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Behavioral, Pathomorphological, and Clinical Observations of a Young Harbor Porpoise (*Phocoena phocoena*) with Congenital Hemihydranencephaly

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Abstract

Internal anatomical disorders in marine mammals often only become apparent during necropsies. A case of hemihydranencephaly (HHAE) in a harbor porpoise (*Phocoena phocoena*) is described herein. HHAE is a rare, severe congenital brain disorder whereby one cerebral hemisphere is replaced by a sac filled with cerebrospinal fluid. The harbor porpoise was a formerly stranded and rehabilitated juvenile female, exhibiting behavior during her life in captivity that fell into two distinct modes. During her normal, “active” mode, she behaved like other harbor porpoises and performed well in training sessions. During her abnormal, “passive” mode, she listed onto her left side and floated with her right side at the water surface for several minutes at a time. At least her right eye would be closed, and she appeared to be in deep sleep. While floating at the surface and tilted over, she probably occasionally inhaled small amounts of water, resulting in recurring pneumonia. Ten months after stranding, at the age of ~24 months, the porpoise suddenly died. She was diagnosed with right-sided HHAE upon necropsy, which suggests that her passive-mode behavior was abnormal sleep. Cetaceans exhibit unihemispheric sleep so that they can maintain voluntary breathing, swimming, thermoregulation, body position, and vigilance. Possessing only one cerebral hemisphere, the porpoise lost the ability to sleep in this way. Following necropsy, the proximate cause of her death was probably an extensive lung edema followed by hypoxia, but the HHAE was assumed to be the ultimate cause. This case report shows that, despite the negative outcome, HHAE in harbor porpoises can be compatible with life and may not result in the cognitive or motor impairments that are seen in some human HHAE patients.

Key Words: behavior, brain, cerebral, congenital, electroencephalogram, pathomorphology, harbor porpoise, *Phocoena phocoena*, hemihydranencephaly, HHAE, odontocete, rehabilitation, sleep, USWS

Introduction

Anatomical disorders can be congenital (present at birth) or acquired later in life due to, for instance, disease or trauma; they may affect function. Congenital anatomical disorders result from failed development *in utero*, which may be caused by genetic issues, trauma to the fetus, or exposure of the mother to toxic substances, nutritional deficiencies, or infections (Slauson & Cooper, 2002). Although commonly reported for terrestrial mammals (Leipold & Troyer, 1995), anatomical disorders are difficult to observe in odontocetes (toothed whales) at sea, unless the disorder is externally conspicuous (such as a deformed vertebral column; see Berghan & Visser, 2000). Consequently, most records of anatomical disorders in wild odontocetes are obtained from necropsies on individuals caught in fisheries (e.g., Van Bressem et al., 2006; Kompanje et al., 2017) or from stranded animals (e.g., Dabin et al., 2004; Kastelein et al., 2009; Powell et al., 2009).

Analysis of anatomical disorders is required to determine their most likely cause. This analysis is important, as it may provide information on developmental processes or identify harmful exogenous factors that disrupt these processes or affect animals later in life.

Herein, a case of hemihydranencephaly (HHAE) in a harbor porpoise (*Phocoena phocoena*) is described. HHAE is a very rare and severe encephalic disorder, characterized by the complete or almost complete absence of either the left or the right cerebral cortex, with preservation of meninges, basal ganglia, pons, medulla, cerebellum, and falx cerebri. The missing cerebral cortex is replaced with a sac filled with cerebrospinal fluid (Mori, 1985; Greco et al., 2001; Ulmer et al., 2005; Pavone et al., 2013). In humans, HHAE is thought to arise from occlusion of either the left or the right carotid artery during fetal development (prior to the third trimester), causing the initially formed cerebral hemisphere on the affected side to be destroyed (Mori, 1985; Myers, 1989).

In humans, only nine definite and two possible cases of HHAE have been reported in the literature to date (see Pavone et al., 2013). Based on the nine definite cases, Pavone et al. (2013) concluded that the left and right cerebral hemispheres are likely to be equally affected and that there is no difference in clinical impairment or cognitive performance outcome based on the affected hemisphere. However, the HHAE patients showed heterogeneity in the extent of motor, language, and cognitive impairment and in outcome, probably due to differences in timing and mechanism of the injury (Pavone et al., 2013). The fact that three of the nine human HHAE patients showed good cognitive development suggests that cortical reorganization is possible if the injury occurs at an early developmental stage (Ulmer et al., 2005; Pavone et al., 2013).

