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Outcome After Therapeutic Hypothermia in Term Neonates With Encephalopathy and a Syndromic Diagnosis

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Abstract
The large randomized, controlled trials of therapeutic hypothermia for hypoxic-ischemic encephalopathy excluded neonates with congenital disorders. The objective of this study was to report our experience using hypothermia in neonates with signs of hypoxic-ischemic encephalopathy and a syndromic disorder or brain anomaly. Subjects were identified from a database of neonates admitted to the Neuro-Intensive Care Nursery at University of California, San Francisco. Of 169 patients fulfilling criteria for hypothermia, 8 (5%) had a syndromic disorder and were cooled per guidelines for nonsyndromic neonates. Perinatal characteristics of infants with and without syndromic disorder were not significantly different. Overall outcome was poor: 38% had evidence of acute hypoxic-ischemic injury, 3 subjects died, and 2 survivors had low developmental quotient (ie, 25). The risk versus benefit of therapeutic hypothermia for hypoxic-ischemic encephalopathy among neonates with congenital brain malformations or syndromic diagnoses is uncertain.

Keywords
hypoxic-ischemic encephalopathy, neonatal encephalopathy, therapeutic hypothermia, cooling, infants with syndromes, congenital abnormalities, neurocritical care

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Hypoxic-ischemic encephalopathy occurs in 1 to 2 per 1000 live births, and is one of the primary causes of long-term neurologic disabilities in children.¹ Therapeutic hypothermia is the only known effective neuroprotective therapy and is standard of care for term neonates with hypoxic-ischemic encephalopathy to reduce death or disability at 18 to 24 months of age.²⁻⁴ The large randomized, controlled trials of hypothermia shared well-defined eligibility criteria, and neonates at risk for adverse outcome independent hypoxic-ischemic encephalopathy (ie, with recognizable congenital anomalies) were excluded. As such, little is known about the outcome of therapeutic hypothermia in term infants with congenital brain anomalies or syndromic disorders and hypoxic-ischemic encephalopathy.

In 2007, our center initiated a therapeutic hypothermia program that did not automatically exclude neonates with congenital brain anomalies or syndromic disorders, as long as they met all other local institutional guidelines for therapeutic hypothermia. The objective of this study was to report our center’s experience with these patients who would not have qualified for the randomized trials.

Methods
Patients who were treated with therapeutic hypothermia were identified from the database of all patients evaluated by the Neonatal Neurocritical Care Service at the University of California San Francisco Benioff Children’s Hospital from July 1, 2008, to July 1, 2011. The UCSF Committee on Human Research approved waiver of consent and data collection.

Eligibility for therapeutic hypothermia were as follows: (1) ≥36 weeks gestational age at birth, (2) moderate to severe encephalopathy within 6 hours of birth, and (3) one or more of the following: cord or first gas pH <7.0, cord or first gas base deficit >12, 10-minute Apgar

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score <5, or prolonged resuscitation. Encephalopathy was defined by altered mental status, abnormal tone or reflexes, absent or weak suck, and/or seizures. Children born at outside institutions were passively cooled during transport. Active whole-body cooling was accomplished via a blanket cooling device (Cincinnati Subzero Blanketrol III, Cincinnati, OH). Core temperatures as measured by a rectal probe were maintained at 33.5°C for 72 hours. Both video electroencephalography (EEG) and amplitude-integrated EEG monitoring were used throughout the duration of cooling and the 24-hour period after rewarming.

Patients with congenital brain anomalies or syndromic disorders were identified on the basis of any one of the following: (1) physical examination findings, (2) genetic, or (3) imaging studies. Medical records were reviewed, including reports from the Intensive Care Nursery Follow Up Program, as well as the Neonatal Neurology Clinic.

Subjects were studied with magnetic resonance imaging (MRI) of the brain at a median of 4 days of life (interquartile range, 4-5) using conventional and diffusion-weighted imaging, as well as magnetic resonance spectroscopy. A pediatric neuroradiologist interpreted all MRI studies.

