Rationale

While the majority of neonatal seizures are provoked by acute or structural causes, for some patients, neonatal seizures are heralding signs of genetic epilepsy that can be the start of refractory epilepsy and developmental stagnation. KCNQ2 accounts for the largest subgroup of the genetic epilepsies presenting in the first week of life, and SCN2A may be the second most common. The identification of neonatal-onset epilepsy genes has led to new strategies for targeted therapies aimed both at stopping seizures and improving long-term outcome. ERGENT is a prospective assessment of newly developed clinical criteria for the identification of newborns at high risk for genetic epilepsy, especially those due to variants in KCNQ2 and Na+,1,2 channels.

Methods

This was a prospective observational cohort study (Fig. 1). Eligibility required (1) EEG-proven seizure(s) requiring ongoing seizure medication; (2) early neonatal seizure onset, (<14 days post term); (3) application within 30 days of seizure onset; (4) negative standard-of-care diagnostic evaluation for acute causes of neonatal seizures. Eligible patients, enrolled after parental informed consent, underwent sponsored CLIA-certified next generation sequencing (panel of 186 epilepsy-associated genes, Invitae, SF, CA). Primary outcomes were: fraction of tests performed with positive results, time to events, and correlation of screening subcriteria with genetic test results.

Results

Over 12 months (Aug 2018-Aug 2019), 33 study applications (Fig 2) were received via study website, www.ERGENT.org. Ten were ineligible due to: MRI abnormalities (5), applied too long after seizure onset, seizure onset too late, or incomplete application (3). Of the 23 eligible, 21 were consented and 18 proband genetic epilepsy panels were performed. Three patients left the hospital before testing was done. Of the 18 proband panels, 11 (61%) were diagnostic (Table).

For the 10 patients with KCNQ2/3, mean age at seizure onset, screening by the study, and initial genetic diagnosis of the proband were 2.5, 7.9, and 27.0 days old (Fig 3A, B). Delay from first seizure to screening, from study acceptance to blood collection, and lab turnover were the 3 largest contributors to age at proband diagnosis. Parental testing, needed to establish de novo status, was offered for PVS and VUS. Both parental samples were tested for 6 of 14 eligible patients; for these, the mean proband age at second parental test report was 65 days (Figure 4). On chart review, 1 accepted patient with a negative genetic test had hypocalcemia, an excluding finding not listed on the initial application. Although analysis is ongoing, we have identified no other differences in eligibility criteria between positive and negative test subgroups.

Conclusions

Patients at high risk of neonatal-onset genetic epilepsy, most often but not always due to KCNQ2 variants, can be rapidly identified soon after birth using a brief checklist. The rate-limiting steps to early confirmed diagnosis are early recognition, rapid trio sample collection, and a rapid genetics laboratory workflow. All are feasible. The approach outlined here can enable early referral to trials of candidate treatments for KCNQ2 encephalopathy and other neonatal-onset genetic epilepsies.

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