A R T I C L E

Management of Children With Holoprosencephaly

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Holoprosencephaly (HPE) is the most common malformation of the embryonic forebrain in humans. Although HPE occurs along a continuous spectrum, it has been categorized into four types from most severe to least severe: alobar, semilobar, lobar, and middle interhemispheric (MIH) variant. Facial malformations are often associated with HPE and usually correlate with the severity of brain malformation. With the most severely affected newborns, there is a high mortality rate in the first month of life, however, with milder forms of HPE, the majority survive beyond infancy. The Carter Centers for Brain Research in Holoprosencephaly and Related Malformations have enrolled 182 living children in a prospective research study. Based on previously published reports using this database, reports from other investigators, as well as our experience and personal observations, the range of developmental, neurological, and medical problems found in children with HPE is described in this article. Virtually all children with HPE have some developmental disability and the severity correlates with the severity of the brain malformation on neuroimaging. Common medical problems include hydrocephalus, seizures, motor impairment, oromotor dysfunction with risk of poor nutrition and aspiration, chronic lung disease, gastroesophageal reflux, constipation, hypothalamic dysfunction with disturbed sleep–wake cycles and temperature dysregulation, as well as endocrine dysfunction. Diabetes insipidus in particular is found in about 70% of children with classic HPE. Recommendations for management of these problems are given based on experiences of the authors and familiarity with the literature. © 2010 Wiley-Liss, Inc.

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INTRODUCTION

Holoprosencephaly (HPE) is the most common malformation of the embryonic forebrain (prosencephalon) seen in humans, occurring in approximately 1 in 250 embryos [Matsunaga and Shiota, 1977], and about 1 in 10,000 births [Croen et al., 1996; Rasmussen et al., 1996; Ong et al., 2007; Orioli and Castilla, 2010]. HPE results from a primary defect of induction and patterning that leads to partial or complete failure of division of the prosencephalon

into two separate hemispheres between the 18th and 28th day after conception [Golden, 1999]. Both genetic and environmental factors play a role in the process of abnormal midline division, which is described elsewhere in this issue. HPE has traditionally been categorized into three classic types, as originally described by DeMyer, ranging from most severe to least severe: alobar, semilobar, and lobar [DeMyer and Zeman, 1963]. With alobar HPE, there is a monoventricle and no interhemispheric fissure. With semilobar HPE, there is partial separation of the hemispheres posteriorly, and with lobar HPE there are almost fully developed cerebral hemispheres, but with some continuity across the frontal cortex. The middle interhemispheric variant of HPE (MIH), which has been more recently described, involves failure of separation of the posterior frontal and parietal lobes and is the least severe form [Lewis et al., 2002; Simon et al., 2002; Hahn and Barnes, 2010]. HPE should be viewed as

a brain malformation with a continuous spectrum of anomalies ranging from the most severe (alobar) form to the milder forms of lobar and middle interhemispheric variant types of HPE.

HPE is associated with a spectrum of midline facial anomalies whose severity typically corresponds with the severity of the brain malformation, which gave rise to the aphorism "the face predicts the brain" [DeMyer et al., 1964], although this does not hold true in a substantial minority of cases [Cohen, 1989; Olsen et al., 1997; Plawner et al., 2002]. The most severe facial malformations such as cyclopia (ranging from a single midline eye to the fusion of two eyes in a single midline orbit), ethmocephaly (close-set eyes with a tube-like nose), and cebocephaly (close-set eyes and a nose with a single nostril, but no lip cleft) are only seen with alobar HPE [Cohen, 1989]. Milder facial malformations can be seen with all types of HPE and include findings such as median cleft lip and palate (premaxillary

agenesis), midface hypoplasia and hypotelorism, congenital nasal pyriform aperture stenosis, and single maxillary central incisor [Ming and Muenke, 1998]. Even children with alobar HPE can have minimal or no facial malformation [Solomon et al., 2010].

