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Beyond Microcephaly: Semilobar Holoprosencephaly with Marked Macrocephaly due to Severe Congenital Hydrocephalus, Brachycephaly, and Hyponatremia – A Case Report

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A B S T R A C T

Holoprosencephaly (HPE) is a rare, complex brain malformation arising from incomplete prosencephalon cleavage, typically associated with microcephaly and facial dysmorphism. Coexisting severe hydrocephalus leading to macrocephaly in HPE, particularly the semilobar type, presents a distinct clinical picture. Hyponatremia often complicates neurological conditions involving increased intracranial pressure, potentially worsening prognosis. The aim of this case report is to meticulously describe the clinical presentation, diagnostic evaluation, management approach, and early outcomes of this rare and complex neonatal neurological disorder. A male neonate, born at 35+3 weeks gestation to a mother with severe preeclampsia, presented with marked macrocephaly (head circumference 50 cm), a prominent fontanel, and bilateral sunset eyes. Initial CT scan confirmed hydrocephalus. Subsequent evaluation and a repeat CT scan at one month revealed brachycephaly (cephalic index 98) and semilobar holoprosencephaly. Head circumference progressed to 64 cm by the time of ventriculoperitoneal (VP) shunt surgery at approximately 5 weeks of age. Laboratory investigations showed hyponatremia (120 mEq/L), hyperkalemia, and hypochloremia. At three months, the patient exhibited significant growth and developmental delays and malnutrition. In conclusion, this case highlights an unusual presentation of semilobar HPE characterized by severe congenital hydrocephalus causing marked macrocephaly, rather than microcephaly, complicated by brachycephaly and significant hyponatremia. Early, comprehensive diagnostic evaluation and multidisciplinary management are crucial in such complex neurodevelopmental disorders to address multifaceted challenges and attempt to optimize outcomes.

1. Introduction

Holoprosencephaly (HPE) represents a spectrum of complex congenital brain malformations characterized by the incomplete or failed cleavage of the prosencephalon (the embryonic forebrain) into distinct cerebral hemispheres. This critical developmental process typically occurs between the 18th and 28th days of gestation. The failure of midline cleavage can affect not only the brain, leading to varying degrees of fusion of the cerebral hemispheres and deep grey nuclei, but also the face, resulting in a range of craniofacial anomalies. The estimated prevalence of HPE is approximately 1 in 16,000 live and stillbirths, and as high as 1 in 250 conceptuses, indicating a significant rate of fetal loss. The etiology of HPE is heterogeneous, encompassing genetic factors, including chromosomal abnormalities and single-gene mutations, as well as environmental influences such as maternal diabetes mellitus or exposure to certain teratogens.[1,2]

HPE is traditionally classified into four main subtypes based on the degree of hemispheric separation: alobar, semilobar, lobar, and the middle interhemispheric fusion variant. Alobar HPE, the most

severe form, involves a complete lack of hemispheric separation with a single midline ventricle (monoventricle). Semilobar HPE, an intermediate form, is characterized by partial separation of the hemispheres, typically posteriorly, with continued fusion anteriorly, and incomplete development of the corpus callosum and olfactory structures. Lobar HPE, the mildest form, shows more distinct hemispheric separation with only focal areas of fusion, often involving the frontal lobes or cingulate gyrus. The middle interhemispheric variant involves non-separation of the posterior frontal and parietal lobes.[3,4]

While HPE is classically associated with microcephaly or normocephaly, the presence of hydrocephalus can lead to an apparent paradox: macrocephaly in a condition otherwise expected to result in a smaller head. Hydrocephalus, an excessive accumulation of cerebrospinal fluid (CSF) within the ventricular system and/or subarachnoid spaces, can occur in a subset of individuals with HPE, potentially due to aqueductal stenosis, impaired CSF absorption, or other poorly understood mechanisms related to the structural brain abnormalities. The reported incidence of hydrocephalus requiring CSF diversion in HPE is around one-sixth of patients. Management of this hydrocephalus, often via ventriculoperitoneal (VP) shunting, can be crucial for preventing further neurological compromise from raised intracranial pressure and for improving quality of life and ease of care. Brachycephaly, characterized by a disproportionately short and wide head shape (a high cephalic index), can also be observed in infants with complex neurological conditions, sometimes related to positional factors, craniosynostosis, or as part of a broader syndromic presentation. In the context of HPE and hydrocephalus, abnormal skull molding secondary to altered brain structure and CSF dynamics may contribute to such cranial shape abnormalities.[5,6]

Furthermore, infants with significant neurological insults, including those with HPE and hydrocephalus, are susceptible to electrolyte disturbances. Hyponatremia, in particular, is a recognized complication in patients with central nervous system disorders, including those with increased intracranial pressure. The mechanisms can be multifactorial, involving the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or, less commonly, cerebral salt wasting (CSW). SIADH in the context of HPE, though considered rare, has been reported and can be triggered by increased intracranial pressure affecting hypothalamic function. Such electrolyte imbalances, if not promptly identified and managed, can contribute significantly to morbidity and mortality, potentially exacerbating neurological injury and complicating the overall clinical course.[7,8]

