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Review Article

The possible clinical correlation between preterm neurodevelopment and alterations in gut eubiosis

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Abstract

In the literature, the topic of neurocognitive development of preterm infants is of current interest. For more than a century, efforts have been made to study and demonstrate what factors may facilitate or interfere with normal neurodevelopment in preterm infants. Recently, attention seems to have focused on the role of gut microbiota. Several studies have shown that the cognitive performance of infants born preterm is lower in general and specific skills; behavior is also reduced in the first year of life; and, by school age, the cognitive development of infants born preterm is lower than that of full-term infants (these deficits are evident in the areas of learning, reading, writing, and mathematical skills, fine motor skills, communication, memory, and attention); however, there is currently no scientific evidence to confirm the existence of premature alterations in the gut microbiota concerning these morbid conditions, although there is evidence for the existence of the gut-brain axis and adverse outcomes on neurobiological function following physical afflictions, such as sepsis, necrotizing enterocolitis and other diseases. Supplementation of prebiotics and probiotics does not appear to correlate with improvement or worsening of future neurobiological and cognitive status, except in the ability to positively influence pathological conditions that indirectly may interfere with healthy neurodevelopmental outcomes of the premature infant.

Background

Introduction

In the scientific literature, the topic of neurocognitive and psychological development of preterm infants is of current interest. For more than a century, efforts have been made to study and demonstrate what factors are capable of facilitating or interfering with normal infant development, to prevent or correct any alterations or projectively predict developmental progress, identifying from time to time the possible factors impacting neurodevelopment, whether pathophysiological or pharmacological (during the gestation and developmental phase of the first three years of birth [1].

Generally, pathological neuroevolutionary findings are a consequence of cognitive (and psychiatric), motor, sensory (hearing, visual, tactile, olfactory, gustatory), neurological (epilepsy, hypoxic and/or ischemic consequences, oncological expansive processes and structural malformations), and genetic disorder [2,4]; such hypotheses may also be triggered or aggravated by stressogenic and algic factors, as well as nutritional and pharmacological [5,8].

Recently, several studies have supported the hypothesis of the correlation between gut dysbiosis and neurodevelopmental impairment in preterm infants [9]: "In preterm infants, predisposes him to various major morbidities including neonatal necrotizing enterocolitis and sepsis in the Neonatal Intensive Care Unit (NICU) and adverse neurological outcomes later in life. There are parallel early developmental windows for the gut microbiota and nervous system during prenatal to postnatal life. Therefore, preterm infants represent a unique population in which optimization of early colonization and microbiota development can influence brain development and improve neurological outcomes" [10]. However, beyond the suggestive hypothesis, there is no current scientific

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evidence confirming premature alterations of the gut microbiota with such morbid conditions, although there is evidence for the existence of the gut-brain axis and negative outcomes on neurobiological function as a result of physical afflictions, such as sepsis, necrotizing enterocolitis and other diseases. Supplementation of prebiotics and probiotics does not appear to correlate with improvement or worsening of future neurobiological and cognitive status, except to affect morbid conditions that indirectly may influence healthy neurodevelopmental outcomes of the premature infant [10].

Clinical examination and follow-up

During periods of hospitalization, caregiver intake during the developmental course, and follow-up appointments, identifying all factors impacting normal neurocognitive and psychological development of preterm infants in advance becomes critical if an extremely complicated clinical task, whether the caregiver's intervention is clinician-assisted or to meet a scientific research need [11].

The neurocognitive examination is a fundamental part of the quality of care in Follow-up programs. It aims to identify and define major abnormalities early, enabling the implementation of the necessary early interventions, guiding the practitioner in communicating the diagnosis, directing support to parents and planning referral to territorial services for children with risk of disabilities or developmental disorders, sharing with the primary care pediatrician the problems encountered and possible solutions. A further objective, starting at 12 months of age, is to identify minor outcomes and further investigate the motor, neuropsychological, and behavioral development of preterm infants. Finally, for children who have developed cerebral palsy or major disabilities, the neuro-rehabilitation team has the task of verifying therapeutic interventions, providing guidance to parents regarding the prevention of musculoskeletal disorders, and sharing guidance on aids, autonomy, and prostheses with territorial services. The prognosis and evolution of clinical signs, but also the child's and parents' resilience pathways are not always easy to define, the lower the gestational ages [12].