The authors of this article are clinicians and researchers in the Carter Centers for Brain Research in Holoprosencephaly and Related Malformations (www.stanford.edu/group/hpe), a national consortium of five institutions that have been studying living children with HPE over the past 11 years. Three of the Carter Centers (Kennedy Krieger Institute in Baltimore, Maryland; Texas Scottish Rite Hospital in Dallas, Texas; and Lucille Packard Children's Hospital of Stanford University) have collaborated on an IRB-approved International Database study to evaluate clinical outcomes in children with HPE. Each child has a brain scan evaluated by our neuroradiology group with confirmation of HPE diagnosis, determination of HPE type, and grading of various structures involved. Each child is also clinically evaluated at one of the Carter Centers, at which time the database questionnaire is completed. A number of studies of children of HPE using the Carter Center database have been published. A more complete description of the database study is available in the article by Plawner et al. [2002]. Of the 182 children (107 female, 75 male) with HPE enrolled in our database study to date, 15% have alobar, 54% semilobar, 18% lobar, and 15% MIH type HPE. In a review of evaluation and management of HPE, Hahn and Plawner [2004] from the Carter Centers previously summarized many of our findings, describing the variety of medical problems seen in children with HPE, including craniofacial malformations, hydrocephalus, seizures and epilepsy, motor and developmental dysfunction, oromotor dysfunction, and hypothalamic and endocrine dysfunction. A group at the Rennes University Hospital Center in France has also studied a large number of children with HPE, and their findings have been similar to ours [Lazaro et al., 2004; Dubourg et al., 2007]. The

purpose of this article is to give an updated review of outcomes and common medical problems found in children with HPE, with recommendations for management. We present data and findings from previous studies, but also include some more recent data and observations from the Carter Center database where appropriate, as well as recommendations based on the authors' personal experience in treating children with HPE.

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OUTCOMES

Survival

Overall, mortality is high for newborns with HPE, however, some patients will survive beyond the neonatal period, with smaller numbers surviving for many years. Of 24 liveborn infants with HPE in the North of England between 1985 and 1998, 33% died within the first 24 hr and 58% died within the first month, yet 29% survived the first year [Bullen et al., 2001]. Higher

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mortality correlates with several factors, including the severity of brain malformation, the severity of facial malformation, the presence of chromosomal abnormalities, and the presence of a multiple congenital anomaly syndrome or other organ involvement [Whiteford and Tolmie, 1996; Olsen et al., 1997; Bullen et al., 2001]. Mason and Barr found in their study of 62 children with alobar HPE, that those with more severe facial malformations such as cyclopia, ethmocephaly, and cebocephaly have very limited survival, rarely surviving beyond the first week of life. Of children with alobar HPE and mild or no facial malformations, about 50% died by 4–5 months of age, but 20–30% lived beyond 1 year of age [Mason and Barr, 1999]. Children with isolated HPE (nonchromosomal and nonsyndromic) tend to have the best survival. In a study of 82 infants with HPE born in New York State between 1984 and 1989, 57% of newborns with syndromal HPE died within the first 2 days after birth, while 54% of children with isolated HPE survived beyond the first year of life [Olsen et al., 1997].

In one of our previous studies, we reported that the mean age of participants was 4 years and that 15% of children with HPE were between 10 and 19 years of age. The mean age of children with alobar HPE was 2 years [Stashinko et al., 2004]. Children with alobar HPE as a group have the highest mortality, while children with milder forms of HPE, that is, lobar HPE and MIH type HPE, should be expected to live for many years. Although survival is associated with the severity of brain malformation, there is still significant variability in survival within each type of HPE. Some children with isolated alobar HPE will survive into adolescence and even into adulthood. Survival of children with semilobar HPE is intermediate between alobar and lobar HPE, with

some early mortality in the first few months of life, though the majority live into childhood. For children with semilobar HPE who survive beyond the first year, there is an ongoing small but not insignificant risk of mortality that is affected by the multiple problems associated with HPE, including impaired mobility, risk of aspiration, epilepsy, temperature instability, and endocrine dysfunction.

Developmental Outcomes

Developmental disabilities are present in virtually all children with HPE. The degree of developmental disability generally correlates with the severity of the brain malformation on neuroimaging. Children with alobar HPE make minimal developmental progress and generally have profound global impairments. They can develop some skills, although never achieve milestones beyond those of an early infant. In our previous study, none of the children with alobar HPE were able to sit independently, reach and attain objects, or utter words [Plawner et al., 2002]. Some could bat at objects. Most children with alobar HPE can hear and some will react to sounds, for example, by turning their head. Most children with alobar HPE who do not have ocular malformations have some vision and can focus on faces or nearby objects, and some of these children will develop the ability to track objects and respond to facial expressions [Barr and Cohen, 1999].