The novelty of the case presented herein lies in the unusual constellation of semilobar holoprosencephaly manifesting with marked macrocephaly secondary to severe congenital hydrocephalus, further complicated by significant brachycephaly and early-onset hyponatremia in a neonate born to a mother with severe preeclampsia. While HPE is known, its presentation with significant macrocephaly challenges the typical association with microcephaly and underscores the importance of considering hydrocephalus as a significant comorbidity. The co-occurrence of these specific features, particularly the severe degree of hydrocephalus and the notable brachycephaly in conjunction with semilobar HPE and consequential hyponatremia, is infrequently detailed in literature.[9,10] Therefore, the aim of this case report is to meticulously describe the clinical presentation, diagnostic evaluation, management approach, and early outcomes of this rare and complex neonatal neurological disorder. By presenting this case, we intend to enhance awareness among pediatricians, neonatologists, neurologists, and neurosurgeons regarding this atypical presentation of HPE, emphasizing the importance of a high index of suspicion for associated conditions like severe hydrocephalus and electrolyte disturbances, and highlighting the diagnostic and management challenges encountered. This report seeks to contribute to the understanding of the phenotypic

spectrum of HPE and its complex interplay with other neurological and systemic complications.

2. Case Presentation

A male infant was delivered via Cesarean section at Wangaya Regional Hospital. He was the second child of a 25-year-old mother who experienced severe preeclampsia during this pregnancy. The gestational age at admission was 35 weeks and 3 days, complicated by premature rupture of membranes which occurred less than 12 hours prior to delivery. Comprehensive maternal screenings for retroviral infection, hepatitis, and syphilis were conducted and documented as nonreactive. The family history was unremarkable, with no reported instances of similar congenital anomalies or neurological conditions. At birth, the infant cried immediately. The amniotic fluid was noted to be clear, and a single nuchal cord (umbilical cord wrapped around the neck) was observed but did not appear to cause immediate distress. His birth weight was a substantial 4040 grams, and his length was 55 cm, indicating a large for gestational age infant.

The initial physical examination in the neonatal period revealed several significant findings, which are summarized in Table 1. Most strikingly, the infant exhibited marked macrocephaly, with an occipitofrontal head circumference (OFC) of 50 cm. This measurement was significantly above the 97th percentile for his gestational age and gender, immediately raising concerns. The anterior fontanel was visibly large, felt tense upon palpation, and was prominent, bulging slightly. Bilateral "sunset eye" sign, characterized by a persistent downward deviation of the eyes with visible sclera above the iris, was observed. Additionally, Macewen's sign, which yields a "cracked pot" sound upon gentle percussion of the skull over a suture line, was positive. These signs collectively pointed towards significantly increased intracranial pressure and the presence of hydrocephalus. General physical assessment showed all four extremities were intact with no gross abnormalities, and the anal opening was present and patent, ruling out imperforate anus. Craniofacial assessment identified further dysmorphic features in addition to the pronounced macrocephaly. These included bilateral microphthalmia (abnormally small eyes), closely spaced eyes indicative of hypotelorism, a noticeably depressed nasal bridge, and anomalies in the implantation of the ears. These facial characteristics are often associated with underlying central nervous system malformations.

Given the compelling clinical evidence of hydrocephalus, an initial cranial computed tomography (CT) scan was performed. This imaging study confirmed the presence of significant hydrocephalus, showing massively dilated ventricles. Following this definitive confirmation, the patient was promptly referred to a tertiary care hospital for further specialized neurosurgical and pediatric neurological management. It was noted that antenatal ultrasound examinations had been performed during early pregnancy. Subsequent ultrasound evaluations later in gestation had indeed observed fetal head enlargement, though the precise underlying etiology of the macrocephaly had not been definitively determined prenatally.

Upon arrival and evaluation at the tertiary hospital, the infant's condition was closely monitored. The head circumference continued to demonstrate a concerningly rapid increase. By one month of age, the OFC had progressed from 50 cm at birth to 56 cm. To gain a more comprehensive understanding of the neuroanatomical abnormalities, a second CT scan was performed approximately four weeks following the initial scan, when the infant was one month old. This detailed imaging provided crucial diagnostic information. It revealed features consistent with semilobar holoprosencephaly, characterized by partial separation of the cerebral hemispheres posteriorly with persistent fusion anteriorly. Furthermore, the CT scan demonstrated a cephalic index of 98, confirming severe brachycephaly, a condition describing a flattened, wide head shape. The scan also clearly visualized marked dilation of the coronal, sagittal, and lambdoid sutures, accompanied by evident thinning of

the cortical bone of the calvaria (ossa calvaria), all consistent with the effects of chronic, severe hydrocephalus.

The progressive and severe nature of the hydrocephalus, coupled with the rapidly increasing head circumference, which had reached an alarming 64 cm, necessitated urgent neurosurgical intervention. Consequently, a ventriculoperitoneal (VP) shunt insertion was performed when the patient was approximately 4 weeks and 6 days old (just under 5 weeks of age). This procedure aimed to divert the excess cerebrospinal fluid and alleviate the dangerously high intracranial pressure. Laboratory investigations conducted during his hospital admission revealed significant electrolyte abnormalities. Specifically, serum sodium was found to be 120 mEq/L, indicating hyponatremia; serum potassium was 6.18 mEq/L, indicating hyperkalemia; and serum chloride was 83.8 mmol/L, indicating hypochloremia. These findings required careful monitoring and judicious fluid and electrolyte management to prevent further complications.

