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REVIEWER REPORTS

Reviewer Comments:

Reviewer 1
This is a well written review of the literature on ABS - illustrated by 3 cases. Complications from ABS are rarely seen in neurosurgery and so this article is of some general educational interest, although, as with any small case series, there is limited academic advancement. The article could be significantly shortened.

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Child's Nervous System <Jhoanna.Hernandez@springernature.com> 23 Mei 2023 pukul 02.29
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~~CASE-BASED REVIEW~~

~~Title:~~

Amniotic band syndrome with CNS involvement: ~~A~~a pediatric neurosurgeon's dilemma—a case series and literature review

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Abstract

Background

-Amniotic band syndrome (ABS) is a rare congenital disease characterized by a broad spectrum of congenital anomalies resulting from the strangulated developing organ(s) by the detached fibrous amniotic band. The prevalence of CNS involvement in ABS is rare, but the mortality rate in these cases is high, while morbidity among the surviving patients is inevitable.

Case report

-Three-month-old male, 9-month-old female, and newborn female babies were presented with head lump(s), severe facial cleft, syndactyly, and finger amputation. The patient's head imaging

confirmed meningoencephalocele as the cause of the head lump in 2 patients; meanwhile, a porencephalic cyst was identified as the origin of head lumps in the other patient. VP shunt placement surgery was performed as the initial management in 2 patients, while one patient directly underwent meningoencephalocele resection surgery. Craniofacial and limb reconstructions were planned as the follow-up management in all cases. Unfortunately, one patient died of complications from suspected aspiration, while another never returned for follow-up treatment.

Conclusion

-Here, we report 3 ABS cases with CNS involvement. Despite the severe disfigurement and disability, the inexistence of fatal malformation might lead to long-term survival. The ~~T~~treatment of malformation(s) that might predispose to another fatal condition and surgery(-ies) to improve functional outcomes and patient's social acceptability should be prioritized in managing the surviving ABS patients.

Keywords: Amniotic band syndrome, Strangulated developing organ, Detached fibrous amniotic band, Head lump, Facial cleft, Syndactyly, Finger amputation

Introduction

Amniotic band syndrome (ABS) is a rare congenital disease where an abnormal detachment of fibrous amniotic band occurs and strangulates fetal's organ(s), causing cleft and amputation of the strangulated organ(s). The prevalence of this complex disease ranges from 1:1,200 to 1:15,000 live births and 1:70 stillbirths [1]. Due to the randomness of the affected organ(s), ABS is characterized by a wide spectrum of congenital defects, most typically limb and finger

amputation [2-3]. The attachment of fibrous amniotic bands to CNS organ(s) would cause CNS involvement in ABS, often leading to fatal consequences. Depending on the severity of CNS involvement and other affected organ(s), morbidity in the surviving patients is inevitable [4-5]. Due to the variety of combinations of congenital defects in ABS, standardized treatment for ABS has yet to be established. Thus, the description of the new ABS spectrum and its medical management are valuable in extending our understanding of this devastating condition and improving ABS patients' outcomes.

Exemplary case description

Case 1

A 3-month-old male baby presented with multiple congenital anomalies, including a large lump on the top of his forehead, facial malformations, finger amputation, and fusion. He was the third child of healthy non-consanguineous parents with no family history of congenital malformation. History of trauma, amniocentesis, misoprostol consumption, and any other incident that may cause vascular insults was denied; hence, the pregnancy was uneventful until he was suspected of encephalocele by ultrasound that was performed when his delivery was stalled. He was delivered by cesarean section at 38 weeks gestation. The parents noticed the presence of all anomalies since his birth. They acknowledged that the lump grew larger over time, measuring 20 × 20 × 8 cm when presented. The transillumination result was positive, indicating that the lump was predominantly filled with cerebrospinal fluid. Facial malformation, including the absence of bilateral bulbi (anophthalmia) and nasal (arrhinia), cleft lip, and cleft palate (labiopalatoschizis) were detected (Figure 1A-B). Moreover, the absence of a distal phalanx of the middle toe of his left foot and fusion of the toes of his right foot and fingers of both hands

(Fig ~~ure~~ 1 C~~-1~~ F) were also acknowledged. Characteristic digital amputation due to constriction band was identified on all extremities.