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Because children with semilobar HPE tend to have severe motor impairment, speech is significantly impaired and typically does not develop beyond a few consonant-vowel vocalizations or single word approximations, even among the older children [Roesler et al., 2006]. Many children with semilobar HPE can learn to communicate through eye gaze, gestures, picture-based communication systems or augmentative communication devices. Of 30 patients with semilobar HPE in our study, 4 had mildly impaired to normal hand function and 2 could speak in multiword sentences [Plawner et al., 2002].

Children with lobar HPE have much better development of motor skills. About one-half have mildly impaired to normal hand function, are able to walk independently or with assistance, and speak single words or multiword sentences [Plawner et al., 2002]. Compared with lobar HPE, children with MIH type HPE have somewhat better hand/arm function and speech and similar mobility [Lewis et al., 2002].

Because of the severe motor and expressive language impairment seen in many children with HPE, their cognitive development cannot be assessed by traditional tests. The Carter Neurocognitive Assessment (CNA) was developed in order to minimize the impact of motor and expressive language impairment on performance and can be used to quantify a range of skills reflecting a cognitive level up to 18−24 months [Leevers et al., 2005]. The CNA has been useful for evaluating abilities in children with HPE, although children with milder forms of HPE often have skills beyond its ceiling level. It was found that social awareness is an area of strength for children with HPE and that most are very socially engaging and respond positively to faces and voices. Educational and therapeutic activities should utilize eye gaze as a primary communicative response and should

focus on the child's ability and desire to engage socially with others [Roesler et al., 2006].

COMMON MEDICAL PROBLEMS AND MANAGEMENT

Hydrocephalus

About one-sixth of children with HPE in our database have had a cerebrospinal fluid (CSF) shunt placed for treatment of hydrocephalus. Children with alobar HPE are more likely to need a shunt than children with other types of HPE. The presence of a dorsal cyst is strongly correlated with lack of separation of the thalami and development of hydrocephalus. It is hypothesized that thalamic nonseparation blocks CSF egress from the third ventricle [Simon et al., 2001].

The challenge in evaluating children with HPE for hydrocephalus is trying to distinguish large CSF spaces from hydrocephalus with increased intracranial pressure. Children with HPE and a dorsal cyst should be followed closely for hydrocephalus. Virtually all children with HPE who do not have hydrocephalus will have microcephaly. A child with HPE and normal head circumference or macrocephaly suggests the presence of increased intracranial pressure. If hydrocephalus is suspected, clinicians can follow serial head circumferences and head ultrasounds. If a child has macrocephaly or their head circumference increases in percentiles over time, then consideration should be given to placing a CSF shunt. We have also had a few cases in which a child with semilobar HPE who was making developmental progress began losing milestones and demonstrated increased oropharyngeal dysphagia. These patients responded to CSF shunting with improvement in development and swallowing. Besides the potential for a better developmental and functional outcome, placing a shunt for treatment of hydrocephalus will help in avoiding a proportionally large head that makes the child difficult to position and care for. Treating hydrocephalus can also reduce irritability. When placing a shunt, the

neurosurgeon also needs to consider the possibility of overdrainage with development of subdural fluid collections. Use of an adjustable valve can allow for the gradual reduction of intracranial pressure without additional surgery and allow the pressure to be individualized for each child, minimizing the risks of overdrainage.

Seizures and Epilepsy

About one-half of children with HPE have had at least one seizure, and epilepsy requiring treatment with antiepileptic medication occurs in only about 40% (73/182) of children with HPE enrolled in the Carter Center database. Onset of seizures is usually during infancy. While a variety of seizure types affect these children, complex partial seizures are the most common type (43%). Although children with alobar HPE have significant disabilities, it may surprise some that only 56% of these children require treatment for epilepsy. Intractable seizures are seen in about one-third of patients with HPE who have epilepsy, and seem to occur more often in patients with more significant cortical malformation.