Aims

The objective of the present work is to evaluate the current clinical evidence (e.g., clinical signs, anthropometrics, and instrumental findings) on the possible correlation between microbial alterations in the gut microbiota and neurodevelopment in the preterm infant, that is, the unborn who have a gestational age of fewer than 36 weeks or a weight of fewer than 1,500 grams.

Materials and methods

We searched Pubmed through December 31, 2022, clinical trials and randomized controlled trials using the keywords "gut microbiota", "preterm infants", "prebiotic" and "probiotic", in combination, selecting 18 useful results. Simple reviews, opinion contributions, or publications in popular volumes were excluded because they were not relevant or redundant for this paper, as they did not present results or statistical samples but only protocol and research proposals, did not specifically address the relationship between the gut microbiota and preterm infants, the data were contradictory, unreliable, or otherwise, the research design had functional shortcomings, or the study sample was not directly preterm infants. Some reviews have been taken into account to justify the concluding assertions, consistent with the outcomes of studies on this research area. The search was not limited to English-language articles. No limit was placed on the year of publication.

Results

To evaluate indicators of quality of care in follow-up, a panel of experts from the same networks defined the areas and timing of evaluations [13].

The literature distinguishes between "major disabilities" and "minor dysfunctions": in the first case fall the hypotheses of moderate or severe cerebral palsy with GMFCS (Gross motor function classification system) ≥ 2, cognitive scores at Bayley III < 70 and GMFCS ≥2, vision with deficits < 1/10 bilateral, permanent hearing impairment that does not allow the child to understand the directions of verbal messages and communicate despite prosthesis or cochlear implant; the second case includes hypotheses of disorders of the motor and postural sphere (clumsiness, clumsiness, coordination problems, organizational problems of movement and gesture, but also postural and morphological abnormalities at the level of the chest, spine, lower limbs and foot, plagiocephaly), difficulties in learning, visual-spatial and perceptual organization, behavioral disorders (adjustment disorders and disorders of the tonic-emotional sphere, hyperactivity or inhibition), and pathologies of adaptive functions (disorders of sleep-wake rhythm, feeding and sphincter control [14-16].

The studies conducted by Prechtl in the last thirty years have introduced into the clinical field the observation and qualitative evaluation of the spontaneous motility of the newborn (General Movements, GM), using ultrasound and ultrasound techniques (jerks, GM, isolated movements of the limbs, contractions, stretches, breathing movements, hiccups, yawning, turning and bending of the head, sucking and swallowing movements) (Table 1) [17].

Subsequent research has shown that GMs are an excellent indicator of early brain dysfunction, as they involve the whole body in a variable sequence of movements of the trunk, neck, legs, and arms and GMs in the preterm are similar to those of the fetus, as they are large, often fast and frequently accompanied by pelvic lift. The evaluation of GMs is based on the collection of video recordings and the subsequent analysis of the movement by properly trained personnel [18-21].

In recent decades, there has been an increasing need then to assess the communicative and language mental development of preterm birth within the first year of life to identify children with developmental problems/difficulties as early as possible and plan individualized habilitative and educational interventions. Many studies are showing a high

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Table 1: Cohort studies. Legend: p (preterm), ft (full-term), pc (preterm-clinic), pp (preterm-placebo), ftc (full-term clinic), ftp (full-term placebo), a (adult).

