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Research Letter

Priorities for Newborn Screening of Genetic Epilepsy

David L. Hess-Homeier, MD [a], Christopher Cunniff, MD [a, b, d], Zachary M. Grinspan, MD, MS [a, b, c, d, *]

[a] Weill Cornell Medical College, New York, New York
[b] Department of Pediatrics, Weill Cornell Medicine, New York, New York
[c] Department of Healthcare Policy & Research, Weill Cornell Medicine, New York, New York
[d] NewYork-Presbyterian Hospital, New York, New York

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Newborn screening is an important tool for secondary prevention of serious morbidity and mortality. Although several metabolic diseases that cause seizures are currently screened, no monogenic epilepsy is on the Recommended Uniform Screening Panel.[1] Importantly, some monogenic epilepsies can be successfully treated when detected early in the newborn period.

To investigate which genetic epilepsies should be prioritized for newborn screening research and development, we interviewed 17 US academic pediatric epileptologists and followed up these interviews with an electronic survey of members of the Pediatric Epilepsy Research Consortium (also all US academic pediatric epilepsy specialists). We asked them to identify which epilepsies best satisfy two conditions for newborn screening: population frequency and benefits of early treatment.

Interviewees identified 16 epilepsies as possible targets for newborn screen development (Table). The most frequently cited were pyridoxine-dependent epilepsy (PDE) and Glut1 deficiency syndrome (Glut1-DS). Each has a specific therapy that improves outcomes.[2,3] Interviewees also identified SCN1A and POLG epilepsies, because early diagnosis would facilitate avoidance of harmful antiepileptic drugs.

Interviewees were enthusiastic about the idea of screening newborns for epilepsy, but many expressed reservations regarding the paucity of disease-modifying therapies. Others expressed reservations about poor genotype-phenotype correlation and the absence of biomarkers suitable for tandem mass spectrometry, the method commonly used for newborn screening.

Of 86 individuals who received the survey, 25 (29%) from 13 states and Washington, DC, responded. When considering the magnitude of potential benefit to an individual child, respondents prioritized Glut1-DS, PDE, and tuberous sclerosis complex (TSC). When considering the potential benefit for overall population health, survey respondents again prioritized Glut1-DS and TSC, and also SCN1A-related epilepsies.

We further evaluated how well these epilepsies meet established newborn screening criteria including incidence, suitable biomarkers, and availability of disease-modifying therapies (Table). We identified PDE, neuronal ceroid lipofuscinosis-2 (NCL-2), and guanidinoacetate methyltransferase (GAMT) deficiency, a cerebral creatine disorder, as most suitable for newborn screening, primarily because of available biomarkers and disease-modifying therapies.[2,4,5]

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* Communications should be addressed to: Grinspan; Room LA 221, 402 East 67th Street; New York, NY 10065.
E-mail address: zag9005@med.cornell.edu (Z.M. Grinspan).

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TABLE.
Interview and Survey Results and Newborn Screening Criteria for Selected Epilepsies

Epilepsy*	Interview Mentions	Survey Ranking (Ind., pop.)†	Incidence‡	Best Available Test or Biomarker	Disease-Modifying Therapy
Glut1 deficiency syndrome	8	4.91, 3.82	<1:90,000	Molecular genetic testing and erythrocyte-based enzyme activity assays	Ketogenic diet
Pyridoxine-dependent epilepsy	10	4.96, 3.41	1:20,000-1:783,000	α-AASA, P6C, and 6-oxo-pipecolate	Pyridoxine; also consider folinic acid, lysine restriction, and arginine supplementation
Tuberous sclerosis complex	2	3.91, 4.14	1:5,800-1:12,000	TSC1 and TSC2 genes	mTOR inhibitors (everolimus), vigabatrin
SCN1A mutations	6	3.70, 3.82	1:20,000-1:40,900§	SCN1A gene	None
POLG-related epilepsies	2	4.30, 3.05	1:10,000	POLG gene	None
Pyruvate dehydrogenase complex deficiency	1	4.26, 2.82	Unknown	Molecular genetic testing and enzyme activity assays	Ketogenic diet
GAMT deficiency	1	4.14, 2.73†	1:114,072-1:250,000	Elevated guanidinoacetic acid in serum and urine	Creatine and ornithine supplementation and arginine restriction
AGAT deficiency	1	4.14, 2.73†	Fewer than 20 cases	Decreased guanidinoacetic acid in serum and urine	Creatine supplementation
Neuronal ceroid lipofuscinosis 2	1	3.09, 2.57	1:11,000-1:450,000	Tripeptidyl peptidase 1 enzyme activity	Intraventricular enzyme replacement (cerliponase alfa)

Abbreviations:
α-AASA = Alpha-aminoadipic semi-aldehyde
AGAT = Arginine:glycine amidinotransferase deficiency
CSF = Cerebrospinal fluid
DEND = Developmental delay, epilepsy, and neonatal diabetes
GAMT = Guanidinoacetate methyltransferase
ind. = Individual
mTOR= mammalian target of rapamycin
P6C = Δ1-piperideine-6-carboxylate
pop. = Population
TSC = Tuberous sclerosis complex

* Other epilepsies mentioned during interviews were nonketotic hyperglycinemia, CACNA1A (idiopathic generalized epilepsy), CSF serine deficiency, DEND syndrome, homocystinuric aciduria, KCNT1-related epilepsy, microdeletion and duplication syndromes (1p36 and dup15q), and Rett syndrome (MeCP2 and CDKL5).

† Epilepsies were ranked using Likert scale. GAMT and AGAT deficiencies were ranked together as "cerebral creatine disorders."

‡ References for disease incidence available by request.

§ Incidence of Dravet syndrome; does not include other SCN1A-associated epilepsies.

There has been some progress toward newborn screening for monogenic epilepsies. Pilot programs for GAMT deficiency have identified a metabolite and screened more than 900,000 newborns, though without finding a single case.[4] For PDE and NCL-2, disease metabolites have been detected in dried blood spots, laying the foundation for studying the feasibility of screening for these epilepsies.[2,5] Additional work is needed to scale these assays and assess their clinical utility.

There are ample opportunities for additional research. Glut1-DS, TSC, pyruvate dehydrogenase complex deficiency, and arginine:glycine amidinotransferase deficiency, another cerebral creatine disorder, have disease-modifying therapies, but lack suitable biomarkers.[3,6-9] Screening for pathogenic variants may be possible, but such methods are currently impractical for population-level deployment. Quantitative polymerase chain reaction assays are used to screen for severe combined immunodeficiency and spinal muscular atrophy, but genetic sequencing is not used in any US newborn screening program.[1] Barriers to using sequencing include economic feasibility and the need to develop effective strategies to report variants of uncertain significance without creating unnecessary anxiety for families.

Although several monogenic epilepsies meet some established criteria for newborn screening, barriers remain. Disease-modifying therapies are available for some epilepsies, but their clinical utility is ill-defined. For others, biomarkers have been identified, but their efficacy for screening is unproven. Also, much remains unknown about the disease spectrum and natural history of these disorders. Despite these limitations, it is important to prioritize newborn screening research for specific monogenic epilepsy syndromes in anticipation of future therapies.

In summary, we have identified PDE, GAMT deficiency, and NCL-2 as future newborn screening candidates, because of the availability of biomarkers. Our findings suggest that Glut1-DS, TSC, arginine:glycine amidinotransferase deficiency, and pyruvate dehydrogenase complex deficiency should be prioritized for biomarker discovery.

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