Outcome was reported using neuropsychological assessment or developmental quotient. For subjects who were able to complete formal neuropsychological testing, the Bayley Scales of Infant Development, 3rd edition, were administered to subjects ≤36 months of age, and the Wechsler Preschool and Primary Scales of Intelligence III were administered to subjects >36 months old. For subjects who could not complete formal testing, a developmental quotient was calculated as the estimated developmental age divided by the chronological age. Outcome was reported as (1) unfavorable, if the subject scored in the bottom 5% on developmental quotients, (2) favorable, if in the borderline to superior range on developmental testing or developmental quotient, or (3) death.

Statistical analyses were performed with Stata software, version 11.1 (Stata Corp, College Station, TX). Clinical characteristics were compared using Fisher exact test for categorical variables, t test for continuous variables, or Wilcoxon rank-sum for nonparametric continuous variables. A P value <.05 was considered significant.

Results

Of 169 eligible participants who met the perinatal criteria for therapeutic hypothermia, 8 (5%) neonates had a congenital brain anomaly or syndromic disorder. The subjects with and without anomalies did not differ with regard to gender, gestational age, birth weight, or other perinatal characteristics at the time of presentation as listed in Table 1.

Subjects with congenital anomalies or syndromic disorders fell into 3 groups: the first group, nonspecific syndromes, contained 2 subjects who had dysmorphic craniofacial features without identified etiology, the second group of isolated brain malformations had 1 subject, and the third group, named syndromes, had 5 subjects.

Overall outcome was poor (Table 2). Six of the 8 subjects had abnormal MRI findings (75%). Four (50%) had brain malformations, whereas the remainder had structurally normal brains. Three subjects (38%) had imaging evidence of acute hypoxic-ischemic injury. The mortality rate was high: 3 subjects (38%) died in the neonatal period. Of the survivors, 4 were seen at a median age of 26 months (interquartile range = 24-40), 3 with unfavorable outcome as detailed below.

### Table 1. Clinical Characteristics of 169 Subjects With Hypoxic-ischemic Encephalopathy Who Were Treated With Therapeutic Hypothermia.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Syndromic disorder (n = 8)</th>
<th>No syndromic disorder (n = 161)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>5 (64%)</td>
<td>78 (48%)</td>
<td>.5</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>38.8 ± 2.0</td>
<td>39.5 ± 1.5</td>
<td>.2</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3121 ± 468</td>
<td>3297 ± 599</td>
<td>.4</td>
</tr>
<tr>
<td>Emergent cesarean section</td>
<td>6 (75%)</td>
<td>90 (56%)</td>
<td>.5</td>
</tr>
<tr>
<td>Apgar score at 5 min</td>
<td>3 (1.5-4)</td>
<td>3 (2-5)</td>
<td>.4</td>
</tr>
<tr>
<td>Cord or first arterial pH</td>
<td>7.02 ± 0.2</td>
<td>6.99 ± 0.2</td>
<td>.7</td>
</tr>
</tbody>
</table>

*There were no differences between subjects with and without a congenital brain anomaly or syndromic disorder. Data are presented as n (%), median (interquartile range), or mean (± standard deviation).

### Nonspecific Syndrome

Two of the neonates had a nonspecific syndromic disorder identified at the time of birth based on dysmorphic features. In both subjects, no underlying etiology was found.

For the first patient, dysmorphic features (low anterior hair line, bitemporal narrowing, posteriorly rotated ears, midfacial hypoplasia, upturned nose with a deformed nasal bridge, broad-spaced nipples, and hypoplastic nails with fifth toe clinodactyly) were noted at birth, and he was seen in consultation by the genetics service on the day of birth. EEG, MRI, and high-resolution chromosomes were normal. At 28 months of age, Bayley Scales of Infant Development, 3rd edition, composite cognitive score was in the very superior range (140), and language and motor function were average (97 and 103).

In the second patient, dysmorphic features (midface hypoplasia and bulbous nose) were noted on admission, and she was seen in consultation by the genetics service on the third day of life. EEG was abnormal because of mild diffuse voltage attenuation. MRI and high-resolution chromosomes were normal. Her last evaluation was in the intensive care nursery at 11 days of life, with neurologic examination notable for mild axial hypotonia and monophasic moro reflex.

### Isolated Brain Malformation

One subject was diagnosed with a brain malformation. Neurosonogram on the second day of life showed a small cerebellum; pontocerebellar hypoplasia was confirmed by MRI. The EEG was abnormal because of excess discontinuity. On the fourth day of life, the parents opted to transition care to palliative measures, and the patient died shortly thereafter.