Author (Year)	Objectives	n	Key Results and Conclusions	Impact on Neurodevelopment of the Preterm
Campbell H, et al. [36]	Neonatal cranial ultrasound findings among infants born extremely Preterm: associations with neurodevelopmental outcomes at 10 years of age.	889(p)	Among children born extremely preterm, cranial abnormalities found on ultrasonography, particularly those indicative of white matter damage, are predictive of neurodevelopmental impairment at age 10 years; moreover, the strongest associations were found with cerebral palsy.	Probable indirect effects
Taylor G,L et al. [35]	Changes in neurodevelopmental outcomes from Age 2 to 10 years for children born extremely preterm.	802(p)	Neurodevelopmental impairment in infancy, predicts about 1/3 in middle childhood (10 years).	Probable indirect effects
Santos Jr, HP et al. [29]	Evidence for the placenta-brain axis: multi-omic kernel aggregation predicts intellectual and social impairment in children born extremely preterm	49(p)	Correlation between the placenta and neurodevelopmental disorders exists.	Probable indirect effects
McCoy TE, et al. [37]	Neurocognitive profiles of preterm infants randomly assigned to lower or higher hematocrit thresholds for transfusion.	56(p)	Possible long-term neurodevelopmental consequences of maintaining higher hematocrit levels.	Probable indirect effects
Steinmacher J, et al. [38]	Iron supplementation in infants with a birth weight of fewer than 1301 grams	164(p)	Early enteral iron supplementation showed a trend toward a beneficial effect on long-term neurocognitive and psychomotor development and showed no evidence of any adverse effect.	Probable indirect effects
Schmid MB, et al. [30]	Prospective risk factor monitoring reduces intracranial hemorrhage rates in preterm infants.	191(p)	The rate of cerebral hemorrhage in premature infants can be significantly lowered (89.5%) by prospective monitoring of risk factors.	Probable indirect effects
Peltoniemi OM, et al. [39]	Early erythropoietin supplementation after preterm birth.	18(pc) + 21(pp)	Weekly administration of erythropoietin decreased iron load in preterm infants but did not cause changes in reactive or plasma iron levels or adverse influences on outcomes during early infancy.	Probable indirect effects
van der Bosch GE, et al. [49]	Prematurity, opioid exposure, and neonatal pain.	19(p)	Although prematurity, opioid exposure, and neonatal pain were significantly associated with brain volume, no major associations with neuropsychological functioning or thermal sensitivity were found. The results suggest that morphine administration during neonatal life does not affect neurocognitive performance or thermal sensitivity during infancy in children born preterm without brain damage during early life.	Probable indirect effects
Frazier JA, et al. [31]	Psychiatric symptoms in adolescents born preterm.	670(p)	Among adolescents born extremely preterm, anxiety, major depression, and ADHD were the most prevalent psychiatric disorders at age 15.	Probable indirect effects
Gadhia MM, et al. [51]	Effects of early inhaled nitric oxide therapy and vitamin A supplementation on the risk for bronchopulmonary dysplasia in premature newborns with respiratory failure.	398(p)	Combination therapy of inhaled nitric oxide + vitamin A in preterm infants with birth weights 750-999 g reduced the incidence of bronchopulmonary dysplasia and death and improved neurocognitive outcomes at 1 year in the average group.	Probable indirect effects
Wapner RJ, et al. [47]	Long-term outcomes after repeat doses of antenatal corticosteroids.	486(p)	Children who had been exposed to repeat versus single courses of prenatal corticosteroids did not differ significantly in physical or neurocognitive measures.	Probable indirect effects
Blakstad EW, et al. [41]	Improved visual perception in very low birth weight infants on enhanced nutrient supply.	31(p)	Results showed a more consistent global movement response among infants who received enhanced feeding. The intervention may have improved the visual perception of a global movement.	Probable indirect effects
Ferguson SA, et al. [50]	Preemptive morphine analgesia in preterm neonates.	5(pc) + 14(pp)	Morphine-treated children's head circumference was about 7% smaller and body weight was about 4% less; however, height did not differ. On the short-term memory task (delayed pairing to sample), morphine-treated children showed significantly longer choice response latencies than placebo children and completed approximately 27% less of the task than placebo children. Parents described morphine-treated children as having more social problems, a specific effect in creating and maintaining friendships.	Probable indirect effects
Mank E, et al. [42]	Enteral bioactive factor supplementation in preterm infants.	26(p)	Despite the encouraging potential effects of several bioactive factors, more high-quality studies with sufficient numbers of preterm infants are needed before a certain factor can be implemented in clinical practice. Breast milk, Vitamin A, and Enteral insulin appear to be most related.	Probable indirect effects
Bhatia J [43]	Human milk and the premature infant	26(p)	Because human milk has unique properties in promoting gastrointestinal maturation and immunological benefits, it is prudent to implement strategies to fortify it appropriately to realize its benefits that include reduced rates of necrotizing enterocolitis, fewer episodes of sepsis and urinary tract infections and improved visual and neurocognitive development.	Probable direct and indirect effects