Head computed tomography (CT) scan revealed extensive craniofacial malformation, partial agenesis of the frontal bone, and extracalvarial herniation of cerebral tissue into the proximal part of the encephalocele. Since the risk of rupture in a patient with giant encephalocele is high, he underwent ventriculoperitoneal (VP) shunt placement (Fig ~~ure~~ 2 A~~-~~ C) prior to encephalocele resection surgery; thus, the size of the encephalocele was reduced to 12 ~~×~~ 10 ~~×~~ 5 cm. Then, he underwent a successful encephalocele resection surgery (Fig ~~ure~~ 2 D~~-~~ F). Afterwards, he was planned to undergo a series of facial reconstruction surgeries to treat his cleft lip and palate, anophthalmia, and arrhinia, and syndactyly release surgery. Unfortunately, prior to these planned surgeries, the patient showed signs of aspiration pneumonia at home, including fever and respiratory distress. After ~~three~~ 3 days, he succumbed to his illness when his parents were just about to take him to the nearest hospital.

Case 2

A 9-month-old female baby consulted with multiple congenital anomalies, including a lump on her left head, facial deformities, amputated left foot, amputated fingers and fusion, and a history of recurrent seizures. She was the first child of healthy non-consanguineous parents with no family history of congenital diseases. History of trauma, amniocentesis, consumption of drugs, and other events that might cause vascular insults during gestation was denied. During gestation, her mother had a routine antenatal check; hence, a lump on the patient's head was detected at 20 weeks gestation, then she was delivered by cesarean section at 39 weeks gestation. Her parents acknowledged the presence of all congenital anomalies since birth. The lump on her head grew

to the size of 20 × 19 × 8 cm when she was presented. Other prominent defects were also detected, including bilateral anophthalmia, bilateral labiopalatoschizis (Figure 3A), syndactyly of both hands, digital amputations of fingers and toes from her right hand and right foot, and complete amputation of her left foot (Figure 3 B–E). Constriction bands were identified on the hands' syndactyly and proximal of the amputated left foot.

A head CT scan confirmed the diagnosis of meningoencephalocele, along with the partial absence of the bilateral frontal, temporal, and parietal bones. She underwent a successful meningoencephalocele resection surgery to eliminate the risk of rupture. The patient's post-surgical assessment was uneventful, and at the time of publication, she is scheduled to undergo labiopalatoschizis reconstruction surgery.

Case 3

A newborn female baby presented with multiple congenital anomalies, including multiple lumps on her head, facial defects, finger amputation, and fusion. She was the first child of non-consanguineous parents with no family history of congenital diseases. The gestation period went uneventful, with a history of trauma, amniocentesis, infection, drug consumption, and other events that might affect fetal vascularization were all absent. Nevertheless, USG at 24 weeks' gestation detected the patient's head lump and other congenital anomalies; hence, she was delivered by cesarean section at 39 weeks gestation.

Physical examination identified three lumps on her head, including one lump on the frontal region with a size of 5 × 4 × 3 cm, one lump on the parietooccipital region of 6 × 5 × 2.5 cm in size, and another lump on the temporooccipital region sized 2 × 2 × 2 cm.

Transillumination results indicated the cystic nature of the lumps. Careful observation of the patient's facial defects acknowledged nasal cleft and labiopalatoschizis (Figure 4A-B). The patient also had anomalies in all extremities, including syndactyly of both hands, constriction bands on multiple toes of both feet, and varus rotation of the left small toe (Figure 4C-F). The patient's head MRI revealed porencephalic cysts as the cause of head lumps. Furthermore, it identified dysgenesis of bilateral parietal bones, lobar holoprosencephaly, agenesis of the corpus callosum and septum pellucidum, and aqueduct stenosis. Malformation of the brain midline was also acknowledged (Figure 5).