HHAE in non-human terrestrial mammals is thought to be caused by virus infections (Blythe, 2011; Schild et al., 2011). Only one account of HHAE in marine mammals has been published—McKnight et al (2005) describe a congenital hemicerebral anomaly in a stranded Pacific harbor seal (*Phoca vitulina richardsi*). Among odontocetes, as far as we know, only one case of HHAE has been observed—in a common dolphin (*Delphinus delphis*; S. H. Ridgway, pers. comm., March 2021). We report herein on the case history of a formerly stranded, rehabilitated female juvenile harbor porpoise with HHAE. The porpoise's behavior and clinical presentation was observed closely during the last few months of her life, and it was possible to conduct a necropsy within hours of her death. The behavioral observations and timely necropsy provided a unique opportunity to study pathomorphological and clinical aspects of this rare congenital brain disorder in a marine mammal.

Methods and Description

Stranding, Rehabilitation, and Transport

On 23 September 2008, a ~15-mo-old female harbor porpoise (identified as "PpSH138") stranded on the North Sea coast of the Dutch island Terschelling and was subsequently transported to the rehabilitation center at Dolfinarium Harderwijk in the Netherlands. She was estimated to have been born in June 2007, during the calving season in the North Sea (May to August; Bjørge & Tolley, 2018), based on her body length of 99 cm (adult females reach ~150 cm; Bjørge & Tolley, 2018). She presented minor superficial wounds and scars (white patches) and emaciation (body mass of 15.2 kg). No other external abnormalities were identified. During her stay at Dolfinarium Harderwijk, she was given antibiotics and antiparasitic drugs to treat frequent coughing and high blood leucocyte counts, which were believed to be diagnostic of pneumonia and lungworm (*Pseudalius inflexus*) infection. Her body temperature varied between 36 and 37°C, which is normal for cetaceans (Whittow et al., 1974; Melero et al., 2015).

Before the end of 2008, she was moved from the rehabilitation center to an outdoor exhibit pool at the Dolfinarium, where she was housed with conspecifics. On 8 March 2009, once the veterinarian at Dolfinarium Harderwijk had declared her to be in good health, she was transported to the SEAMARCO Research Institute in Wilhelminadorp, the Netherlands, for participation in scientific research. On the day of transport, daily care staff from the Dolfinarium informed the transport staff from SEAMARCO of abnormal passive behavior regularly exhibited by the porpoise since her arrival at Dolfinarium Harderwijk. This behavior entailed floating on her left side with her right side above the water surface. When she was tilted in this way, the skin on her right side became warm and dark as if after prolonged exposure to sunlight, even during the night, and had to be moistened by the staff to prevent dehydration of the tissue and cracking of the skin.

Body Parameters, Behavior, and Death

On arrival at the SEAMARCO Research Institute, the harbor porpoise was estimated to be 20 mo old. Her body mass was 25 kg, her total body length was 107 cm, and her girth at axilla was 74 cm. Her dorsal fin was bent to the left (30° from the vertical line), as is sometimes seen in captive odontocetes when they are ill for prolonged periods of time (Kastelein et al., 1997a, 2016). During her time at the SEAMARCO Research Institute (~4 mo), her food consumption increased from 1,800 to 2,200 g per day, with her diet consisting mainly of capelin (*Mallotus villosus*), herring (*Clupea harengus*), mackerel (*Scombrus scombrus*), and sprat (*Sprattus sprattus*). The porpoise's body weight fluctuated around 25 kg, her daily mean respiration rate varied between 20 and 27 breaths per 5 min, and her total body length increased from 107 to 110 cm. Apart from being slightly stocky, her external appearance was similar to that of other harbor porpoises of her sex and age (Figure 1). The external morphology of her head was normal (Figure 2).

The porpoise's motivation to participate in training sessions for husbandry and planned psychophysical research was very high. She always scored 11 or 12 on a scale from 0 (lowest) to 12 (highest) that was used to describe her performance during her four daily training sessions. Her training progressed at a similar rate to that observed in about 15 other harbor porpoises that had been under the care of the first author.

Despite her treatment for pneumonia and lungworm during her 5-mo stay at Dolfinarium Harderwijk, the porpoise seemed to remain extremely prone to health issues, suffering from recurring bouts of pneumonia during her 4-mo stay at SEAMARCO. In total, over her 9 mo in captivity, she required seven courses of antibiotics.