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Upadhayay RP, et al. [44]	Effect of prebiotic and probiotic supplementation on neurodevelopment in preterm very low birth weight infants.	275(p)	The use of prebiotics and probiotics in preterm infants did not significantly decrease or increase cognitive and motor impairment, cases of cerebral palsy, and visual and auditory deficits.	No effects
Wu W, et al. [45]	Neurodevelopmental outcomes and gut Bifidobacteria in term infants fed an infant formula containing high sn-2 palmitate.	199(p)	High stereo-specific palmitate (sn)-2 in a formula promotes intestinal Bifidobacteria in infants, improving motility.	Probable indirect effects
Ai Y, et al. [34]	Antibiotic exposure and childhood attention-deficit/hyperactivity disorder.	726(p)	Maternal antibiotic intake during pregnancy may be associated with an increased risk of ADHD in offspring. However, there was insufficient evidence for an association between antibiotic intake after birth and the risk of ADHD.	Probable indirect effects

incidence of developmental atypia in preterm low birth weight (VLBW) infants [22].

In the early years of a child's life, motor, cognitive, communicative, and perceptual skills, and competencies are interdependent; we speak of "sensory and motor competencies" to emphasize the close overlap and interdependence of the motor, cognitive, perceptual, linguistic and communicative domains. The most widely used scales for assessing mental development in early childhood are the Bayley scales (with cognitive, motor, language, social-emotional, and adaptive behavioral subscales) and Griffiths (with locomotor, social, hearing-language, hand-eye coordination and performance subscales). Developmental scales are a standardized method of observing and assessing the developmental lines of a child's behavior. The purpose of the scales is to assess the child's current level of development and how far it deviates from the general population, intending to develop early habilitative programs. They do not measure an individual's intelligence but assess the achievement of key developmental milestones (Figure 1) [23].

Cognitive assessment in early childhood is not aimed at determining an IQ. The tools intended for this age group are defined as "development tests" because they primarily evaluate the achievement of the fundamental stages of the growth path. Cognitive functions from 0 to 2 years being sensorimotor, are not separable or well differentiable. The Bayley-III provides a snapshot of the child's development at a given moment and allows for the assessment of individual functional domains with flexible but highly standardized procedures. It consists of 5 scales, 3 direct administration scales and 2 scales aimed at parents. It is also accompanied by a report for the caregiver. The Cognitive scale consists of items written in such a way as to minimize the influence of children's receptive language and motor skills in performing the task. The following are evaluated: sensorimotor development, exploration, and manipulation, memory, formation of concepts, the relationship between objects, and other aspects relating to the cognitive process. The motor scale assesses the child's motor skills through two subscales: gross motor skills and fine motor skills. Fine-motor items assess praxis, motor-perceptual integration, planning, and motor speed. Gross motor items primarily measure limb and chest movement, assessing static positioning and dynamic movement, including locomotion and coordination, balance, and motor planning. The Language scale consists of two subscales: Receptive Communication and Expressive Communication (CE). Receptive communication items assess