Most children with HPE do not have epilepsy. Of the ones who do have epilepsy, most can be treated with a single antiepileptic medication such as carbamazepine or levetiracetam. A smaller group may require the addition of second line agents such as topiramate, zonisamide, or lamotrigine for treatment of refractory epilepsy. Some children with refractory epilepsy respond well to high dose phenobarbital. We have treated a few patients successfully by pushing phenobarbital levels to the high 50 mcg/ml without apparent adverse effects. The detrimental cognitive effects of phenobarbital may be more acceptable in children with alobar HPE who have minimal function at baseline.

As with other children, seizures can be triggered by hypoglycemia or fluid and electrolyte disturbances, especially rapid fluctuations in sodium level or significant dehydration. Hyponatremia as an iatrogenic consequence of treatment of diabetes insidipus has been the precipitant of seizures in some children who have never had seizures before. It is important to remember that some antiepileptic medications can have effects on blood sodium level. Carbamazepine and oxcarbazepine augment release of antidiuretic hormone and tend to cause hyponatremia in normal children. These affects can be used to the advantage of the child with HPE who also has diabetes insipidus and elevated sodium levels at baseline.

Motor Impairment

Abnormal muscle tone and impaired coordination are seen to some extent in virtually all children with HPE, although some children with MIH and lobar HPE seem to have minimal motor impairment. Most children with HPE can be said to have cerebral palsy. Mixed patterns are common, with many children showing truncal hypotonia, dystonia of the upper extremities and more spasticity of the lower extremities. Hypotonia in infancy can progress to spasticity and/or dystonia as the child grows and develops.

As with other children with cerebral palsy, children with HPE may benefit from physical and occupational therapy, bracing, and in some cases, orthopedic surgery. A number of patients with severe spasticity and/or dystonia have benefited tremendously from placement of intrathecal baclofen pumps. For treatment of dystonia, we have used oral trihexyphenidyl with some success, including improved oromotor and upper extremity function. Trihexyphenidyl, an anticholinergic drug which crosses the blood–brain barrier, is available as a 2 mg/5 ml elixir and most older infants can be started at 1 ml (0.4 mg) three times daily. The dose can be escalated, monitoring for adverse effects with each increase in dose, up to a maximum of about 2 mg/kg/day. Common adverse effects of trihexyphenidyl include those typical of anticholinergic medications such as dry mouth, dry eyes, constipation, decreased sweating, and potential for overheating. Trihexyphenidyl can exacerbate acute narrow-angle glaucoma and should not be used in patients at risk. Some patients with HPE have stopped the medication because of increased hyperkinetic movements or a significant change in behavior.

Oromotor Dysfunction, Feeding and Nutrition

Children with more severe motor impairment tend to have more severe impairment of swallowing function, so some swallowing problems are seen in almost all children with alobar and semilobar HPE. About two-thirds of these children have required placement of a gastrostomy tube because of risk of aspiration or inadequate oral intake. Common symptoms of oropharyngeal dysphagia include choking, coughing, or gagging with feeds or increased respiratory symptoms following feeds, such as wheezing, coughing, and increased secretions. Problems in coordinating suck and swallow can lead to aspiration of food and secretions into the airway. Penetration and aspiration of food below the vocal cords can be documented by videoflouroscopic swallow study. Children with impaired swallowing are at risk for acute aspiration pneumonitis as well as development of chronic lung disease. Recurrent micro-aspiration can lead to chronic lung disease without a history of acute aspiration events. Children with oromotor dysfunction have a more difficult time managing their secretions when they have increased secretions and nasal congestion due to a viral respiratory infection, making them more susceptible to severe illness with common viral infections, such as influenza. Children without frank aspiration may have oromotor difficulties that make feeding slow and laborious, leading to poor oral intake and failure to thrive.

Besides oromotor dysfunction, facial anomalies such as cleft lip and palate and congenital nasal pyriform aperture stenosis contribute to feeding problems as well. Nurses experienced in feeding infants with cleft lips and palates may be able to offer some guidance. Special nipples designed for children with cleft palates may also help. Some of

these children may need a gastrostomy tube.