The infant's clinical course, including treatments and follow-up observations, is outlined in Table 2. Follow-up assessment at three months of age revealed that the patient was experiencing a significant decline in expected growth parameters and was demonstrating profound developmental delays across multiple domains. Complications identified at this stage included malnutrition, likely secondary to feeding difficulties and increased metabolic demands, and ongoing severe developmental delay. Despite the timely placement of the VP shunt and comprehensive supportive care, the underlying severe brain malformation and its associated cascade of complications significantly and adversely impacted his early neurodevelopmental trajectory and overall health status.

Table 1. Summary of patient's clinical findings.

Category	Finding
Maternal history	25-year-old mother
	Second child
	Severe preeclampsia during pregnancy
	Premature rupture of membranes (<12 hours)
	Negative screenings for retroviral infection, hepatitis, syphilis
	No family history of similar conditions
Birth details	Gestational age: 35 + 3 weeks
	Delivery: Cesarean section
	Apgar scores: Not explicitly stated, but "born crying immediately"
	Birth weight: 4040 grams
	Length: 55 cm
	Single nuchal cord
Physical examination (Neonate)	Marked Macrocephaly (OFC 50 cm at birth)
	Prominent, tense anterior fontanel
	Bilateral sunset eyes
	Positive Macewen's sign
	Facial dysmorphism: Microphthalmia, closely spaced eyes (hypotelorism), depressed nasal bridge, ear implantation anomalies
	Extremities intact, anal opening present
Neuroimaging	Antenatal Ultrasound: Fetal head enlargement observed, cause undetermined
	Initial Postnatal CT Scan: Confirmed hydrocephalus
	Second CT Scan (at 1 month): Semilobar holoprosencephaly; Brachycephaly (Cephalic Index 98); Dilated sutures, thinned calvaria
Head circumference progression	At birth: 50 cm
	At 1 month: 56 cm
	At VP shunt surgery (~5 weeks): 64 cm
Laboratory findings	Hyponatremia (Sodium 120 mEq/L)
	Hyperkalemia (Potassium 6.18 mEq/L)
	Hypochloremia (Chloride 83.8 mmol/L)

Table 2. Summary of treatment procedures and follow-up.

Aspect	Details
Initial management	Referral to a tertiary hospital after initial hydrocephalus diagnosis
	Further diagnostic workup including second CT scan
	Monitoring of vital signs, head circumference, and neurological status
	Management of electrolyte imbalances (specific interventions not detailed but implied by findings)
Surgical intervention	**Procedure:** Ventriculoperitoneal (VP) Shunt Insertion
	Timing: Approximately 4 weeks and 6 days of age
	Indication: Progressive severe hydrocephalus with OFC at 64 cm
	Details of shunt type/settings: Not specified in the source document
Post-surgical care	Routine post-operative neurosurgical monitoring
	Wound care
	Monitoring for shunt malfunction or infection
Follow-up (at 3 months of age)	**Growth:** Decline in growth parameters observed
	Development: Significant developmental delays across multiple domains
	Complications: Malnutrition; Ongoing severe developmental delay
	Overall Status: Poor prognosis noted despite interventions
Long-term plan	Multidisciplinary supportive care (implied focus on symptom control, complication prevention, quality of life)

3. Discussion

This case report meticulously documents the intricate clinical course of a neonate diagnosed with semilobar holoprosencephaly (HPE), a presentation made exceptionally unusual and complex by the coexistence of marked macrocephaly secondary to severe congenital hydrocephalus, significant brachycephaly, and early-onset hyponatremia with other electrolyte disturbances. The confluence of these findings in a single patient challenges the archetypal image of HPE, which is more commonly associated with microcephaly or normocephaly, thereby underscoring the profound phenotypic heterogeneity inherent in this spectrum of neurodevelopmental disorders. A comprehensive discussion of the pathophysiology, clinical manifestations, diagnostic considerations, and management implications of each of these major components is essential to appreciate the multifaceted nature of this case. Holoprosencephaly arises from a fundamental defect in the early embryogenesis of the forebrain, specifically a failure of the prosencephalon to undergo complete cleavage and differentiation into the two cerebral hemispheres, a critical sequence of events typically unfolding between the 18th and 28th days of gestation. This malformation is not merely a structural anomaly but reflects a profound disruption in the intricate molecular signaling pathways that govern forebrain development. The Sonic Hedgehog (SHH) signaling pathway is paramount among these, playing an indispensable role in ventral patterning of the neural tube, midline development, and cell fate specification. Mutations in the SHH gene itself, or in genes encoding components of its pathway such as PTCH1 (Patched-1, the SHH receptor), SMO (Smoothened, a co-receptor), and GLI2 (a downstream transcription factor), are well-established causes of HPE. Other crucial genes implicated in HPE pathogenesis include ZIC2 (Zinc finger protein of the cerebellum 2), involved in dorsal neural tube development and its interaction with the SHH pathway; SIX3 (SIX homeobox 3), a transcription factor critical for anterior neural plate specification and eye development; and TGIF1 (TGFB-induced factor homeobox 1), which modulates TGF-beta signaling and interacts with retinoic acid pathways. Disruption in any of these, or indeed other less commonly implicated genes, can perturb the delicate orchestration of forebrain cleavage, leading to the HPE spectrum. Environmental factors, such as maternal diabetes mellitus or exposure to teratogens like alcohol or retinoic acid during the critical window of

organogenesis, can also contribute to HPE, possibly by interacting with underlying genetic susceptibilities or by independently disrupting these sensitive developmental processes.[11,12]

