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Changing the outcome in genetic brain disorders

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Tuberous sclerosis complex (TSC) has historically been seen as a hopeless and devastating disease against which little could be offered except symptomatic treatment. This is embodied in the classic view that the inevitable hallmarks of TSC are Vogt's triad: intellectual disability, intractable epilepsy, and facial angiofibromas. Even today this perspective is encountered in patients referred for specialist treatment.

In actual fact the majority of people with TSC have a normal full-scale IQ, can have effective control or even freedom from seizures, and live healthy full lives with aggressive and appropriate management of the wide variety of symptoms to which an individual may be subject. For TSC results from hyperactivation of mammalian target of rapamycin (mTOR), a protein kinase that is critical for the growth and development of every organ and tissue in a person's body. Finally, approved mechanistic therapies exist for the most significant manifestations of TSC in the mTOR inhibitors rapamycin and everolimus.

It is axiomatic that the earlier one intervenes in a chronic disorder such as TSC, the greater the impact on the acute and long-term outcome of the disease. Zhang et al.[1] show that, in addition to renal and cardiac involvement, there is a higher risk of perinatal adversity both in infants who have TSC and in pregnant females with TSC, whether their unborn child is affected or not. Wang et al.[2] report improved outcomes in infants with TSC following prenatal or early postnatal diagnosis, apparently as result of subsequent intervention with vigabatrin and/or rapamycin (sirolimus).

Given the critical role of mTOR in fetal and placental development, the findings of increased risk of perinatal adversity are unsurprising and highlight how early the challenges began for children with TSC. Interestingly, this increased adversity did not correlate with worse developmental outcomes. Perhaps because developmental delay and autism are more closely related to the advent of seizures or epileptiform activity on electroencephalogram.[3] A straightforward example of TSC-related perinatal adversity is hemodynamically significant cardiac rhabdomyomas which can cause substantial perinatal morbidity and death. Increasingly, mTOR inhibitors administered to the mother during the last trimester, or shortly after birth, have caused regression of cardiac rhabdomyomas, preventing or minimizing this infrequent but serious clinical problem. Based on multiple case reports, this has been well-tolerated. Treatment can be short term, with no evidence of lesion regrowth.[4]

Zhang et al. report that prenatal or early postnatal diagnosis, followed by treatment with vigabatrin and/or sirolimus, appears to improve developmental outcomes, decrease seizure frequency as well as the incidence of intractable epilepsy. Postnatal treatment was often presymptomatic, i.e. before the onset of clinical seizures or developmental delay. This was not a prospective clinical trial, but a retrospective analysis of what has become widespread practice in China. It nonetheless provides important circumstantial evidence that early and presymptomatic treatment of epilepsy in TSC is associated with improved long-term outcomes and seizure control. This finding is being evaluated prospectively in three randomized clinical trials currently ongoing in the United States and Europe.

These findings offer hope, not only for patients with TSC, but for those with other genetic diseases affecting development. Despite the complexity of the mTOR pathway and much less brain development, these studies typify the promise of proactive and presymptomatic therapy of supposedly 'untreatable' conditions through mechanism-based insights and genetic diagnosis.[6]

DATA AVAILABILITY STATEMENT

Not required

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This commentary is on the original articles by Wang et al. and Zhang et al. on pages 1230–1236 and 1237–1245 of this issue.

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Respiratory morbidity and neurodevelopmental outcomes in infants born preterm: A complex web

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Yu et al. report the identification of distinct early-life longitudinal trajectories of respiratory support that are associated with neurodevelopmental outcomes in infants born preterm.[1] The most widely used marker of respiratory status in the neonatal intensive care unit (NICU), bronchopulmonary dysplasia, is known to correlate with long-term neurodevelopmental outcomes.[2] This study enriches prior work linking respiratory status in the NICU with neurological outcome by incorporating detailed early-life longitudinal data, as well as by using objective clustering analyses, as opposed to expert opinion, to identify distinct groups.

The causal pathways underpinning the relationship between respiratory support in the NICU and neurodevelopmental outcomes are likely to be complex.[3] One possibility is simply that respiratory status acts as a marker of severity of illness, either cross-sectionally or longitudinally, and that its link with neurodevelopment is not of a directly causal nature. A second possibility is that pulmonary and neurological morbidity share common causal antecedents, such as infection, inflammation, or microbiome alterations. Preterm birth itself is of course the most significant common antecedent for both pulmonary and neurological morbidity. Third, pulmonary disease, and the interventions we use to support it, may trigger biological mechanisms that directly contribute to neurological injury. Possible mechanisms could include, but are not limited to, inflammation, intermittent hypoxia, and altered early-life human interactions.[2,4] However, it is probable that all three types of potential causal relationships between respiratory disease and neurological morbidity are at play. The lung-brain axis in infants born preterm is likely a complex web rather than a straightforward pathway.

The current findings reported by Yu et al. identify infants at high risk for neurodevelopmental impairment by 8 weeks of age, based on clinical variables and respiratory trajectory.[1] This risk stratification could facilitate targeted referrals for intensive neurodevelopmental monitoring and intervention, as well as selection of infants for trials of novel interventions. Future research directions could include identification of biomarkers associated with each respiratory trajectory, which could further elucidate the biological mechanisms underlying the associations of the trajectories with neurodevelopmental impairment.

DATA AVAILABILITY STATEMENT

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