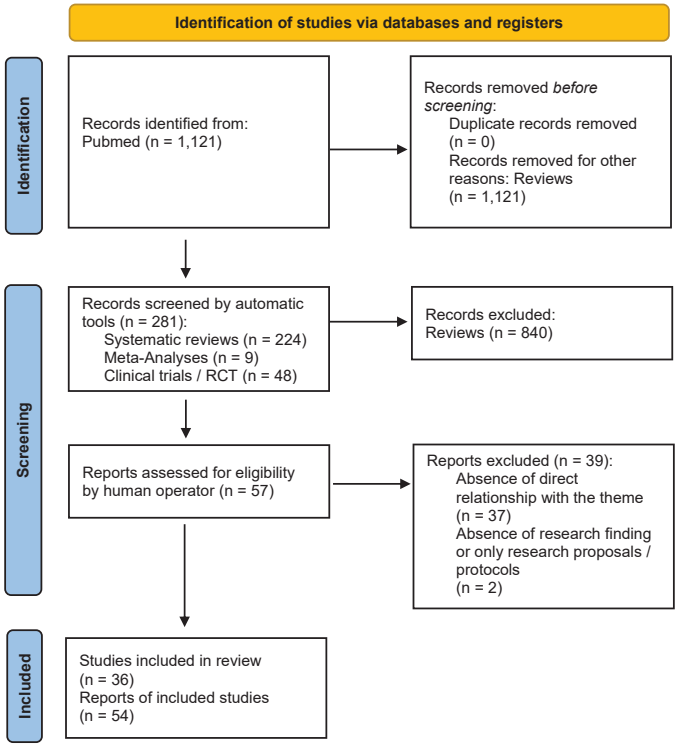

Figure 1: PRISMA flow diagram template for systematic reviews. Matthew J Page et al. BMJ 2021;372:bmj.n71.

preverbal behavior; vocabulary development; the development of vocabulary related to the morphological aspect (e.g., pronouns and prepositions); understanding morphological indicators (e.g., plural "i" or "e"), tense indicators (e.g., "while" and gerund) and possessives; referential communication and verbal comprehension. Expressive Communication items assess preverbal communication (e.g., basic phonetics, gestural communication, references to conjunctions, respect for conversational turns); vocabulary development (e.g., naming objects, images and attributes, such as colors and sizes); morphosyntactic development (e.g., the use of expressions with two terms, plurals, and verb tenses). The Socioemotional scale evaluates the management of emotions, communication needs and the ability to relate to others. The items consider the domain of emotional-functional ability; the need for communication; commitment in relationships with others; the use of emotions for interactive purposes; use of emotional cues or gestures to solve problems. Finally, the Adaptive Behavior scale measures what the individual habitually does and what she may be able to do in some areas: Communication: speech, language, listening, and non-verbal communication skills;

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Preschool skills: letter recognition, counting, and drawing simple shapes; Self-control: following simple directions and orders and making choices; Game: play and follow rules; Social: getting along with other people, using good manners, helping others, and recognizing emotions; Community: interest in activities outside the home and recognition of different situations; Living at home: helping adults with household chores and taking care of their belongings; Health and safety: self-care and avoidance of physical hazards; Autonomy: eating, going to the bathroom and washing; Motor: movement and manipulation of objects. Scores for all skill areas combine to form a series of composites, including the Overall Adaptive Composite, which is an overall measure of a child's adaptive development. The Griffiths III, on the other hand, develop along 5 scales, one less than the previous version with two main innovations: the Performance (E) and Ragionamento Pratico (F) scales have merged into a single Scale A (Fundamentals of learning) and Scale D (Personal-social-emotional) aspires to a much more sophisticated assessment which is not satisfied with assessing only adaptive behavior but aims at assessing the ability to read emotional expressions, empathy, theory of mind, self-awareness, self-judgment and morality. The age range taken into consideration (0 - 6 years) is narrower than the previous tool which was aimed at two age groups (0 - 2 and 2 - 8), considering the identification of possible disorders or developmental delays superfluous between the ages of 6 and 8.