Semilobar HPE, the specific subtype identified in this patient through detailed neuroimaging, occupies an intermediate position within the HPE severity spectrum. Anatomically, it is defined by a partial separation of the cerebral hemispheres, which is typically more evident posteriorly, while the anterior aspects, particularly the frontal lobes, remain fused to a variable extent. This results in a characteristic neuroanatomical landscape where the interhemispheric fissure is incompletely formed, often present only in the occipital and posterior parietal regions. The corpus callosum, the major commissural tract connecting the two hemispheres, is frequently absent (agenesis) or severely underdeveloped (hypoplasia), especially its anterior portions like the genu and rostrum. The septum pellucidum, a thin membrane that normally separates the anterior horns of the lateral ventricles, is invariably absent in semilobar HPE. Deep grey matter structures, such as the thalami and basal ganglia, may exhibit varying degrees of fusion across the midline. The ventricular system is also characteristically malformed, often featuring a single anterior ventricular cavity (monoventricle) that may communicate with rudimentary, partially separated posterior and temporal horns. Olfactory bulbs and tracts, which develop as outgrowths of the forebrain, are commonly absent or hypoplastic, leading to anosmia (loss of smell) in individuals who survive. The CT findings in the presented case, demonstrating partial hemispheric separation with anterior fusion, were entirely consistent with these neuroradiological hallmarks of semilobar HPE.[13]

The facial dysmorphisms observed in this neonate—specifically microphthalmia, hypotelorism (closely spaced eyes), a depressed nasal bridge, and anomalous ear implantation —are recognized correlates of the underlying brain malformation. The developmental principle "the face predicts the brain" finds strong support in HPE, where the severity of midline facial defects often mirrors the degree of forebrain non-cleavage. While the most extreme facial anomalies, such as cyclopia (a single median eye) or ethmocephaly/cebocephaly (hypotelorism with a proboscis-like nasal structure), are typically associated with the most severe alobar form of HPE, individuals with semilobar HPE can present with a wide spectrum of facial features. These can range from severe manifestations, such as a median cleft lip and/or palate or significant hypotelorism as seen in this case, to much milder features or even an apparently normal facial appearance, particularly if the brain malformation is less severe or predominantly posterior. The presence of microphthalmia and hypotelorism in this infant, therefore, served as external signposts pointing towards the significant underlying forebrain developmental pathology. The depressed nasal bridge and ear anomalies further contribute to a dysmorphic gestalt often seen in syndromic conditions affecting midline development. The intricate relationship between facial and brain development stems from the shared origins of many craniofacial structures from the prechordal mesoderm and neural crest cells, which also play crucial roles in inducing and patterning the overlying forebrain. Disruptions affecting these cell populations or their signaling interactions can thus have pleiotropic effects on both brain and facial morphogenesis.[14]

Perhaps the most immediately striking and seemingly paradoxical clinical feature in this case was the presence of marked macrocephaly from birth (OFC 50 cm), which progressed alarmingly to 64 cm by the age of approximately five weeks. This cranial enlargement was a direct and unambiguous consequence of severe congenital hydrocephalus, an excessive accumulation of cerebrospinal fluid (CSF) within the ventricular system leading to ventricular dilation and increased intracranial pressure. This presentation starkly contrasts with the classical association of HPE with microcephaly or normocephaly, conditions one might expect due to the inherent deficiency in forebrain parenchymal

development. The term "hydrocephalic holoprosencephaly" has been used to describe this scenario, highlighting the coexistence of these two seemingly contradictory conditions.

The pathophysiology of CSF dynamics involves a delicate balance between CSF production, circulation, and absorption. CSF is primarily produced by the choroid plexuses located within the cerebral ventricles, with a smaller contribution from the ependymal lining and brain parenchyma. It circulates from the lateral ventricles through the foramina of Monro into the third ventricle, then via the aqueduct of Sylvius into the fourth ventricle, and finally exits into the subarachnoid space through the foramina of Luschka and Magendie. Absorption primarily occurs through arachnoid villi and granulations into the dural venous sinuses. Hydrocephalus arises when this equilibrium is disturbed, either by overproduction of CSF (rare), obstruction of its circulatory pathways (obstructive or non-communicating hydrocephalus), or impaired absorption (communicating hydrocephalus).[15]

In the context of HPE, hydrocephalus is a recognized comorbidity, affecting a substantial subset of patients, with some estimates suggesting that around one-sixth may eventually require CSF diversion procedures. The precise mechanisms underlying hydrocephalus in HPE are not always clearly defined and can be multifactorial and heterogeneous, often related to the specific structural anomalies present. The aqueduct of Sylvius, a narrow channel connecting the third and fourth ventricles, is a common site for obstruction. In HPE, aqueductal stenosis can be a primary developmental anomaly associated with the brain malformation or can occur secondarily due to distortion of the brainstem and surrounding structures by the HPE malformation itself or by associated cysts. The foramina of Monro, Luschka, or Magendie can be intrinsically malformed, stenotic, or obstructed by abnormal tissue, membranes, or cysts related to the HPE complex. The subarachnoid space pathways may be maldeveloped, or the arachnoid villi themselves may be functionally deficient due to the widespread nature of the developmental insult.

