circuit en ziet het geen daglicht. Alle materialen die met het water in contact komen, of het nu gaat om leidingen of verpakkingen, worden regelmatig getest en geanalyseerd om te garanderen dat zij inert en niet-verontreinigend zijn. Ook de verpakking garandeert de kwaliteit en de zuiverheid van het water. De productielijnen worden continu gecontroleerd. Al deze procedures en controles, van de bron tot de fles, maken het mogelijk om een water van hoge kwaliteit en met een onberispelijke zuiverheid aan te bieden en te garanderen.*

DAGELIJKSE ANALYSES, UITGEVOERD DOOR EEN ERKEND LABORATORIUM

AC: *Het Spa-water voldoet aan alle vereisten van de Europese regelgeving op dit gebied. Zo wordt het water dagelijks geanalyseerd om zijn microbiologische kwaliteit en chemische samenstelling te evalueren. Het wordt gecontroleerd bij de bron, en voor en na het bottelen. Om uitmuntendheid te garanderen, gaat de controle van het water zelfs verder dan de regelgeving met regelmatige controles op een brede waaier aan microbiologische, fysisch-chemische en organische parameters door het Spadel Laboratorium (gecertificeerd volgens ISO 17025). Bovendien controleren onafhankelijke laboratoria het water regelmatig op de afwezigheid van opkomende verontreinigende stoffen (bestrijdingsmiddelen en hun metabolieten, residuen van geneesmiddelen, hormoonverstoorders, virussen...). Naast de wekelijkse microbiologische controles analyseerde Spadel in 2020 zo'n 53.204 parameters van het Spa-water.*

CRITERIA VOOR HET LABEL "GESCHIKT VOOR DE BEREIDING VAN BABYVOEDING"

AC: *Om het label "geschikt voor de bereiding van voeding voor zuigelingen" te verkrijgen, moet water aan verschillende criteria voldoen: een zeer hoge zuiverheidsgraad, constant in de tijd en een lage minerale samenstelling, wat het geval is voor Spa® Reine omdat het laag gemineraliseerd is met een zeer laag gehalte aan calcium, fluoride, chloride en natrium, maar ook aan nitraten en nitrieten. Spa® Reine beantwoordt perfect aan al deze criteria. Daarom is het water van Spa® Reine de eerste keuze voor baby's en voor moeders die borstvoeding geven.*

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neonatal period (e.g. enterocolitis, sepsis, bronchopulmonary dysplasia…), or with impaired brain growth or maturation. Deficits in working memory and data processing are specifically observed (24-26).

ASD, especially symptoms of impaired social communication, is also associated with premature birth. Twenty percent of a 2 years cohort of ELGANs scored positively on a screening scale for ASD comparing 5% of term newborns. At adolescence, 8% of a cohort of extremely preterm born children was diagnosed with ASD using a standardized assessment protocol compared to 0.6% in a term born cohort. ASD is frequently associated with low cognitive outcome (IQ), but even in an absence of severe NDI prevalence is increased by a forth times. Associated factors are white matter and cerebellar injury while genetic factors are more often found in autistic children born at term (24-26).

At school age, the prevalence of *anxiety* is 3 to 4 times more frequent than in term born: 9% versus 2%. Again, strong association with low IQ is found. The occurrence of depressive symptoms is more controversial (24-26).

In addition to their mental health disorder, those adolescents are more often the subject of *bullying*, which can exacerbate their mental health symptoms.

The management of these mental health disorders is increasingly complex. It requires coordinated care by a child psychiatrist or psychologist including guidance at school.

Parental mental health as a crucial factor in the development of the preterm born child

Maternal mental health is a factor that might be crucial in the prevention of psychopathology in preterm children. Mothers of preterm infants are significantly more likely to experience postpartum depression, anxiety, and posttraumatic stress disorder than mothers of full-term born infants (26). The experience of preterm birth and its consequences may affect the parent's well-being and mental health. Parents whose children need to be admitted to the NICU, experience feelings of shock, uncertainty, fear, guilt, anger, grief, depression, loss of control, blame, helplessness, and anxiety (27). Preterm birth and hospitalization are highly stressful experiences for parents. Preterm delivery interrupts the normal process of becoming a parent and parenting distress seems to persist long beyond hospital discharge, with parents showing ongoing concerns about their child's health and development.