Children with HPE tend to be small for a number of reasons, including nutritional and hormonal causes, so their weight may be low for age, but may be appropriate for their height. When evaluating nutritional status, it is important to look at weight for height centile or body-mass index centile for age. For tube fed patients, it is the primary author's practice to set a goal to keep the weight-for-height of patients with HPE between the 10th and 25th centiles.

Pulmonary Issues

As mentioned above, children with HPE and oromotor dysfunction are at risk for aspiration and development of recurrent respiratory problems and/or chronic lung disease. Children with HPE can also have upper airway obstruction due to facial anomalies. Some children with HPE and facial anomalies have had a tracheostomy tube placed during the neonatal period for treatment of upper airway obstruction. Central apnea can be present in those more severely affected and, in children with alobar HPE, likely contributes significantly to the high mortality during the first few months of life.

Symptoms of chronic lung disease can include chronic cough, recurrent wheezing, and eventually low oxygen saturations at baseline. Children with chronic lung disease have less pulmonary reserve and are more susceptible to severe pneumonia when they do become ill. Children with HPE can be treated similarly to children with cerebral palsy in regards to pulmonary management. Inhaled beta-agonists such as albuterol and inhaled steroids can be used to treat bronchospasm and chronic inflammation. Because of motor impairment, clearance of airway secretions is often poor. Suctioning and chest physiotherapy can be helpful. Some children have benefited greatly from physiotherapy vests that utilize high frequency chest wall oscillation (e.g., The Vest Airway Clearance System) for improved mobilization and clearance of secretions. Children with HPE should have yearly

influenza vaccination starting at 6 months of age and administration of the 23-valent pneumococcal vaccine (Pneumovax) should be considered after 2 years of age.

Gastrointestinal Problems

As with children with cerebral palsy and other neurodevelopmental disabilities, gastrointestinal problems are common in children with HPE. In general, the GI tract is normal, however, patients have functional GI disorders including poor gastric emptying, gastroesophageal reflux, and constipation, presumably due to abnormal regulation by the nervous system. Use of H2 blockers or proton-pump inhibitors to suppress acid production is appropriate. Use of a prokinetic to improve gastric emptying can also be helpful, however, clinicians need to use caution in prescribing metoclopramide (Reglan) as it can be associated with significant adverse effects, including exacerbating dystonia, seizures, and irritability. Low-dose erythromycin can be used as a prokinetic and may improve gastric emptying and reflux. With children who are tube fed, adjusting the rate, volume and schedule of tube feedings can help with feeding tolerance, as can selection of formula. Some children do not tolerate feeds when asleep, while others do. Slowing the rate down can improve comfort and GERD. If reflux continues to be a problem despite medical management, an anti-reflux procedure such as Nissen fundoplication or gastrojejunostomy tube placement can be considered. Frequent venting of air through the gastrostomy tube can help reduce distension and irritability due to excessive air swallowing. Simethicone drops may be helpful and are a relatively benign intervention. Constipation can be exacerbated by poor fluid intake or relative dehydration due to diabetes insipidus. More aggressive treatment of constipation can also decrease reflux, distension, and irritability. Often a combination of polyethylene glycol 3350 (Miralax) and rectal suppositories is effective.

Hypothalamic Dysfunction

The hypothalamic nuclei play an important role in homeostasis and in regulating important bodily functions such as sleep, temperature, appetite, and thirst. Hypothalamic nonseparation by imaging correlates with hypothalamic dysfunction in children with HPE [Plawner et al., 2002]. Abnormal sleep–wake cycles, temperature instability, and impaired thirst mechanisms are common in children with HPE.

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Altered and erratic sleep–wake cycles are common in children with HPE, with various patterns observed, including day–night reversal, fragmented sleep patterns with children only sleeping for a few hours at a time, reduced need for sleep, and increased need for sleep. As these problems can be very frustrating for parents and caregivers and contribute to caregiver burden, they should not be taken lightly. Parents are instructed in good sleep hygiene including setting a regular bedtime for their child, and minimizing light and loud noises. Melatonin is a naturally occurring hormone that is important for regulation of the sleep–wake cycle. It is available as an over-the-counter nutritional supplement in the U.S. We often trial patients on a 1-month course of melatonin before trying other medications, typically recommending a 1–5 mg dose 30–60 min before bedtime. Some children have a dramatic response to melatonin, while others do not seem to respond at all. Antiepileptic medications, tone medications, and other sedating medications can be adjusted to give a larger dose at bedtime, using their sedative effects to

aid with sleep. While chloral hydrate and diazepam may help, these medications may become habit forming and after prolonged use often lose their effectiveness. Clonidine and gabapentin have been used effectively in some patients.

