Commentary

Reinterpreting Circulating Neuron- and Oligodendrocyte-Derived Extracellular Vesicles for Non-invasive Monitoring of Neonatal Brain Development

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The first month of life represents a critical window for brain development, during which rapid and coordinated maturation of neuronal and oligodendroglial networks establishes the foundation for long-term neurodevelopmental outcomes. However, current clinical approaches based on neurological examination and neuroimaging provide only indirect and intermittently accessible measures of these dynamic processes, highlighting the need for minimally invasive biomarkers capable of longitudinal assessment. Extracellular vesicles derived from neurons and oligodendrocytes can be detected in peripheral blood using immunoassays targeting cell-specific markers. We hypothesize that paired analysis of umbilical cord blood at birth and heel-prick blood at one month may enable non-invasive monitoring of early brain development. In this framework, neuron-derived and oligodendrocyte-derived extracellular vesicles reflect gray and white matter maturation, respectively. Longitudinal changes in circulating neuron-derived and oligodendrocyte-derived extracellular vesicles may capture individualized trajectories of early brain development. This approach aims to provide continuous rather than categorical assessment of neonatal brain maturation and may support development of scalable biomarkers for early neurodevelopmental evaluation.

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Introduction

The first month of life represents a critical window for neonatal brain development, characterized by rapid maturation of both neuronal and glial networks [1][2]. During this period, neurons undergo

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extensive synaptogenesis, dendritic arborization, and activity-dependent circuit refinement that establish the foundation for sensory processing, cognition, and behavior [2][3]. In parallel, oligodendrocyte (OL) precursor cells proliferate and differentiate into mature myelinating OLs, initiating the formation of white matter tracts and enhancing the efficiency and synchronization of neuronal communication [2][4]. This coordinated development of gray matter neurons and white matter OLs is highly sensitive to genetic, hormonal, nutritional, and environmental influences, making the neonatal period particularly important for long-term neurodevelopmental outcomes [2][4][5].

Neonatal brain assessment is therefore clinically important, as early identification of deviations from normal brain development may facilitate timely intervention, improve neurodevelopmental outcomes, and help mitigate the long-term consequences of perinatal insults, prematurity, and other risk factors [6] [7].

Current Approaches for Assessing Neonatal Brain Development

Current assessment of neonatal brain development relies primarily on neurological examination and neuroimaging [2][8]. Neurological assessment and developmental milestone evaluation are routinely performed and remain essential components of pediatric care. However, these approaches are inherently intermittent and may have limited sensitivity for detecting early biological changes during early brain maturation. Neuroimaging modalities, including cranial ultrasonography and magnetic resonance imaging, provide valuable structural information but are not readily suited for frequent longitudinal monitoring of ongoing neuronal and oligodendroglial development.

Extracellular Vesicles as Emerging Biomarkers of Brain Biology

Neurons and OLs are known to release extracellular vesicles (EVs) within the central nervous system, and a subset of these EVs can be detected in peripheral blood. Following the initial discovery of neuron-derived extracellular vesicles (NDEs) in human plasma more than a decade ago [9], circulating NDEs have been quantified using a sandwich immunoassay with antibodies against the neuronal surface marker CD171 (L1 cell adhesion molecule, L1CAM) for capture, followed by detection using EV-enriched markers such as CD9 [10]. Subsequently, OL-derived extracellular vesicles (ODEs) have been measured by replacing the capture antibody with an oligodendrocyte-associated marker such as myelin oligodendrocyte glycoprotein (MOG) [11]. Collectively, these findings suggest that circulating NDEs and ODEs constitute a

minimally invasive liquid biopsy of the central nervous system, providing an opportunity to monitor cellular processes occurring within the brain through peripheral blood sampling. This established analytical platform forms the basis for the translational concept proposed in this article.

Author's Opinion: Reinterpreting NDEs and ODEs for Neonatal Brain Development

Although these NDE and ODE assays were originally developed and applied primarily in adult populations for neurodegenerative research, their potential utility for monitoring neonatal brain development has not been explored. This is notable because two clinically accessible sample types are available during the neonatal period: umbilical cord blood, which reflects fetal circulation at birth, and heel-prick blood, which is routinely collected around the 1-month health check for newborn screening. Importantly, both samples can be obtained in very small volumes that are sufficient for NDE and ODE measurements without additional risk or burden to the infant.

We therefore propose that paired analysis of cord blood and 1-month heel-prick samples may enable quantitative assessment of early postnatal brain development. Specifically, longitudinal changes in circulating NDEs and ODEs may provide a minimally invasive window into dynamic gray and white matter maturation in individual infants.

Strengths

The principal strength of this framework is that paired cord blood and 1-month heel-prick blood samples can be obtained as part of routine neonatal care without imposing additional burden on the infant. Furthermore, NDE and ODE assays have already been technically established and require only very small plasma volumes. These paired samples provide a unique opportunity to longitudinally evaluate neuronal and oligodendroglial biology during the first month of life in individual infants.

Limitations

Based on the rapid onset of postnatal myelination, ODE-related changes are expected to be greater than NDE-related changes during the first month of life, reflecting preferential white matter maturation during this developmental period [2][3][4][5]. However, this hypothesis has not yet been validated experimentally. The longitudinal behavior of circulating NDEs and ODEs during normal neonatal

development remains unknown, and reference developmental trajectories have not been established. Furthermore, the influence of gestational age, prematurity, perinatal complications, and other biological variables requires systematic investigation.

Importantly, this approach is not intended to provide binary clinical classifications such as “normal” or “abnormal” development. Rather, it is designed to characterize individualized trajectories of early brain maturation by capturing dynamic changes in neuronal and oligodendroglial activity across time.

Given substantial inter-individual variability in early neurodevelopment, this framework emphasizes a personalized developmental profile rather than categorical diagnosis. In cases where atypical or unexpected trajectories are observed, follow-up measurements using additional heel-prick sampling or alternative minimally invasive blood collection strategies may be considered to refine longitudinal interpretation.

Future Directions

Beyond measuring total NDE and ODE levels, future studies may incorporate additional EV surface and molecular biomarkers to provide a more comprehensive characterization of neuronal and oligodendroglial development. Future studies should establish normative developmental trajectories, determine the influence of gestational age and perinatal conditions, and evaluate correlations with neuroimaging and long-term neurodevelopmental outcomes.

Conclusions

We propose that paired analysis of circulating NDEs and ODEs in cord blood and one-month heel-prick blood represents a novel framework for longitudinal assessment of neonatal brain development. Although substantial biological and clinical validation is required, this approach has the potential to establish a new direction in neonatal brain development research by enabling individualized, minimally invasive monitoring of gray and white matter maturation.

Statements and Declarations

Funding

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Potential Competing Interests

The author declares a conflict of interest because he is a co-founder and Chief Technology Officer of NanoSomiX, Inc., and an inventor on issued patents and patent applications relevant to this manuscript.

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Declarations

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