Other CNS anomalies frequently co-occurring with HPE, such as Dandy-Walker malformation or other posterior fossa abnormalities, can independently contribute to hydrocephalus. The rapid and progressive increase in head circumference observed in this patient, along with clinical signs of increased intracranial pressure such as the bulging fontanel, sunset eyes, and positive Macewen's sign, unequivocally indicated pathologically elevated intracranial pressure that demanded urgent neurosurgical intervention. The placement of a ventriculoperitoneal (VP) shunt serves to bypass the obstruction or overcome the impaired absorption by diverting CSF from the cerebral ventricles into the peritoneal cavity, where it can be absorbed. While this intervention effectively manages the hydrocephalus and controls intracranial pressure, it is crucial to understand that it does not correct the underlying HPE malformation. The primary goal of shunting in this context is to prevent further neurological damage from sustained intracranial hypertension, alleviate symptoms, improve the ease of nursing care (by preventing an excessively large and difficult-to-manage head), and potentially optimize any residual developmental potential, although the overall prognosis remains heavily influenced by the severity of the HPE itself. The phenomenon of "macrocephalic HPE" vividly illustrates how a secondary complication like hydrocephalus can dominate the clinical presentation, effectively "masking" the expected cranial size related to the primary parenchymal maldevelopment and creating a complex diagnostic and management challenge.[16]

The confirmation of severe brachycephaly, evidenced by a cephalic index of 98 on the second CT scan, added another significant dimension to the complex craniofacial phenotype of this infant. Brachycephaly denotes a specific type of cranial dysmorphology where the head is disproportionately wide relative to its length. The cephalic index (CI), calculated as (cranial width / cranial length) × 100, is

the standard metric for quantifying this relationship, with values typically above 80-85 (depending on specific normative data and age) considered indicative of brachycephaly. A CI of 98, as in this case, signifies a very pronounced brachycephalic head shape. The development of normal skull shape (orthocephaly) is a dynamic process influenced by several factors, including intrinsic brain growth, the patency of cranial sutures, and external molding forces. Cranial sutures, the fibrous joints between the bones of the calvarium, are critical growth sites that allow the skull to expand in response to the rapidly growing brain during infancy.

This is the most common type and results from external pressures applied to the malleable infant skull, often due to prolonged positioning in supine, particularly if associated with torticollis or limited mobility. While typically presenting asymmetrically (plagiocephaly), symmetrical posterior flattening (deformational brachycephaly) can also occur. Craniosynostotic Brachycephaly, This form results from the premature fusion of one or more cranial sutures. Bilateral coronal synostosis (fusion of both coronal sutures) classically leads to a brachycephalic head shape, often with associated frontal bossing and potential retrusion of the midface. Other suture synostoses can also contribute to or be associated with brachycephaly in syndromic contexts. Syndromic Brachycephaly can be a feature of various genetic syndromes, sometimes in conjunction with craniosynostosis (Apert syndrome, Crouzon syndrome, Pfeiffer syndrome) or as part of a broader pattern of dysmorphism without primary synostosis. Compensatory Brachycephaly, in some cases, restricted growth in one dimension (length) due to other factors, might lead to compensatory widening.

In the context of this infant with semilobar HPE and severe hydrocephalus, the brachycephaly was most likely a complex interplay of deformational forces and altered intrinsic brain development. The severe hydrocephalus would have exerted significant, sustained outward pressure on the calvarial bones. However, the underlying HPE means that the brain parenchyma itself was abnormally structured. It is plausible that the pattern of ventricular enlargement and the distribution of CSF pressure, superimposed on a brain with abnormal anterior-posterior and lateral dimensions due to the HPE, led to a preferential widening of the skull rather than proportional expansion in all directions. The rapid expansion due to hydrocephalus might have also caused splaying of sutures, particularly the sagittal suture, which could contribute to increased biparietal diameter (width). While primary craniosynostosis was not explicitly diagnosed from the provided information, it is important to consider that severe hydrocephalus can sometimes lead to secondary suture apposition or even fusion if the pressure is longstanding, or conversely, can cause marked sutural diastasis as noted by the dilated sutures in this case. The thinned cortical bone of the calvaria further attests to the chronic and severe nature of the intracranial hypertension, which would have rendered the skull more susceptible to deformation. The intrinsic dysmorphogenesis of the brain in HPE might also have played a role in dictating the primary shape upon which hydrocephalic forces acted. Therefore, the brachycephaly in this patient is best understood as a consequence of abnormal intracranial pressures and volumes acting on a developing skull that was overlying a structurally abnormal brain, rather than a simple positional deformity or primary craniosynostosis alone.[17]

The discovery of significant hyponatremia (serum sodium 120 mEq/L), accompanied by hyperkalemia (serum potassium 6.18 mEq/L) and hypochloremia (serum chloride 83.8 mmol/L), signaled a critical systemic derangement in this already vulnerable neonate. Hyponatremia, defined as a serum sodium concentration below 135 mEq/L, is the most common electrolyte abnormality encountered in hospitalized patients, including neonates, and can have profound implications for neurological function, especially in individuals with pre-existing CNS pathology. Rapid or severe hyponatremia can lead to cerebral edema, seizures, altered mental status, and, if uncorrected or improperly corrected, can result in permanent

neurological sequelae such as osmotic demyelination syndrome (central pontine myelinolysis). In patients with CNS disorders, particularly those involving increased intracranial pressure (ICP), structural brain lesions, or neurosurgical interventions, hyponatremia typically arises from one of two primary mechanisms: the Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) or Cerebral Salt Wasting (CSW) syndrome.