### Named Disorder

In 5 subjects, a named disorder was identified: Treacher Collins, Emanuel, Joubert Plus, and Wiedemann-Steiner syndromes, and presumed congenital myotonic dystrophy. Craniofacial features consistent with Treacher Collins syndrome were noted in this patient at birth. MRI showed
Table 2. Clinical Characteristics and Outcome of 8 Subjects Who Had Congenital Brain Anomaly or Syndromic Diagnosis and Underwent Therapeutic Hypothermia.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Birth history</th>
<th>Conventional MRI</th>
<th>DWI</th>
<th>MRS</th>
<th>EEG</th>
<th>Length of stay (d)</th>
<th>Age at follow up (mo)</th>
<th>G-tube</th>
<th>Post neonatal seizures</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonspecific syndrome</td>
<td>• 40 wk 4 d&lt;br&gt;• Emergent C/S for prolonged decelerations (nuchal cord)&lt;br&gt;• Apgars 1/2/4&lt;br&gt;• UV 7.26/-8&lt;br&gt;• Postresuscitation examination: encephalopathy, hypotonia, and depressed primitive reflexes</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>11</td>
<td>28</td>
<td>No</td>
<td>No</td>
<td>Favorable Bayley 3rd ed</td>
</tr>
<tr>
<td>Nonspecific syndrome</td>
<td>• Estimated 36 wk&lt;br&gt;• Emergent C/S for decelerations (uterine rupture)&lt;br&gt;• Apgars 0/3/4&lt;br&gt;• UA 6.77/-17&lt;br&gt;• Postresuscitation examination: irritable, hyperalert, ventilated, intact primitive reflexes</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Mild diffuse voltage attenuation</td>
<td>9</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td>Isolated brain malformation</td>
<td>• 38 wk 6 d&lt;br&gt;• C/S for breech presentation&lt;br&gt;• Apgars 2/4/5&lt;br&gt;• No cord gas&lt;br&gt;• Postresuscitation examination: unresponsive neonate, intubated and ventilated, generalized hypotonia, absent reflexes</td>
<td>Pontocerebellar hypoplasia and decreased white matter volume</td>
<td>Normal</td>
<td>Diminished NAA, and increased lactate</td>
<td>Excess discontinuity</td>
<td>Excess discontinuity</td>
<td>Excess discontinuity</td>
<td>Excess discontinuity</td>
<td>Deceased</td>
<td></td>
</tr>
<tr>
<td>Treacher Collins syndrome</td>
<td>• 40 wk 1 d&lt;br&gt;• SVD&lt;br&gt;• Multiple intubation attempts at birth failed, no stable heart rate until 40 min of life&lt;br&gt;• Apgars 2/1&lt;br&gt;• First gas pH was 6.7/-26&lt;br&gt;• Postresuscitation examination: no spontaneous movements, profound hypotonia, minimal response to painful stimuli</td>
<td>T1 shortening in the depths of central sulci and insula bilaterally</td>
<td>Reduced diffusion in central sulci, insula, and deep gray nuclei bilaterally</td>
<td>Small lactate peak in basal ganglia</td>
<td>Excess discontinuity</td>
<td>Excess discontinuity</td>
<td>Excess discontinuity</td>
<td>Excess discontinuity</td>
<td>Deceased</td>
<td></td>
</tr>
<tr>
<td>Emanuel syndrome</td>
<td>• 37 wk 2 d&lt;br&gt;• C/S for failure to progress and abruption&lt;br&gt;• Apgars 1/3/7&lt;br&gt;• First gas 7.0/-22&lt;br&gt;• Postresuscitation examination: encephalopathic neonate with hypotonia and hyperreflexia</td>
<td>Cerebellar hypoplasia, diffusely hyperintense white matter on T2 and 2 punctate foci of T1 shortening in the left periventricular white matter</td>
<td>Normal</td>
<td>Reduced metabolite peaks in white matter</td>
<td>Asymmetric voltage attenuation</td>
<td>118</td>
<td>24</td>
<td>Yes</td>
<td>No</td>
<td>Unfavorable DQ</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Birth history</td>
<td>Conventional MRI</td>
<td>DWI</td>
<td>MRS</td>
<td>EEG</td>
<td>Length of stay (d)</td>
<td>Age at follow up (mo)</td>
<td>G-tube</td>
<td>Post neonatal seizures</td>
<td>Outcome</td>
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<tr>
<td>Joubert Plus syndrome</td>
<td>• 40 wk 2 d</td>
<td>Hypoplastic superior vermis with midline cleft, thickened/dysplastic inferior medulla and midbrain with thickening and horizontal course of the superior cerebellar peduncles (ie, “molar tooth” appearance); diffuse supratentorial polymicrogyria</td>
<td>Reduced diffusion in the right occipital lobe</td>
<td>Normal</td>
<td>Excessive discontinuity</td>
<td>48</td>
<td>24</td>
<td>No</td>
<td>Yes</td>
<td>Unfavorable</td>
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<td></td>
<td>• Emergent C/S maternal eclampsia and prolonged fetal bradycardia during and after a maternal seizure</td>
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<td></td>
<td>• Apgars 0/0/2</td>
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<td></td>
<td>• UA 7.0/-11</td>
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<td></td>
<td>• Postresuscitation examination: responsive neonate, intubated and ventilated, with exaggerated tendon reflexes and depressed primitive reflexes</td>
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<tr>
<td>Wiedemann-Steiner syndrome</td>
<td>• 41 wk 2 d</td>
<td>Global, symmetric reduced white matter volume; focal T1 shortening in the right posterior putamen</td>
<td>Normal</td>
<td>Normal</td>
<td>Discontinuous with low-amplitude bursts and prolonged interburst intervals</td>
<td>81</td>
<td>51</td>
<td>No</td>
<td>No</td>
<td>Unfavorable WPPSI-III</td>
</tr>
<tr>
<td></td>
<td>• Emergent C/S for decelerations</td>
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<td></td>
<td>• Apgars 2/6/7</td>
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<td></td>
<td>• UA 6.9/-13</td>
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<tr>
<td></td>
<td>• Postresuscitation examination: encephalopathic infant with truncal hypotonia and depressed primitive reflexes</td>
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<tr>
<td>Myotonic dystrophy (presumed)</td>
<td>• 35 wk 5 d</td>
<td>Simplified sulcation, and cerebellar hypoplasia</td>
<td>Reduced diffusion in the periventricular white matter</td>
<td>Normal</td>
<td>Burst suppression and electrographic seizures</td>
<td>4*</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Deceased</td>
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<td></td>
<td>• C/S decreased fetal movements</td>
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<td></td>
<td>• Apgars 1/4</td>
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<td></td>
<td>• UA 7.38/–2</td>
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<tr>
<td></td>
<td>• Postresuscitation examination: minimally responsive neonate, intubated and ventilated, with hypotonia and absent reflexes</td>
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Abbreviations: Bayley, Bayley Scales of Infant Development; DQ, developmental quotient; MRS, magnetic resonance spectroscopy; DWI, diffusion-weighted imaging; C/S, cesarean section; UA, umbilical artery; UV, umbilical vein; WPPSI-III Wechsler Preschool and Primary Scale of Intelligence III.