The porpoise's behavior fell into two distinct modes. In "active" mode, she was alert and behaved like other harbor porpoises, participating very well in training sessions. In "passive" mode, which usually lasted ~5 to 10 min and occurred at least once per hour (possibly more often, but observation was not continuous), she listed onto her left side and floated passively, with her right side above the water surface. Her blowhole was only just above the water surface, and her right eye was closed; it was unknown whether her left eye was closed as well. This behavior was as described by the Dolfinarium staff. In this passive mode, the porpoise seemed to enter a very deep sleep from which awakening was difficult. In many cases, she floated with the weak current towards the skimmer drain until she touched the side of the pool, upon which she would wake up, become alert again, and start swimming normally.

Floating at the surface in passive mode caused the porpoise's skin to become very warm in specific locations, up to 30°C. Harbor porpoise skin temperature, measured laterally, increases by about 3°C in 10 min when out of the water (Kastelein et al., 1997c). This rapid increase in temperature resulted in skin dehydration, followed by sloughing of patches of skin on the porpoise's right side that had been relatively warm and dry (Figure 3). The skin sloughing, in turn, resulted in presumed itching in those areas, which the porpoise attempted to relieve by rubbing against the pool wall (when in active mode).

During the last 3 wks of the porpoise's life, the skin on her head became very hot, causing dark spots at the top of her head that she would rub against the pool wall. The day before her death, the porpoise behaved normally and had a very good appetite (better than in the preceding months). At 0830 h on the day she died, she had no appetite. She was in her active mode until minutes before her death when she suddenly started swimming very fast and jumped out of the water as if she were in pain or experiencing a seizure. She then sank to the bottom of the pool, after which she rapidly accelerated to the water surface. Finally, she floated at the surface with foam coming from her mouth and died at 1130 h on 25 July 2009. She was ~24 mo of age.

Necropsy

The necropsy of the harbor porpoise was conducted according to standard protocols used at the Veterinary Pathology Diagnostic Centre of Utrecht University, the Netherlands, a few hours after she died. It included macroscopic examination and photography of fresh organs and tissues, as well as histological examination of samples of various organs. Organs were fixed in 4% phosphate-buffered formalin, embedded in paraffin, cut into 4 µm sections, and stained with hematoxylin and eosin.

No abnormalities were found in the organs in the thoracic and abdominal cavities except for the liver and the lungs. The liver was pale beige in color and showed a low volumetric mass density. Histologically, the liver showed slight ductular hyperplasia with minimal infiltrates of lymphocytes and plasma cells. The cytoplasm of the hepatocytes was micro-vacuolized. A beige color (instead of brown) and diffuse vacuolization of the cytoplasm are diagnostic of fatty liver, which is associated with hypoxia. The lungs were hyperemic and edematous, with foam in the trachea. Histologically, the lungs were confirmed to be diffusely hyperemic and showed alveolar edema (some very small hyaline membranes were present focally), with focally foamy macrophages, fibrin deposits (diagnosed from morphology), and colonies of rod-shaped bacteria (no change in interstitial lymphatics was observed). No evidence of recurrent aspiration pneumonia was found, despite the fact that the porpoise had suffered from recurring bouts of pneumonia during her 9-mo stay in captivity. The abnormalities were consistent with pneumonia, but, together with the liver abnormalities, were not considered severe enough to have been the cause of the porpoise's death.

Examination of the cranium revealed clear abnormalities. The cranial bones around the fontanelle were only partially closed, with a 10 × 5 mm gap between them. There was no sign of hemorrhage in the surrounding tissue. The gross anatomy of the left cerebral hemisphere was similar to that of other harbor porpoises (Rawitz, 1903; Gierlich, 1916; Friant, 1953; Moris, 1969; Revishchin & Garey, 1990; Behrman, 1993; Kastelein et al., 1997e; Walløe et al., 2010). However, instead of brain tissue within the right cerebral hemisphere, there was transparent colorless cerebrospinal fluid (Figure 4), contained within a thick (~5 mm) layer of fibrotic tissue (Figure 5). Histology showed that the small amount of brain tissue within the right hemisphere

Figure 1. Left-side lateral view of the 2-year-old female harbor porpoise (*Phocoena phocoena*) swimming in active mode a few days before her death. The porpoise's body condition was good, but she was relatively short for her age and weight (i.e., she was stocky). Note that her dorsal fin is bent to the left.

Figure 2. Almost frontal view of the 2-year-old female harbor porpoise shortly before her death. Externally, there was no indication of hemihydranencephaly; the shape of the porpoise's head and melon appeared to be normal.