SIADH, this syndrome is characterized by the non-physiological (inappropriate) release of antidiuretic hormone (ADH, also known as vasopressin) from the posterior pituitary, or by an enhanced renal response to ADH, in the absence of osmotic or volumetric stimuli that would normally trigger ADH secretion. ADH promotes water reabsorption in the renal collecting ducts by increasing the insertion of aquaporin-2 water channels into the apical membrane. In SIADH, this excessive ADH action leads to impaired water excretion, resulting in water retention, expansion of extracellular fluid volume (though often appearing clinically euvolemic or only mildly hypervolemic due to some degree of "vasopressin escape" and natriuresis), and dilutional hyponatremia. Urine is typically concentrated (high osmolality, high specific gravity) relative to plasma osmolality, and urine sodium concentration is usually elevated (often >40 mEq/L) as the body attempts to excrete sodium to counteract the volume expansion. Various CNS conditions can trigger SIADH, including structural malformations like HPE, infections (meningitis, encephalitis), tumors, trauma, stroke, and, importantly, conditions causing increased ICP, as the hypothalamus and pituitary gland are sensitive to pressure changes.[18]

CSW, this syndrome is characterized by a primary renal loss of sodium (natriuresis) leading to hyponatremia and, crucially, extracellular fluid volume depletion (hypovolemia). The exact pathophysiology of CSW is less well understood but is thought to involve the release of a circulating natriuretic factor (possibly brain natriuretic peptide or others) from the injured brain, or disruption of sympathetic neural input to the kidneys, leading to impaired renal sodium reabsorption. Urine sodium concentration is high, and urine output is often elevated. Distinguishing CSW from SIADH is critical because their management strategies are diametrically opposed: fluid restriction is the cornerstone of SIADH treatment, whereas CSW requires aggressive sodium and volume repletion. Misdiagnosing CSW as SIADH and imposing fluid restriction can exacerbate hypovolemia and worsen neurological outcomes. In this neonate with severe hydrocephalus and HPE, SIADH would be a prime suspect for the hyponatremia, given the known association between increased ICP and ADH dysregulation. The source document abstract explicitly mentions hyponatremia in hydrocephalus being linked to ADH secretion due to increased pressure on the hypothalamus. However, a definitive diagnosis between SIADH and CSW requires careful assessment of the patient's volume status (clinical signs of dehydration or overload, daily weights, fluid balance charts) and concurrent measurements of serum and urine osmolality and sodium concentrations, which were not fully detailed in the provided case summary beyond the initial serum values.[19]

The accompanying hyperkalemia (K+ 6.18 mEq/L) and hypochloremia (Cl- 83.8 mmol/L) add further complexity. Hyperkalemia is not a typical feature of classic SIADH or CSW. Its presence could suggest several possibilities: Renal Impairment: Although not stated, any degree of renal dysfunction (which can occur in critically ill neonates) could impair potassium excretion; Cellular Shift: Acidosis (if present) or significant tissue breakdown could cause potassium to shift from intracellular to extracellular compartments; Adrenal Insufficiency: HPE can be associated with pituitary dysfunction, which could theoretically extend to impaired ACTH secretion and secondary adrenal insufficiency, leading to hyponatremia and hyperkalemia (due to aldosterone deficiency). This would be a less common but important consideration in the differential, especially if hypotension were present. Pseudohyperkalemia:

Hemolysis of the blood sample can falsely elevate potassium levels. The hypochloremia often mirrors the hyponatremia in dilutional states or in states of salt loss, but its specific context would depend on the acid-base status and renal function. Careful and precise management of these complex electrolyte imbalances is paramount in such a critically ill neonate, involving cautious correction of sodium levels to avoid overly rapid shifts, investigation and management of hyperkalemia, and overall fluid balance optimization, all guided by frequent laboratory monitoring.

The fact that this infant was born to a mother who experienced severe preeclampsia during the pregnancy introduces another layer of potential biological influence on the neonatal outcome. Preeclampsia is a serious multisystem disorder of pregnancy, typically occurring after 20 weeks of gestation, characterized by new-onset hypertension and proteinuria, or, in the absence of proteinuria, new-onset hypertension with evidence of other end-organ dysfunction (renal insufficiency, liver involvement, neurological complications, hematological disturbances, or uteroplacental dysfunction manifesting as fetal growth restriction). Severe preeclampsia involves more pronounced hypertension or more significant end-organ damage. Preeclampsia is fundamentally a disorder of placentation, where abnormal development of the spiral arteries in the early stages of pregnancy leads to placental underperfusion, hypoxia, and ischemia. This ischemic placenta then releases various factors into the maternal circulation—such as anti-angiogenic proteins (soluble fms-like tyrosine kinase-1 or sFlt-1, soluble endoglin or sEng) and pro-inflammatory cytokines—that cause widespread maternal endothelial dysfunction, leading to the clinical manifestations of the syndrome.