*Also age at death.
abnormal areas of T1 shortening and reduced diffusion in the depths of the central sulci, posterior insula, and deep gray nuclei bilaterally in keeping with acute hypoxic-ischemic injury. Because of brain injury and medical need for tracheostomy, the parents opted to transition care to palliative measures and the patient died shortly thereafter.

For the patient with Emanuel syndrome, dysmorphic craniofacial features were noted at birth (bilateral absence of the ears, retrognathia, mandibular hypoplasia, multiple auricular pits, cleft chin, and right facial paresis) and he was evaluated by the genetics service on the second day of life. MRI showed diffuse hyperintensity of the white matter and low metabolite peaks, and 2 areas of focal, noncystic white matter injury. Comparative genomic hybridization array in the neonatal period showed findings that were in keeping with Emanuel syndrome. At 24 months of age, the patient had minimal to no expressive language and inability to maintain sitting position for prolonged times (developmental quotient ~ 25).

For the patient with Joubert Plus syndrome, congenital brain malformation was suspected on fetal ultrasound and confirmed by fetal MRI, which demonstrated cerebellar vermian hypoplasia with thickened cerebellar peduncles (“molar tooth” sign), and polymicrogyria. Dysmorphic craniofacial features (hypertelorism, broad nasal bridge, and unilateral coloboma) and preaxial polydactyly were noted at birth. Postnatal MRI confirmed the malformations that were noted on the fetal study, and also showed a focal area of reduced diffusion within the right occipital lobe. At 24 months of age, the patient had minimal expressive language and sits with assistance (developmental quotient ~ 25).