The *caregiving environment* has even been reported to be more influential on the development of infants born preterm compared to those born full-term. It is demonstrated that prematurity may act as a susceptibility factor, enhancing above-average social functioning in the context of low-stress and supportive environments. In addition, a low-stress environment may reduce the cognitive gap between preterm and full-term infants (28,29).

Altogether, this strongly underlines the importance of monitoring parental mental health after preterm birth and the possible strength of interventions supporting the quality of early family interactions.

Adolescence and adulthood

Few follow-up studies expand to adolescence. Differences in *motor performances* persist but consequences thereof on the quality of life seem to regress. *Lower cognitive scores* appear to be conserved over childhood and adolescence and contribute to reduced attainment at school and lower employment opportunities (30).

Health related quality of life and social inclusion remain lower in ELGAN adults, especially in the presence of neurosensory impairments and poor health conditions. However, the gap with term born individuals does not increase with age. Data are nonetheless conflicting. Nevertheless, a lot of adults born extremely preterm report a good quality of life (30).

Conclusion

Improvement in neonatal intensive care management has resulted in an increased survival rate of ELGAN children. However, the risk of medical complications and developmental disabilities increases with decreasing GA, stressing the need to closely follow-up the growth and development of these children, which will facilitate early diagnosis and starting up early interventions. Although these children are only followed until 5 years of age within the RIZIV-INAMI Convention, we recommend to remain attentive for mild developmental disabilities and psychiatric disorders, even up until adolescence. Finally, parental mental health and secure attachment should always be considered, given the impact it has on the child's development.

Disclosure

There is no conflict of interest for any of the authors.

REFERENCES:

1. Goldstein RF, Malcolm F. Care of the NICU Graduate after discharge. Pediatr Clin N Am. 2019;66(2):489-508.
2. Bergman N . Birth practices: maternal-neonate separation as a source of toxic stress. Birth Defects Res.2019;111(15):1087-1109.
3. Morgart K , Harrison JN, Hoon AH Jr, Wilms Floet AM. Adverse childhood experiences and developmental disabilities: risks, resiliency, and policy. Dev Med Child Neurol. 2021,63(10):1149-1154 .
4. Villar J, Giuliani F, Barroso F, Roggero P, Alejandra I, Zarco C et al. Monitoring the postnatal growth of preterm infants: a paradigm change. Pediatrics. 2018;141(2):e20172467.
5. Patel DR, Neelakantan M, Pandher K, Merrick J. Cerebral palsy in children: a clinical overview. Transl Pediatr. 2020;9(1):125-35.
6. Gano D, Andersen SK, Partridge JC, Bonifacio SL, Xu D, Glidden D V et al. Diminished white matter injury over time in a cohort of premature newborns. J Pediatr. 2015;166(1):39-43.
7. Inder TE, Warfield SK, Wang H, Hüppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. Pediatrics. 2005;115(2):286-94.
8. Himmelmann K. Epidemiology of cerebral palsy. Handb Clin Neurol. 2013;111;163-7.
9. Pascal A, Govaert P, Oostra A, Naulaers G, Ortibus E, Van den Broeck C. Neurodevelopmental outcome in very preterm and very-low-birthweight infants born over the past decade: a meta-analytic review. Dev Med Child Neurol. 2018;60(4):342–55.
10. Novak I, Morgan C, Adde L, Blackman J, Boyd RN, Brunstrom-Hernandez J, et al. Early, Accurate Diagnosis and Early Intervention in Cerebral Palsy: Advances in Diagnosis and Treatment. JAMA Pediatr. 2017;171(9):897–907.
11. Himpens E, Van Den Broeck C, Oostra A, Calders P, Vanhaesebrouck P. Prevalence, type, distribution, and severity of cerebral palsy in relation to gestational age: A meta-analytic review. Dev Med Child Neurol. 2008;50(5):334–40.
12. Blank R, Barnett AL, Cairney J, Green D, Kirby A, Polatajko H, et al. International clinical practice recommendations on the definition, diagnosis, assessment, intervention, and psychosocial aspects of developmental coordination disorder. Dev Med Child Neurol. 2019;61(3):242–85.