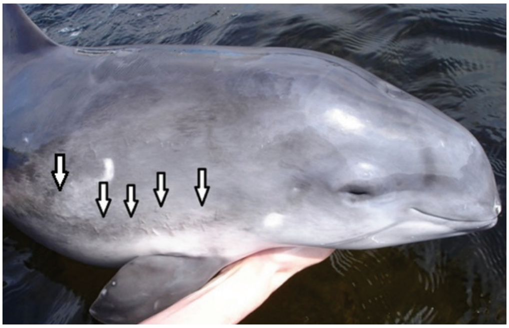

Figure 3. Right-side lateral view of the 2-year-old female harbor porpoise shortly before her death. Her skin was sloughing (indicated with arrows) following dehydration. This occurred in passive mode, when the porpoise was listing towards her left side while floating with her right side at the water surface.

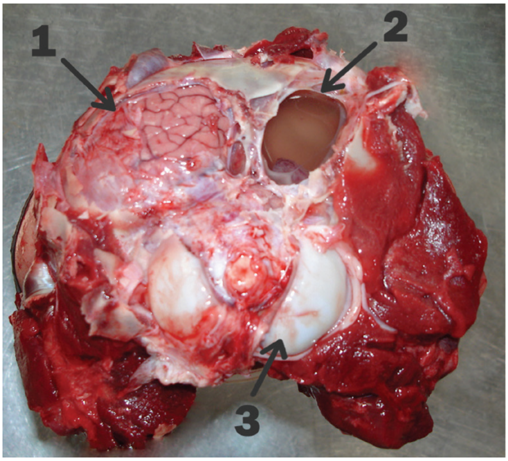

Figure 4. Caudal view of the head of the young female harbor porpoise, with part of the cranium and the meninges removed. On the left, there is a normal cerebral cortex (1). On the right, the cerebral cortex is replaced by a cerebrospinal fluid-filled sac (2). The right occipital condyle is indicated for orientation (3).

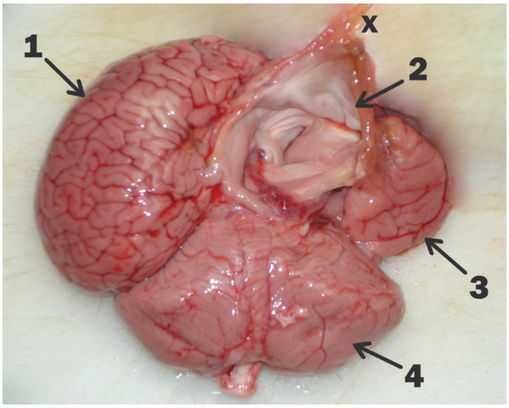

Figure 5. Dorsal view of the brain after removal from the harbor porpoise's cranium, showing the normal cerebral cortex on the left side (1). On the right side, the opened lining of the (now drained) cerebrospinal fluid-filled cavity is visible (2); the lining is being lifted towards location x. The right temporal lobe (3) and the right cerebellum (4) are indicated for orientation.

was compressed at the peripheral area; there was practically no normal brain tissue. The meninges, basal ganglia, pons, medulla, cerebellum, and falx cerebri appeared to be normal. No evidence of previous parasitic infestation was found. In the absence of evidence suggesting that the disorder (i.e., loss of the right cerebral cortex) was acquired later in life, congenital HHAE was diagnosed.

The proximate cause of death was probably the extensive lung alveolar edema followed by hypoxia that had developed in the last few minutes of the porpoise's life. In humans, neurogenic pulmonary edema is characterized by the sudden onset of respiratory failure after an injury to the central nervous system and is typically associated with raised intracranial pressure. It remains unknown whether intracranial pressure was raised in this study animal.

Discussion

Effect of Hemihydranencephaly on General Functioning and External Appearance

During life, the harbor porpoise was quite functional despite having only one cerebral hemisphere. She was able to survive for a total of ~24 mo, 9 mo of which she spent in captivity. Her ~15 mo in the wild would have included a suckling period of ~10 mo (Bjørge & Tolley, 2018), after which she was probably able to catch live prey to nourish herself until she stranded. While in captivity, the porpoise exhibited active-mode behavior that was similar to that of normal porpoises. This suggests that the porpoise's HHAE arose at an early developmental stage and that some cortical reorganization had taken place, allowing the left hemisphere to take over a large part of the function of the missing right hemisphere (Ulmer et al., 2005; Pavone et al., 2013).