The assessment of Developmental Quotient (QS) obtained from developmental scales differs from IQ and has a predictive purpose. Serious measurements of a child's development over time can be made in the first 2 years of life. It is necessary to keep in mind that it is possible to detect variations in results between assessments that may be a sign of pathology or may be the result of measurement artifacts and/or physiological changes in the child's performance. For prognostic purposes, it is useful to remember that physiological variations are also observable in children who are developing a disability, particularly mild-to-moderate disabilities. Some authors identify 2 years of corrected age as a key stage at which to conduct an assessment of cognitive development aimed at early identification of possible disabilities. At 2 years of corrected age, a broad assessment of the developmental domains: motor, cognitive (verbal and nonverbal), communicative, and relational can be conducted. The assessment of mental development in the preterm infant should be supplemented with detailed neuropsychological assessment, observation of regulatory skills, and attachment bonding [24-28].

In the literature, clinical studies focus on analyzing the correlations between defective neurodevelopment of preterm infants and serious events such as brain hemorrhage, sepsis and major respiratory, cardiac, and intestinal disorders (capable of interfering with normal brain function) and recently even the correlation with placental defects and neurological damage emerges [29] but the monitoring of risk factors decreases the negative impact on the patient's health and neurodevelopment by almost 90% [30] including psychological profiles that in school age and adolescence detect the presence of anxious, depressive and hyperarousal behaviors [31-34].

All of these hypotheses have the potential to produce permanent impairment of normal neurocognitive and psychological development, which usually impacts severe forms of neurodevelopmental deficits in one out of three cases [35]; in particular, among children born extremely preterm, cerebral palsies and cranial abnormalities found on ultrasonography (and in those indicative of white matter damage) are predictive of neurodevelopmental impairment at age 10 years [36], but correlations have also been found between neurodevelopmental disorders and high hematocrit values, prolonged over time [37], without, however, finding an exact clinical correlation between this laboratory finding and the neurodevelopmental consequences.

On the subject of supplementation, on the other hand, there emerges a need for prior correction of disease profiles related to ai values of plasma iron [38,39] and folate deficiency [40], as well as an increased preference for fortified milk to improve the kinaesthetic performance of preterm infants [41], as well as the addition of vitamin A and enteral insulin to breast milk, under certain clinical hypotheses, positively correlated [42].

"Human milk has unique properties in promoting gastrointestinal maturation and immunological benefits, it is prudent to implement strategies to fortify it appropriately to achieve its benefits, including reduced rates of necrotizing enterocolitis, fewer episodes of sepsis and urinary tract infections, and improved visual and neurocognitive development" [43].

Discussion

However, such clinical evidence, relating precisely to the health status of preterm infants, is not directly reflected in any published studies on the correlation between unhealthy neurodevelopment and alterations in gut eubiosis; instead, there is evidence on the indirect effects of diseases caused or aggravated by gut dysbiosis, such as necrotizing enterocolitis and sepsis, as there is evidence of the brain-gut axis and the importance of the microbial role in our body [44].

The use of probiotics and prebiotics to regulate intestinal dysbiotic processes, in preterm infants, has not been significantly shown to play an important role in his neurodevelopment, apart from the positive effects related to the stabilization of eubiosis [45].

Correcting intestinal dysbiotic forms, especially in preterm infants, could promote proper microbial eubiosis of the whole organism, but such clinical operation does not seem to be correlated with direct damage to the normal neurodevelopment of the preterm infant, in the current state of medical knowledge, although there is evidence that alterations in the gut-brain axis can promote or aggravate many morbid conditions in adults [9]; however: "The impact of nutrition on brain development in preterm infants has been increasingly appreciated. Early postnatal growth and nutrient intake have been demonstrated to influence brain growth and maturation with subsequent effects on neurodevelopment that persist into childhood and adolescence. Nutrition could also potentially