The patient with Wiedemann-Steiner syndrome was not evaluated by the genetics service until 1 month, when the primary team felt that poor feeding that was out of keeping for the degree of hypoxia-ischemia, and also noted dysmorphic craniofacial features. She was initially thought to have Cornelia de Lange syndrome based on her craniofacial features; however, genetic testing at age 6 confirmed Wiedemann-Steiner syndrome. The MRI showed global volume loss with marked symmetric white matter loss and a focal area of T1 shortening within the right posterior putamen, consistent with chronic hypoxic-ischemia.

Discussion

Among 169 infants treated with therapeutic hypothermia, we identified 5% who would have been excluded from the randomized, controlled trials because of dysmorphic craniofacial features, a syndromic diagnosis, and/or congenital brain anomaly. Six of the 8 subjects (75%) had a suspected underlying diagnosis at the time of the decision to proceed with therapeutic hypothermia. All subjects qualified for therapeutic hypothermia based on Apgar scores, pH or base excess, or need for prolonged resuscitation, as well as neurologic examination indicating encephalopathy. It is not known whether resuscitation or examination features were affected by underlying diagnosis such that the patient appeared to qualify for hypothermia but was presenting signs or symptoms of the syndrome rather than hypoxic-ischemic injury. Three subjects (38%) were deceased in the neonatal period, and 3 of 5 survivors had an unfavorable developmental outcome.

The large randomized, controlled trials of therapeutic hypothermia for perinatal hypoxic-ischemic encephalopathy excluded subjects with recognizable congenital anomalies. The reason for excluding these subjects from the trials is 2-fold. First, syndromic diagnoses and congenital anomalies often confer a risk for adverse developmental outcome that is independent of hypoxic-ischemic injury. Several large studies indicated that restricted growth and/or congenital anomalies are important risk factors for death and cerebral palsy. Second, it may be impossible to distinguish neonates with encephalopathy due to hypoxic-ischemic brain injury, from those with abnormal neurologic examination due to underlying congenital anomalies. Badawi et al examined a large cohort of term infants with moderate or severe encephalopathy in Western Australia, and found birth defects among 23.2% of affected infants. In a separate study, the same group and found a strong association between birth defects and encephalopathy: birth defects were found in 27.5% of neonates with encephalopathy, as compared with only 4.3% of those without. The birth defect was considered the probable cause of the encephalopathy in only 36%, suggesting that other causes of encephalopathy, such as hypoxia-ischemia, may be more common in the setting of birth defects. As such, it is impossible to know whether the abnormal neurologic findings among the subjects presented here was due to the underlying anomaly or due to acute brain injury. In all cases, the attending neonatologist and/or neurologist decided that the potential benefit of therapeutic hypothermia outweighed the risks.

Our study is limited by a relatively small sample size and retrospective design. Furthermore, follow up was variable among subjects. Finally, we were not able to capture subjects that were not cooled, either by our center or outside referral centers, so we cannot determine the true proportion of neonates that may present with both signs of hypoxic-ischemic encephalopathy and findings that suggest a syndromic diagnosis.

In conclusion, the risk versus benefit of therapeutic hypothermia for neonates with congenital brain anomalies and syndromic disorders who present with signs of perinatal
asphyxia is uncertain. Larger numbers of cases from multiple institutions or a randomized, controlled trial will be necessary to better understand and standardize an approach to these patients, especially considering the lack of other therapeutic interventions.

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Author Contributions
AM and HCG collected data, performed data interpretation, and wrote the first draft of the manuscript. SLB collected data and, along with TKS, assisted with data interpretation. EER provided oversight for follow-up data collection and interpretation. HCG mentored the first author. SLB, EER, TKS, and HCG cared for the patients. All authors approved the final version.

Author Note
This work was presented at the Pediatric Academic Societies’ Annual Meeting, Vancouver, Canada, May 3-6, 2014.

Declaration of Conflicting Interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval
The UCSF Committee on Human Research approved waiver of consent and data collection (IRB# 10-02694).

References