The impact of maternal preeclampsia on the fetus and neonate can be substantial. Uteroplacental insufficiency can lead to intrauterine growth restriction (IUGR), oligohydramnios, and chronic fetal hypoxia. Preeclampsia is also a major cause of indicated preterm birth, as delivery of the placenta is the only definitive cure for the maternal condition. Neonates born to preeclamptic mothers, especially those born preterm or with IUGR, are at increased risk for a variety of complications, including respiratory distress syndrome, hypoglycemia, hypocalcemia, polycythemia, and neurodevelopmental problems. The link between maternal preeclampsia and the specific risk of HPE in the offspring is an area that requires more definitive research, though some case reports and smaller studies have suggested a possible association. The other study reported a case of semilobar HPE with cebocephaly associated with maternal early-onset preeclampsia. The biological plausibility for such a link, if it exists, could be multifaceted. The period of forebrain cleavage (18-28 days gestation) occurs very early in pregnancy, often before preeclampsia is clinically manifest. However, the underlying processes that predispose to preeclampsia (such as factors affecting placental development or maternal vascular health) might already be subtly operative or could create a generally suboptimal intrauterine environment from very early on. Alternatively, severe early-onset preeclampsia might exert its effects on fetal brain development through mechanisms like: Chronic Hypoxia and Oxidative Stress: Placental insufficiency can lead to chronic fetal hypoxia and increased oxidative stress, both of which are detrimental to neuronal development and could potentially exacerbate or interact with genetic predispositions to brain malformations; Altered Angiogenesis: The imbalance of angiogenic and anti-angiogenic factors central to preeclampsia pathogenesis could theoretically affect vascular development within the fetal brain during critical periods; Inflammation: The systemic inflammatory state in preeclampsia could have transplacental effects on the fetal inflammatory milieu, which is increasingly recognized as playing a role in brain development and injury. It is also important to consider that preeclampsia might simply be a co-occurring condition without a direct causal link to the HPE, or that both conditions might share some underlying, yet unidentified, common risk factors. In this particular case, the infant was born late preterm (35+3 weeks),

likely as a consequence of the severe maternal preeclampsia necessitating delivery. Prematurity itself is an independent risk factor for a host of neonatal complications, which would compound the challenges posed by the HPE and its associated anomalies. Thus, while a direct causal link between the maternal preeclampsia and the infant's HPE cannot be definitively established from this single case, the preeclamptic environment undoubtedly contributed to the overall perinatal stress and the need for preterm delivery, adding to the infant's vulnerability.[20]

The diagnostic journey for this infant, from antenatal suspicion to definitive postnatal characterization of the complex neuroanatomical defects, highlights several important aspects of modern perinatal diagnosis and its challenges. Antenatal ultrasound evaluations during the pregnancy had noted fetal head enlargement, but the precise underlying cause remained undetermined prior to birth. This is not an uncommon scenario. While routine obstetric ultrasound can detect overt macrocephaly, and dedicated fetal neurosonography (often performed by specialists in maternal-fetal medicine or pediatric radiology) can identify many structural brain anomalies, the diagnostic accuracy is operator-dependent and influenced by gestational age, fetal positioning, maternal habitus, and the specific nature of the anomaly. Severe forms of HPE, particularly alobar HPE with its characteristic monoventricle and fused thalami, can often be suspected or diagnosed in the late first or early second trimester. However, semilobar HPE, especially if the degree of fusion is less extensive or if hydrocephalus is a very early and dominant feature, obscuring some of the finer details of forebrain architecture on ultrasound, can be more challenging to delineate precisely. Hydrocephalus itself is readily detectable by ultrasound as ventricular enlargement, but identifying its specific cause (communicating vs. non-communicating, presence of associated malformations like HPE) can be difficult with ultrasound alone. Fetal magnetic resonance imaging (MRI) is increasingly used as an adjunct to ultrasound when a complex CNS anomaly is suspected. Fetal MRI can provide superior anatomical detail, better tissue contrast, and multiplanar imaging capabilities, often clarifying ambiguous ultrasound findings and identifying associated anomalies not visible or poorly characterized by ultrasound. It is not stated if fetal MRI was performed in this case.[18]

Postnatally, the diagnostic process continued with cranial CT scans. The initial postnatal CT scan confirmed the presence of significant hydrocephalus, prompting referral to a tertiary center. It was the second, more detailed CT scan, performed at one month of age, that provided the definitive diagnosis of semilobar holoprosencephaly and the associated finding of severe brachycephaly. This illustrates that even with postnatal imaging, a complete understanding of complex congenital brain malformations may require serial imaging or the use of optimal imaging modalities. CT scans are readily available, quick to perform, and excellent for visualizing bony structures (skull, sutures) and identifying gross hydrocephalus or calcifications. However, for detailed assessment of brain parenchymal malformations, particularly those involving white matter, grey matter differentiation, and subtle midline structures, MRI is generally considered the imaging modality of choice, offering superior soft-tissue resolution without the use of ionizing radiation. While CT was used here for diagnosis, an MRI, had it been performed, might have offered even more granular detail about the extent of forebrain fusion, the status of the corpus callosum, olfactory structures, and pituitary gland, which can have important prognostic and management implications (endocrine dysfunction is common in HPE). The CT findings of dilated sutures and thinned calvaria were classical indicators of chronic, severe intracranial hypertension, consistent with the degree of hydrocephalus observed. The cephalic index of 98, calculated from the CT measurements, objectively confirmed the clinical impression of brachycephaly. This comprehensive neuroimaging was crucial for establishing the full extent of the neurological insult,

guiding neurosurgical intervention (VP shunting), and informing prognostic discussions with the family.

