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Avoidable Brain Injury and the Hope of Minimizing Developmental Dysfunction

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Premature birth exposes the developing brain to signals and insults not intended by evolution but made possible by the successes of neonatal intensive care (NIC).

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Premature birth exposes the developing brain to signals and insults not intended by evolution but made possible by the successes of neonatal intensive care (NIC).

The extraordinary achievement of NIC – ensuring survival of more than 80% of extremely low gestational age neonates (ELGAN; 24 - 28 weeks of gestation), a group whose survival was negligible before the modern era of newborn intensive care - is tempered by the recalcitrant persistence of cognitive and motor deficits in many survivors even when other organs have fully recovered. Many ELGANs are severely handicapped with combinations of cognitive delay, cerebral palsy (CP), hearing loss, blindness, mental retardation, and epilepsy.

The reported risk of severe neurodevelopmental impairment for ELGANs at 2 years PMA ranges from 10% to 20%, with CP affecting from 7% to 20% of these children depending on the definitions applied. Anatomical correlates of later neurologic impairment can be defined by early MRI and suggest that some of the changes seen may be preventable. A major priority in newborn medicine must be to translate these extraordinary gains in survival into gains in *healthy* survival without the current high frequency of major and minor neurodevelopmental impairments.

CP is the most common cause of physical disability in children, with a prevalence of about 2 per 1,000 live births and up to 3 to 4 per 1,000 school-age children. Commonly considered a disability of children, improved survival has made it a lifelong condition, persisting into adulthood, with many more adults affected than children. Globally, fewer than 10% of births occur in high-income countries, thus it is likely that more than 90% of the public health impact of CP is borne by populations outside of these countries.

Surprisingly little of our knowledge for prevention or intervention/therapy of the most common forms of CP (unexplained or "*developmental*" form) are based on randomized clinical trial research and more efforts are needed to address it and other causes of cognitive delays during development – distinct from those clearly recognized as direct tissue injuries like: hypoxemia, intracranial hemorrhage, environmental toxins or infection.

In the following paragraphs, we comment on three types of interventions:

a) *replacement* of a normal biological signal (thyroxine; T_4) (see our July 2016 NeoReviews article "Transient Hypothyroxinemia of Prematurity"), and two forms of prophylaxis;

b) *amplification* of a normal biological signal (supra-physiological doses of erythropoietin); and

c) *drug* therapy (magnesium sulfate, caffeine) used in an attempt to ensure the normal pattern of brain growth and function.

A) Thyroid Hormone Sufficiency is Critical to Normal Brain Development: ELGANs are born during a key *in utero* transition period from *maternal-to-fetal* thyroid hormone dependence. Although the etiology of cognitive deficits and CP is multifactorial, the low levels of thyroid hormone commonly found in the first weeks after a premature birth are a strong, *independent* risk factor for adverse neurodevelopmental outcome and CP. Low thyroid hormone levels arise directly from:

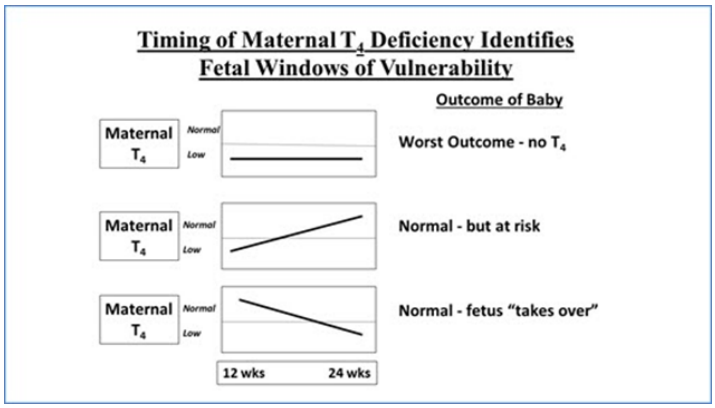

Figure. See the July 2016 NeoReviews article "Transient Hypothyroxinemia of Prematurity."

i) the loss of maternal and placenta transfer of T_4 and iodine,

ii) immaturity of the hypothalamic-pituitary-thyroid- (HPT-) axis,

iii) limited thyroid capacity to increase synthesis and metabolism,

iv) iodine imbalance, and

v) other adverse perinatal events affecting degradation of active hormone.