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protect against injury. Inflammation and perinatal infection play a crucial role in the pathogenesis of white matter injury, the most common pattern of brain injury in preterm infants. Therefore, nutritional components with immunomodulatory and/or anti-inflammatory effects may serve as neuroprotective agents. Moreover, growing evidence supports the existence of a microbiome-gut-brain axis. The microbiome is thought to interact with the brain through immunological, endocrine, and neural pathways. Consequently, nutritional components that may influence gut microbiota may also exert beneficial effects on the developing brain. Based on these properties, probiotics, prebiotic oligosaccharides and certain amino acids are potential candidates for neuroprotection. In addition, the amino acid glutamine has been associated with a decrease in infectious morbidity in preterm infants. In conclusion, early postnatal nutrition is of major importance for brain growth and maturation. Additionally, certain nutritional components might play a neuroprotective role against white matter injury, through modulation of inflammation and infection, and may influence the microbiome-gut-brain axis" [46].

Finally, recent pharmacological findings rule out the correlation between neurodevelopmental deficits and pregnancy exposure to corticosteroids [47] and morphine (despite less recent contrary studies that also speak of a negative impact on growth and linear brain measures) [48-51], but confirm that combination therapy of inhaled nitric oxide and vitamin A in severely premature infants reduces the incidence of bronchopulmonary dysplasia and life-threatening complications, actually improving neurocognitive outcomes in the first year of life [52].

Understandably, the lower gestational age and presence of independent factors besides prematurity may lead to intellectual & developmental disabilities (you mentioned repeatedly). Worth noting is the perinatal and neonatal factors associated with improved outcomes. The long surveillance involves significant long-term medical challenges with major concerns of high-priced health care costs and the negative impact on the unprepared parents requiring repeated counseling on the complexity of the information. Several studies have shown that the cognitive performance of infants born preterm is lower in general and specific skills, such as visuoconstructive and visuoperceptual skills, receptive and expressive language, visuomotor integration, working memory and attention, gross and fine motor skills and social-emotional skills; exploratory and reaching behavior is also reduced in the first year of life. In fact, at school age, the cognitive development of children born preterm is lower than that of children born full term, except for special morbid conditions occurring later in life. These deficits are evident in the areas of learning, reading, writing and mathematics, fine motor skills, communication, memory and attention. There is also an increased presence of psychological problems such as anxiety, somatization, hyperactivity, oppositional defiant disorder, depression and socialization difficulties. Finally, in adolescence, data show that preterm children have an increased risk of hospitalization and general cognitive deficits, in verbal and visuomotor skills, executive functions such as inhibition and cognitive flexibility. Indeed, there is an increased risk of developing psychiatric disorders, particularly depression and anxiety disorders.

Limitations

No specific limitations were found, except for a few studies where an insufficient population sample size was reported. In addition, studies involving the intake of prebiotics and probiotics do not take into account their combined interaction, with and without drug therapy, and the nutritional and dietary profiles of patients, which therefore may override or diminish the efficacy of administration. Finally, the studies do not include an exact distinction between the pharmaceuticals used and the appropriate dosage, as well as the timing and duration of administration. These elements, insufficiently analyzed, may invalidate all or part of the outcome of the studies.

Conclusion

There is no conclusive clinical evidence that there is a direct correlation between gut dysbiosis and unhealthy neurodevelopment or that the use of probiotics and prebiotics enhances, reduces, or nurtures healthy neurocognitive development of preterm infants, although there is evidence of a correlation between various biological dysfunctions and altered gut eubiosis, especially in preterm infants, who from birth have a pattern of structural and functional alteration of Bifidi and other types of bacteria. In the future, it is suggested that more attention be paid to this study profile, and during clinical follow-ups consider the data to assess possible correlations between the maintenance of gut dysbiosis and adverse neurodevelopmental consequences in preterm infants, in order also to facilitate early intervention to support various cognitive, motor and language skills and any developmental delays that might create limitations in the performance of normal daily activities.

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