In human HHAE patients, clinical impairments generally arise within the first months of life (see Pavone et al., 2013). Motor functions are initially normal, as motor control is thought to be subcortical in young infants (Altschuler et al., 2005). Impairments may include contralateral hemiparesis (weakness of the body on the side opposite to the missing cerebral hemisphere); delayed and/or impaired motor, language, and cognitive development; and seizures (see Pavone et al., 2013). In the harbor porpoise of the present study, no motor impairments were apparent from her active-mode swimming behavior. Furthermore, she learned and was trained as quickly as captive conspecifics, which is comparable to human HHAE patients who have good cognitive development outcomes. Her erratic swimming behavior just prior to her death (i.e., rapid acceleration, followed by sinking, followed by another acceleration) may have been due to some sort of seizure related to her HHAE, but this remains speculative.

HHAE in humans does not seem to be linked to specific external characteristics, except for possible facial asymmetry due to mild unilateral paralysis (Van Doornik & Hennekam, 1992; Balpande et al., 2009), possible disuse atrophy due to hemiparesis, and possible pupil asymmetry (Dias et al., 2011). The external appearance of the porpoise was mostly normal (Figures 1-3), although pupil symmetry was never checked. In one human HHAE case, delayed growth was reported: the 27-mo-old patient's body length fell below the third percentile for age (Hassanein et al., 2011). The porpoise of the present study was short for her age (and weight) as well; she was somewhat stocky (Figure 1). At an estimated 15 mo, she was 99 cm long, whereas wild female porpoises may reach 125 cm by the end of their first year (Bjørge & Tolley, 2018). It is unknown whether the human patient reported by Hassanein et al. (2011) eventually reached normal length or whether the other reported human HHAE cases experienced delayed growth during (early) childhood.

The necropsy showed that the porpoise's cranial bones around the fontanelle were only partially closed, although this was not externally visible and was not necessarily linked to the HHAE. These bones are normally closed in porpoises of similar age to the study animal (Gol'din, 2007). In the surrounding tissue, there was no evidence of injury that would suggest traumatic reopening of formerly closed cranial bones. It is possible that a failure in fetal development resulted in the HHAE and also in abnormal development of the skull, but this remains speculative.

Effect of Hemihydranencephaly on Resting Behavior and Health

The postmortem diagnosis of HHAE provided an explanation for the porpoise's abnormal passive-mode behavior—it was probably sleeping behavior that might be expected in a cetacean with only one cerebral hemisphere. Sleep can be defined as a periodically necessary behavior for mammals in which they assume a typical body posture, close their eyes, and have a raised sensory threshold, decreased motor activity, and distinctive electrographic signs (Mascetti, 2016). In most animals, sleep involves the entire body and brain. However, recordings of electrographic signs from the brain via electroencephalograms (EEGs) reveal that in cetaceans, one cerebral hemisphere sleeps while the other is awake (see Lyamin et al., 2008). Such unihemispheric slow-wave sleep (USWS) was shown on EEGs of several odontocetes, including bottlenose dolphins

(*Tursiops truncatus*; Mukhametov et al., 1976, 1977; Mukhametov, 1984, 1988; Mukhametov & Lyamin, 1994; Ridgway, 2002), Amazon river dolphins (*Inia geoffrensis*; Mukhametov, 1987), belugas (*Delphinapterus leucas*; Lyamin et al., 2002), and harbor porpoises (Mukhametov & Polyakova, 1981; Oleksenko & Lyamin, 1996). USWS allows cetaceans to have the benefits of sleep while maintaining their surfacing behavior for breathing, continuous motion, position in the water column, thermoregulation, group cohesion, and vigilance (see Lyamin et al., 2008).

Lyamin et al. (2008) reviewed three types of resting behavior observed in both captive and wild cetaceans: (1) resting while swimming slowly, (2) resting at depth (or at the pool bottom), and (3) resting while floating at the surface. EEG recordings of captive odontocetes show that USWS occurs in each of these three resting states (see Lyamin et al., 2008). However, different species spend different amounts of time in each resting state. For instance, bottlenose dolphins prefer to sleep while swimming slowly or floating at the surface (e.g., Mukhametov et al., 1977; Mukhametov & Lyamin, 1997), whereas harbor porpoises seem to be "obligate swimmers" and sleep only while swimming slowly (Mukhametov & Polyakova, 1981; Oleksenko & Lyamin, 1996; Lyamin & Siegel, 2006).