To treat the porencephalic cysts, she underwent VP shunt placement surgery. The post-surgical observation was uneventful; thus, she was discharged and planned to undergo a series of reconstruction surgeries to treat the defects of her craniofacial and extremities. Nonetheless, two months after the VP shunt placement surgery, the patient was readmitted and diagnosed with shunt malfunction. She underwent shunt repair surgery, and no surgical complication was identified afterward. Unfortunately, she never returned to the hospital for routine follow-up; thus, her current condition is unknown.

Discussion

Although the clinical description of this particular entity in a scientific publication could be found as early as 1946, it was not until 1971 that the term "amniotic-band syndrome" (ABS) was coined in a case series about a spectrum of deformities that were identified in infants who were born from a mother with a history of lysergic acid diethylamide (LSD) intake [6]. In brief, partial detachment of the amniotic layer from the chorion causes the free amniotic band to

entangle and strangulate the developing organ(s) of the growing fetus, leading to the decrease of the vascular supply, thus causing atrophy, cleft, or amputation of the strangulated organ(s), such as nose, finger(s), and toe(s) [1,2,6]. As the loose amniotic band can randomly attach to any organ(s), ABS is arguably a generic name for a wide spectrum of congenital defects. In cases where ABS patients are presented with CNS anomalies, a neurosurgeon's familiarity with recognizing the clinical presentation of this syndrome would be pivotal to diagnosing and treating the patients accordingly.

Clinical presentation and diagnosis

ABS has a vast spectrum, depending on the part(s) of the fetal body where the band attaches to and strangulates [1]. Based on the published case reports, some findings are pathognomonic of ABS. These include finger(s) or toe(s) amputation, finger(s) or toe(s) fusion, and identification of constriction bands on the affected organ(s) [2]. In many cases, including ours, congenital defects can be detected by prenatal ultrasound [7-13]. Nevertheless, any findings from ultrasound examination will generate multiple differential diagnoses. Hence, ABS can only be diagnosed during the neonatal period or later.

In addition to the pathognomonic findings, many other clinical phenotypes of ABS have been reported, such as facial cleft, severe nasal deformity, cleft lip and/or palate, gastroschisis, omphalocele, clubbed feet, and abnormal dermal ridge pattern [14]. Several CNS anomalies had been identified in ABS patients, including encephalocele [15-17], meningoencephalocele [1,18], absence of tentorium [7], acrania [8,9,11,12,15], merocrania [1], acalvaria [19], anencephaly [9,10], exencephaly [12,20], holoprosencephaly [21], abnormal skull base [21], constricted head

and brain [13], periventricular nodular heterotopia [22], periventricular leukomalacia [21], dilatation of lateral ventricles [13], fused thalami [21], hypothalamic hamartoblastoma [21], agenesis of the corpus callosum [21], absent falx cerebri [21], aqueduct atresia [21], leptomeningeal heterotopia [21], cerebellar cortical dysplasia [21], shallow sella turcica [21], ectopic pituitary [21], pituitary hypoplasia [4], optic nerve hypoplasia [4], limited dorsal myeloschisis [5], and dysplasia of cervical laminae [5] (see Table 1).

In this study, all patients were presented with pathognomonic signs of ABS, including fusion and amputation of fingers and toes, and constriction bands on some affected limbs. Additionally, all patients in this study presented with severe nasal deformity and labiopalatoschizis. Interestingly, the underlying etiology of the head lump in patients 1 and 2 was meningoencephalocele, while the cause of head lumps in patient 3 was porencephalic cyst. Bilateral anophthalmia was detected in patients 1 and 2, but not in patient 3. A few different brain anomalies were specifically identified in patient 3, including dysgenesis of bilateral parietal bones, lobar holoprosencephaly, agenesis of the corpus callosum and septum pellucidum, and aqueduct stenosis. Interestingly, a head MRI from patient 3 suspected severe congenital cerebral midline malformation. To our knowledge, this abnormal feature has never been reported elsewhere. As this is the first report of this abnormality in an ABS patient, no theory could explain its pathogenesis. However, it is tempting to speculate that dysgenesis of bilateral parietal bones and porencephaly might have disrupted the cranial bones and cerebral ventricles' integrities, thus affecting cerebral midline formation.