Hypothalamic control of body temperature control is often impaired [Barr and Cohen, 1999]. In our study, 32% of children had abnormal temperature regulation and the degree of dysfunction correlated with the degree of hypothalamic nonseparation [Plawner et al., 2002]. Some children with HPE have lower than normal body temperatures at baseline, while some have elevated temperatures in the absence of infection, and some go to both extremes. Knowing the usual temperature range for each child is important in identifying illness and abnormal fluctuations that should be further evaluated and treated. Relative hypothermia can manifest as lethargy, low heart rate and blood pressure, and decreased respirations. Relative hyperthermia is often accompanied by increased seizures and irritability and can be exacerbated by dehydration. End-organ dysfunction is possible, especially when body temperature goes below 33°C. Fluctuations in body temperature can be attributed to the effects of ambient temperature, state of arousal, endocrine dysfunction, medications, and sometimes infectious illness. Management of temperature instability in children with neurologic disabilities has not been studied or well-described. Most children can be managed by modifying their environment. An individualized protocol, including steps for monitoring and responding to temperatures out of their usual range, can be developed for children with HPE and significant temperature instability. Guidelines to families should be written with a goal of avoiding moderate to severe hypothermia (<33−34°C) or hyperthermia (>40−41°C) while not requiring excessive vigilance and intervention. In some cases, a water-filled medical heating/cooling pad has been used for temperature modulation with some success.

Endocrine Dysfunction

In one of our previous studies of 117 patients with HPE, central diabetes insipidus (DI) occurred in approximately 70% of patients with classic HPE. Anterior pituitary hormone deficiencies such as hypothyroidism (11%), hypoadrenocorticism (7%), and growth hormone (GH) deficiency (5%) were much less common [Hahn et al., 2005].

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None of the children with MIH HPE had DI although a few had anterior pituitary hormone deficiency. The degree of DI correlated with the degree of hypothalamic separation but did not correlate with the degree of pituitary abnormality by neuroimaging. In a study that included 29 patients with HPE referred to a pediatric endocrinology center, 54% were found to have DI, 42% had GH deficiency, and 21% had deficiency of multiple pituitary hormones [Traggiai and Stanhope, 2002]. The higher rate of GH deficiency in this study could be because of referral bias and their use of stimulation tests for diagnosis.

Children with HPE should be evaluated for endocrine dysfunction during the neonatal period with a low threshold for repeat evaluations, as deficiencies can evolve over time. Possible symptoms of anterior hormone deficiencies include hypoglycemia, poor feeding, poor linear growth, lethargy,

and apnea. ACTH deficiency can be life-threatening, especially in the setting of acute illness. Hormone replacement therapy should be initiated depending on severity and clinical context. Diabetes insipidus can be detected by monitoring plasma sodium levels for hypernatremia. We have observed that a number of children with HPE have stable hypernatremia at baseline, in the range of about 148−153 meq/L, and remain asymptomatic without signs of dehydration. Some have interpreted similar children as having neurogenic hypernatremia, which they differentiate from true diabetes insipidus [Lazaro et al., 2004]. These children may in effect have an altered osmostat or set-point for plasma sodium due to hypothalamic dysplasia, rather than more typical central DI due to an abnormal pituitary gland. In our study, about 73% of patients with HPE diagnosed with DI were treated with DDAVP and the remainder was treated with fluid management alone [Hahn et al., 2005]. Some children with HPE and DI will decompensate with illness, so it is reasonable to check serum electrolytes in the acute setting.