Possessing only one cerebral hemisphere, the female porpoise in the present study could not enjoy the benefits of USWS. She was never observed resting while swimming slowly, only while floating at the surface. This is unsurprising because, with only one cerebral hemisphere, sleeping while swimming slowly would have resulted in her either drowning or having to arouse frequently to surface for breathing. As in other mammals, respiration in cetaceans can be either under voluntary control or automatic (McCormick, 1969), so floating at the surface allowed the porpoise to maintain regular automatic breathing while asleep.

In addition to being unable to breathe voluntarily while sleeping, the porpoise was also unable to maintain her body position during passive mode. During normal USWS while floating at the water surface, cetaceans produce enough tail-fluke and pectoral flipper movement to maintain a stable position at the surface and ensure that the blowhole is above water for each breath (see McCormick, 1969). With only one cerebral hemisphere, the sleeping porpoise would float at the surface completely passively and list onto her left side (i.e., the side with the intact cerebral hemisphere). Her right side (i.e., the side with the missing cerebral hemisphere) was facing upwards, and her blowhole was only just above the water surface, probably causing her to sometimes accidently inhale small amounts of surface water. Pneumonia is often observed in stranded and captive harbor porpoises (Kastelein et al., 1990, 1997a; Jepson et al., 2000; Siebert et al., 2001, 2009; Neimanis et al., 2022), but regular inhalation of water during periods of passive-mode behavior is likely to have contributed to the abnormally frequent bouts of pneumonia of the study animal.

The porpoise may have also been more susceptible to pneumonia due to a reduced body temperature resulting from her reduced locomotion in passive mode. During normal USWS, movement facilitates muscle thermogenesis and postural thermoregulation in cetaceans (Lyamin & Siegel, 2019), and the evolution of sleep phenomenology in cetaceans may have been driven in part by the need to compensate for heat loss (Pillay & Manger, 2004). Continuous movement is especially important in the harbor porpoise, as this relatively small odontocete has a large surface-to-volume ratio, bringing a relatively large body surface area (Andersen, 1981; Irschick et al., 2020) into contact with the relatively cold water in temperate regions of the northern hemisphere (Bjørge & Tolley, 2018). Harbor porpoises compensate for their unfavorable surface-to-volume ratio by having a relatively thick layer of blubber with a relatively high insulation value (Worthy & Edwards, 1990) and a high metabolism (Koopman et al., 1996; Kastelein et al., 1997b, 1997d, 2018; Koopman, 1998; Reed et al., 2000; Elmegaard et al., 2016; Wisniewska et al., 2016). Continuous swimming, even while sleeping, also generates heat.

Bottlenose dolphins and belugas usually keep the eye contralateral to the waking hemisphere open or in an intermediate state, and the eye contralateral to the sleeping hemisphere closed or in an intermediate state (Lyamin et al., 2002, 2004). Sleeping Pacific white-sided dolphins (*Lagenorhynchus obliquidens*) and bottlenose dolphins seem to direct their open eye towards conspecifics, maintaining visual contact between group members (Goley, 1999; Gnone et al., 2001), although they also communicate acoustically. Maintaining visual contact even during sleep is especially important in mother–calf pairs, as calves are vulnerable to predation (see Lyamin et al., 2008). The porpoise in the present study kept her right eye (which was above the water) closed when she was in passive mode. Only the left cerebral hemisphere was present, so it can be assumed that both eyes were closed, though the state of her left eye was never recorded. Closing both eyes would have made it easier for the study animal to become separated from her mother when she still lived at sea, but her estimated age at stranding suggests that she was already independent at that time. Having both eyes closed would also have reduced her vigilance compared to unilateral eye closure in normal sleeping cetaceans (Mukhametov & Lyamin, 1997), which would have increased her vulnerability to predation at sea.

Conclusion

Congenital hemihydranencephaly is a very rare brain disorder that has been documented in fewer than a dozen humans. The first case of this disorder in a harbor porpoise is reported herein. During life, the porpoise displayed undiagnosed abnormal sleeping behavior that was consistent with the absence of one cerebral hemisphere as revealed by postmortem diagnosis. Despite the negative outcome of this case, HHAE in harbor porpoises could be compatible with life and does not necessarily result in the cognitive or motor impairments that are seen in some human patients. This porpoise's long-term chances of survival in the wild would have been extremely slim, but her stranding and consequent life in captivity provided a unique opportunity to observe the behavioral impacts of a severe brain disorder in a marine mammal.

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