Management

As the affected organs may vary, the management of ABS patients should be tailored as patient specific. When ABS is suspected during prenatal ultrasound examination, termination of pregnancy has been reported as the treatment of choice in many cases [1,7-12,15,19]. Meanwhile, when ABS is diagnosed during the neonatal period or later, it might be considerate to perform an initial evaluation of the survival prognosis of the ABS patients. For example, palliative management might be considered if a uniformly fatal condition, such as acrania, is identified [8,9,11,12,15]. However, if the ABS patient is presented without fatal anomalies, the caring physician must set the order of treatment priorities. As ABS patients are always presented with limb anomalies, limb reconstruction surgery, such as syndactyly release surgery, might always be included as one of the therapeutic components. Nevertheless, in ABS patients presenting with brain anomalies, limb reconstruction surgery might be less prioritized than surgical treatment for brain abnormalities. Like the principles of treatment for any other diseases, treatment of any abnormalities that have the potential to become fatal must be prioritized. In our cases, management of head lump(s), including VP shunt and meningoencephalocele resection surgery, is the initial treatment of choice. Craniofacial and limb reconstruction surgeries can be suggested as the next treatment phase. Nonsurgical treatment, such as antiseizure medication, might be given when necessary.

Prognosis and outcomes

In many cases, ABS patients who also acquired CNS abnormalities died in their early period of life. On the other hand, lifelong morbidity is inevitable in those who survived longer, depending on the severity of the identified phenotypes. Based on the reviewed ABS cases with CNS involvement in Table 1, the mortality rate of this clinical entity is as high as 76% (19/25). Of

these 19 patients, 12 died of intrauterine fetal death, stillbirth, or neonatal death, while three died less than 24 hours after their deliveries. Based on the reported anomalies, the CNS involvement in ABS patients who survived longer was arguably less severe.

Nevertheless, the association of the severity of CNS involvement with functional outcomes in ABS patients remains speculative, as no studies ever reported ABS patient evaluation in their adulthood. This could mean that there are no ABS patients with CNS anomalies that reach adulthood, or there are no studies that have ever evaluated it. Future studies that evaluate the surviving ABS patients with CNS anomalies in their later period of life are critical to unravel the long-term prognosis of these patients.

In this study, although all patients presented with debilitating and disfiguring anomalies, none were fatal; hence, they were expected to survive longer. Unfortunately, as patients with cleft palate are subjected to a high risk of aspiration, patient 1 was suspected of developing respiratory distress and pneumonia due to aspiration; then, he succumbed to his illness. This suggests that prognoses of ABS patients with CNS anomalies are not always the direct consequences of the malformation.

Conclusion

In cases where constricting amniotic bands cause severe malformation/disfigurement but are nonfatal, several conditions should be prioritized when planning the comprehensive management of ABS patients. First, treatment should be directed to treat malformation(s) that can become risk factor(s) for other debilitating conditions. Secondly, treatment should be directed to improve long-term functional outcomes. Lastly, since severe disfigurement is an essential issue in a

patient's long-term survival, facial reconstruction surgery might be considered an effort to make the patient as "acceptable" as possible in society.

Author contributions

MS, DH, AF, BER, HFP, AAI, ADD, and MAP treated the patient; MS, DH, AF, HFP, ADD, and MAP wrote the main manuscript, and prepared the figures and table; MS, DH, AF, BER, HFP, AAI, ADD, and MAP reviewed the manuscript.

Declarations

Consent to participate of patient consent

Appropriate consent forms for the publication of this case study were obtained from the patient's family. The patient and his family understood that the patient's name and initial would not be published and that due efforts would be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interest. no competing interests.