Low levels of thyroid hormones are more severe in infants born at lower gestational ages, vary inversely with the severity of neonatal illness, typically show a serum nadir at approximately 7-10 days' postnatal age, and can persist for several weeks following birth.

Although rudimentary fetal capacities for thyroid hormone signaling exist at a time before the period of viability (~23 weeks' gestation), the emergence of successful neonatal intensive care of "*fetal-neonates*" (ie, ELGANs) at a gestational age where a nearly absolute dependency on maternal thyroid hormone is present in over 50% of neonatal patients, poses a novel risk to the developing brain arising directly from successes of perinatal medicine.

THOP and Iodine Deficiency Compared to Congenital Hypothyroidism vs. Extreme Prematurity. The ELGAN population has a propensity to develop sensorineural hearing loss, visual-spatial deficits; cognitive and neurological dysfunction, and, specifically, spasticity — all arising from brain regions susceptible to deficient thyroid hormone during development. More strikingly, all ELGAN neurodevelopmental outcomes including internalizing (eg, anxiety, sadness), externalizing (e.g. attention, aggression), and autistic behavior scores are analogous to:

i) term neonates with early postnatal congenital thyroid deficiency and

ii) newborns affected by maternal hypothyroidism in the third trimester, especially when due

to endemic iodine deficiency.

These important similarities are thought to arise from *lost* maternal thyroid hormone effects on the fetal brain that occur in women with hypothyroidism during the second-third trimester or an equivalent hormonal deficiency arising from an ELGAN birth. Persistence of an independent effect of thyroid hormone treatment (5.7 and 10 years later) is an important observation since it separates issues of cognitive improvement attributed to subsequent environmental influences, like parenting and socioeconomic status, from those arising entirely from THOP.

Strikingly, there is a stark absence of any properly powered, large-scale RCT to determine whether intervention with thyroid hormone supplementation during THOP can improve patient outcomes.

B) Erythropoietin (Epo) as a Neuroprotectant? The neuroprotective and neuroregenerative effects of high dose Epo are well documented in experimental models of neonatal brain injury. Yet just 2 or 3 phase I/II trials have been published to date, and larger samples are needed. There is a clear potential that Epo's anti-apoptotic, anti-inflammatory, oligodendrocyte protective and neurogenic effects will decrease acute and chronic brain injury and thus improve the neurologic outcomes of ELGANs. It is currently undergoing a large scale, multisite clinical trial as prophylaxis (PENUT Trial; see ClinicalTrials.gov).

C) Magnesium Sulfate in Labor and Postnatal Caffeine Prophylaxis? Currently, the tipping point for the expanded use of magnesium sulfate used for neuroprotection during labor became the standard of care based upon the results of one large-scale RCT in the *New England Journal of Medicine*. The combined primary outcome did not retain long-term significance but its robust effect on CP did. The issue was a proportionately larger number of deaths compared to the N of CP. In a statistical *"thought experiment,"* moving just 2 or 3 cases from one group to the other eliminated its significant effect, raising a concern about how influential some observations can become when using the tyranny of the *P* value without direct inspection of the data in complex clinical questions. In any case, several additional trials confirmed a reduction in CP. Ongoing review of the broad use of magnesium sulfate for this purpose is necessary.

Similar hopes were dashed regarding use of caffeine beginning on postnatal day 1 to improve neurologic outcomes: unfortunately, early improvements faded when examined in long-term outcome studies. The two-year and later follow-ups of the Schmidt trial are nearly identical, but power was lower in the second inspection. Ultimately, this leaves us wondering whether we can truly affect "normal" brain development therapeutically outside the womb.

The Future of Brain Therapies: From a more optimistic perspective, the brain remains actively growing for several years after birth. As such, it is conceivable that eventually, some clinically applicable method to ensure the trajectory of growth of the developing immature brain can be found. The belief is rooted in the premise that this structure remains "*plastic*" and is thus amenable to postnatal influences as already recognized by the impact of socioeconomic status, parenting behavior and even enhanced use of human milk on development. There is a growing emphasis on the first 1,000 days after birth, where exposures — whether social, chemical or physiological — have important effects on improving outcomes. The future, as ever, leaves us with hope that springs eternal.

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REFERENCE

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Further Reading

- Advancing Neurologic Care in the Intensive Care Nursery
- Neonatal Biomarkers of Brain Injury
- Neonatology Review on Facebook
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