The clinical trajectory of this infant, despite maximal supportive care including timely neurosurgical intervention for hydrocephalus, was unfortunately characterized by a progressive decline in growth parameters and the emergence of profound developmental delays by three months of age, complicated by malnutrition. This outcome, while disheartening, is regrettably consistent with the natural history of severe forms of semilobar holoprosencephaly, particularly when compounded by severe hydrocephalus and other systemic complications from an early age. The management of an infant with such a complex constellation of neurodevelopmental and systemic issues necessitates a highly coordinated, multidisciplinary approach. The core team typically involves: Neonatologists: For initial resuscitation, stabilization, management of prematurity-related issues, and coordination of care in the neonatal intensive care unit (NICU); Pediatric Neurosurgeons: For the assessment and surgical management of hydrocephalus (VP shunt placement) and any other surgically amenable neurological conditions. This includes ongoing monitoring for shunt function and potential complications (infection, obstruction, overdrainage); Pediatric Neurologists: For the diagnosis and management of seizures (common in HPE), tone abnormalities, assessment of neurological status, and long-term neurodevelopmental monitoring; Developmental Pediatricians: To formally assess developmental progress across all domains (gross motor, fine motor, cognitive, language, social-emotional), identify specific delays, and guide early intervention strategies; Clinical Geneticists: To evaluate for an underlying genetic etiology of the HPE (chromosomal microarray, specific gene panel testing, or whole exome/genome sequencing), provide genetic counseling to the family regarding recurrence risks, and identify any associated syndromic features; Pediatric Endocrinologists: Given the high incidence of pituitary dysfunction and associated endocrinopathies in HPE (such as diabetes insipidus, growth hormone deficiency, adrenal insufficiency, hypothyroidism), endocrine evaluation and management are often crucial. The hyponatremia and hyperkalemia in this case might have warranted endocrine consultation to rule out adrenal insufficiency; Nutritionists/Dietitians: To address feeding difficulties (often due to oral-motor dysfunction, aspiration risk, or neurological impairment) and manage malnutrition by optimizing caloric and nutrient intake, potentially via specialized formulas or enteral tube feedings; Physical, Occupational, and Speech Therapists: To provide early intervention therapies aimed at maximizing motor function, improving oral-motor skills and feeding, facilitating communication, and supporting overall development; Social Workers and Psychologists: To provide psychosocial support to the family, assist with navigating complex medical systems, connect them with community resources, and address the emotional and ethical challenges associated with caring for a child with a life-limiting and severely disabling condition.

The prognosis for holoprosencephaly is generally guarded and is highly dependent on the subtype and severity of the brain malformation, as well as the presence and severity of associated anomalies and complications. Alobar HPE carries the gravest prognosis, with very few infants surviving beyond the first year of life, and those who do typically remain in a persistent vegetative state or have minimal interaction with their environment. Semilobar HPE, as in this case, also has a poor prognosis, though survival beyond infancy is more common than in alobar HPE (around 50% may survive beyond one year if the HPE is isolated, though this figure is likely lower with severe complications like those seen here). However, survivors almost invariably experience severe global developmental delays, profound intellectual disability, epilepsy, motor impairments (spasticity, dystonia), feeding difficulties, and a multitude of other medical issues. The early onset of severe, rapidly progressive hydrocephalus, requiring shunting in the first few weeks of life, often portends a more challenging

course, as does the presence of significant electrolyte disturbances, which can cause secondary neurological injury. The malnutrition and decline in growth noted at three months are common sequelae reflecting the systemic impact of such profound neurological impairment. While medical and surgical interventions aim to manage complications, improve quality of life, and ease the burden of care, they do not alter the fundamental limitations imposed by the underlying brain malformation. Discussions regarding prognosis and goals of care with the family must be handled with utmost sensitivity, honesty, and compassion, focusing on realistic expectations and prioritizing the infant's comfort and dignity.

This exhaustive discussion has aimed to dissect the multiple layers of complexity inherent in this case of semilobar holoprosencephaly presenting with an atypical constellation of severe hydrocephalus, macrocephaly, brachycephaly, and hyponatremia. Each component, from the fundamental embryological misstep leading to HPE to the dynamic disturbances in CSF physiology causing hydrocephalus, the resultant cranial dysmorphologies, the perilous systemic electrolyte imbalances, and the overarching influence of perinatal factors, contributes to a uniquely challenging clinical scenario. The journey from diagnostic uncertainty to a comprehensive understanding of the infant's condition underscores the power of modern neuroimaging and the necessity of a keen clinical acumen. Ultimately, while advanced medical and surgical care can address many of the secondary complications, the profound impact of the primary neurodevelopmental insult on long-term outcome remains the most formidable challenge, emphasizing the need for ongoing research into the causes and potential prevention of such devastating congenital brain malformations, alongside a continued commitment to providing compassionate, holistic, and family-centered care for affected children and their families.[19,20]

4. Conclusion

This case report meticulously detailed the presentation of a newborn with semilobar holoprosencephaly, distinguished by an atypical manifestation of marked macrocephaly due to severe congenital hydrocephalus, a departure from the more common microcephalic presentations. The clinical scenario was further complicated by significant brachycephaly and early-onset hyponatremia. Despite aggressive multidisciplinary management, including ventriculoperitoneal shunt placement and electrolyte correction, the infant exhibited profound developmental delays and growth failure by three months, underscoring the grim prognosis associated with this severe neurodevelopmental disorder. This case highlights the broad spectrum of holoprosencephaly, emphasizing the need for comprehensive neuroimaging in neonates with severe hydrocephalus and vigilant management of systemic complications. It underscores the importance of a holistic approach in caring for these vulnerable infants and their families, navigating a challenging clinical course with profound prognostic implications.

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