13. Van Hoorn JF, Schoemaker MM, Stuive I, Dijkstra PU, Rodrigues Trigo Pereira F, van der Sluis CK, et al. Risk factors in early life for developmental coordination disorder: a scoping review. Dev Med Child Neurol. 2021;63(5):511–9.

14. Kaul Y, Johansson M, Mansson J, Sternqvist K, Faroqui A, Serenius F et al. Cognitive profiles of extremely preterm children: Full-Scale IQ hides strengths and weaknesses. Acta Paediatri. 2021;110(6);1817-26.

15. Johnson S, Marlow N. Early and long-term outcome of infants born extremely preterm. Arch Dis Child. 2017;102(1):97-102.

16. Rushe T. Language function after preterm birth. In: Chiara Nosarti, Robin Murray, Maureen Hack, editors. Cambridge: Cambridge University press; 2010. P 176-184.

17. Lee E, Yeatman J, Luna B, Feldman HM. Specific language and reading skills in school-aged children and adolescents are associated with prematurity after controlling for IQ. Neuropsychologia. 2011;49(5):906-913.

18. Ortibus EL, De Cock PP, Lagae LG. Visual perception in preterm children: what are we currently measuring? Pediatr Neurol. 2011;45(1):1-10.

19. Sakki H, Dale N, Sargent J, Perez-Roche T, Bowman R. Is there consensus in defining childhood cerebral visual impairment? A systematic review of terminology and definitions. Br J Ophthalmol. 2018;102(4):424-432.

20. Fazzi E, Bova S, Giovenzana A , Signorini S. Uggeti C, Bianchi P. Cognitive visual dysfunctions in preterm children with periventricular leukomalacia. Dev Med Child Neurol. 2009; 51(12):974–981.

21. Ortibus E, Fazzi E, Dale N. Cerebral Visual Impairment and Clinical Assessment: The European Perspective. Semin Pediatr Neurol. 2019;31:15-24.

22. Stiers P, Van den Hout BM, Haers M, Vanderkelen R, de Vries LS, van Nieuwenhuizen O. The variety of visual perceptual impairments in pre-school children with perinatal brain damage. Brain Dev. 2001;23(5):333–348.

23. Guzzetta A, Mercuri, E, Cioni G. Visual disorders in children with brain lesions: 2. Visual impairment associated with cerebral palsy. Eur J Paediatr Neurol. 2001;5(3): 115-119.

24. Johnson S and Marlow N. Preterm birth and Psychiatric disorders. Pediatr Res. 2011;69(5 Pt 2):11R-18R.

25. Montagna A , Nosarti C. Socio-emotional development following preterm birth: pathways to psychopathology. Front Psychol 2016;7:80.

26. Fitzallen G, Taylor H, and Bora S. What do we know about the preterm behavioral phenotype. A narrative review. Front Psychiatry 2020;11:154.

27. Treyvaud K. Parent and family outcomes following preterm birth or very low birth weight birth: a review. Semin Fetal Neonatal Med. 2014,19(2):131-5.

28. Shah P, Robbins N, Coelho R, Poehlmann J. The paradox of prematurity: the behavioral vulnerability of late preterm infants and the cognitive susceptibility of very preterm infants at 36 months post-term. Infant Behav Dev. 2013;36(1):50-62.

29. Gueron-Sela N, Atzaba-Poria N, Meiri G, Marks K. The caregiving environment and developmental outcomes of preterm infants: diathesis or differential susceptibility effects? Child Dev.2015;86(4):1014-1030.

30. Saigal S, Ferro MA, van Lieshout RJ, Schmidt LA, Morrison KM, Boyle MH . Health related quality of life trajectories of ELBW survivors into adulthood. J Pediatr. 2016;179:68-73.