APPROACH TO MANAGEMENT

The parents of children with HPE need to be given a balanced and realistic prognosis for their child in order to make decisions about ongoing medical care. Some newborns with HPE will need interventions such as tracheostomy, mechanical ventilation, and tube feeding in order to survive. The decision-making process works best when the parents are fully informed, but do not feel pressured by the medical team. Parents should be offered support and guidance and should feel that they will be supported by the medical team no matter what they decide. No matter how grim the prognosis, some parents will want to do everything possible for their

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child [Redlinger-Grosse et al., 2002]. Parents need to feel that their beliefs and opinions are respected, especially when medical team members may have views that are contrary.

There is a common misperception that most children with HPE have limited survival, without consideration of type of HPE, presence of chromosomal abnormalities, severity of facial malformations, or other organ system involvement. It has been our experience that many newborns with HPE are discharged to home with their parents with the expectation that they will not live beyond a few months of age [Barr and Cohen, 1999; Stashinko et al., 2004]. Patients are sometimes inappropriately referred to hospice care. In some cases, parents have been told not to do anything for their child, and not to seek any routine or specialty medical care. Unfortunately, The Carter Centers are often contacted after a period of time by parents who have an infant with HPE who has survived, and they feel abandoned by their medical providers and no longer trust them. These parents often turn to The Carter Centers in order to ask us what to do next and are actively looking for direction.

Because most deaths occur within the first few days to weeks of life [Whiteford and Tolmie, 1996], even children with alobar HPE who survive the first month are likely to survive beyond infancy. Once newborns with HPE are discharged to home, unless death is imminent, clinicians should provide them with all routine childcare including immunizations and pediatric visits. These patients should be evaluated and treated for acute illnesses as would

other children their age. At the time of newborn discharge, the parents may decide that if their child were to have an acute life-threatening event, that they would not want their child resuscitated. Other than decisions about resuscitation, decisions can usually be made as situations arise. At some point, they may need to consider a feeding tube or whether to provide life-sustaining care in the event of serious illness. It is reasonable to discuss these scenarios in advance, but parent and provider perspectives are likely to change as time goes by. Some children with HPE are resilient and have few illnesses while others are extremely fragile.

At the time of discharge, newborns with HPE should have at least one medical provider who has agreed to follow them closely for several months and help coordinate their care. The provider could be a Geneticist, Neonatalogist, Pediatric Neurologist, Developmental Pediatrician or Primary Care Pediatrician. Parents need to have someone they trust who they can call to ask questions or to discuss ongoing medical care. Depending on medical issues that arise, the child can be referred to Endocrinology, Neurology, Pulmonology, and Gastroenterology as appropriate. If death seems imminent, hospice care can be arranged. The first several months after birth are the most critical for the child with HPE and the parents, whether the child lives or dies. Families need support and guidance along with respect for their beliefs and wishes. They should not feel abandoned by the medical system.

Because HPE is a rare condition among living children, most parents of children with HPE do not know anyone else with a child with HPE, and feel that their medical and other providers lack familiarity with the condition. HPE is a cause of cerebral palsy, which is a much more common condition, and one with which most medical and other service providers are familiar. Empowering parents with the concept that their child has cerebral palsy due to HPE can help them in finding appropriate medical providers, services, and resources, and help them in communicating with

providers as well as other family members and friends. Many parents of children with HPE also find great benefit in sharing their experiences with each other. Families for HoPE (www.familiesforhope.org) is an online community that connects parents of children with HPE with each other and has a forum for discussion of various issues.

SUMMARY AND CONCLUSIONS

Although there is high early mortality with severe cases of HPE, some children with alobar HPE and most children with milder forms will survive beyond infancy. Virtually all children with HPE will have some developmental disability, the severity correlating with the severity of the brain malformation. Children with HPE typically have multiple medical problems, many that are typical of other children with cerebral palsy. Because HPE is a midline defect commonly involving the hypothalamus, it is associated with temperature instability, disturbed sleep−wake cycles, and endocrine dysfunction in a high percentage of patients. Because survival of newborns with HPE is often uncertain after discharge, parents are often desperate for the support and guidance of medical providers, yet often feel abandoned. Not only do parents need clinicians who are familiar with the natural history and common medical problems associated with HPE, they need a clinician who can serve as a point person after discharge. Medical care of the child with HPE often requires coordination of multiple medical and rehabilitative specialists and a plan of care that changes as the outlook, treatment goals, and parents' priorities evolve.

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