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~~Figure and table legends~~

Fig~~ure~~ 1 ~~:~~——Physical examination revealed ABS characteristics in patient 1. ~~(~~**A** and **B~~)~~** In addition to microcephaly, a giant frontal encephalocele ~~that~~ is predominantly filled with CSF. Moreover, craniofacial cleft, anophthalmia, and arrhinia were also present. ~~(~~**C**–**F~~)~~** Syndactyly and digital amputation due to constriction band was identified on patient's extremities

Fig~~ure~~ 2 ~~:~~——Head imaging and treatment of patient 1. ~~(~~**A**–**C~~)~~** Head 3D reconstruction confirmed that CSF predominated the content of encephalocele. However, infiltration of cerebral tissue also existed. ~~(~~**D**–**F~~)~~** Thus, VP shunt placement followed by frontal encephalocele resection was performed on this patient

Fig~~ure~~ 3~~:~~—— Clinical and head CT scan images of patient 2. ~~(~~**A~~)~~** Meningoencephalocele and severe craniofacial anomalies were presented, including bilateral anophthalmia and labiopalatoschizis. ~~(~~**B~~)~~** Head CT scan identified meningoencephalocele and partial agenesis of frontal, temporal, and parietal bones leading to exencephaly. ~~(~~**C**–**F~~)~~** Multiple defects in all

extremities were identified, including syndactyly of both hands, amputation of multiple fingers of right hand and foot, and complete amputation of the left foot

Fig ~~ure~~ 4 Clinical presentation and head CT scan of patient 3 at 2 months old. **(A–B)** In addition to multiple lumps on her head, nasal cleft and labiopalatoschizis were recognized. **(C–F)** Observation of the patient's extremities acknowledged syndactyly of both hands, constriction bands on multiple toes of her feet, and left small toe deformity

Fig ~~ure~~ 5 Head MRI images from patient 3. **(A–C)** Multiple cranial and brain anomalies were identified, including dysgenesis of bilateral parietal bones, lobar holoprosencephaly, agenesis of the corpus callosum and septum pellucidum, aqueduct stenosis, and malformation of brain midline

Table 1. Summary of previously reported cases of amniotic band syndrome (ABS) patients with CNS involvement

Author, year of publication	Number of cases	Gender	Family history of ABS	Age and obstetrics status of the mother	History of trauma during pregnancy	Other significant histories	CNS involvement
Aitken et al, 1984 [7]	1	Female	Not present	26-year-old, G1P0	Not present	Not present	Fusion of meninges an amnion, absence of tentorium
Hughes and Benzie, 1984 [8]	1	Female	Not present	30-year-old, G1P0	Not present	Not present	Acrania
Ito et al, 1986 [9]	1	Female	Not present	23-year-old, G1P0	Not present	Not present	Acrania, anencephaly
Chen and Gonzalez, 1987 [16]	4	Female	Not present	16-year-old, G1P0	Not mentioned	History of marijuana smoking, cocaine inhalation, amphetamine administration, and heroin injections during pregnancy	Meningoencephalocele absent posterior fossa
		Female	Not mentioned	26-year-old, G3P2	Not mentioned	Vaginal bleeding for 3 weeks before delivery	Abnormal fetal head with complex structure arisin from the front of the hea irregular cranioschisis w a large and irregular

							meningoencephalocele containing remnants of central nervous tissue ar meninges
		Male	Not present	31-year-old, G2P1	Not mentioned	Viral infections during the 2nd and 7th week of gestation	Irregular cranioschisis; meningoencephalocele
		Male	Not present	25-year-old, not mentioned	Not mentioned	The mother took contraceptives for 5 years, and just stopped taking them a month before prior to the conception. Fibroid tumor was identified in the uterine in the 3rd month of gestation; then, it was successfully resected	Irregular cranioschisis, meningoencephalocele
Chandran et al, 2000 [17]	1	Male	Not present	Age not mentioned, G6P4	Not present	Not present	Acalvaria
Chen CP et al, 2001 [10]	1	Male	Not present	21-year-old, G1P0	Not mentioned	Not present	Anencephaly
Cincore et al, 2003 [11]	1	Male	Not mentioned	Age not mentioned, G1P0	Not present	History of anemia, illicit drug consumption, including marijuana, lysergic acid diethylamide, methamphetamine, as well as, tobacco	Acrania

						use, and alcohol consumption	
Chen et al, 2004 [12]	2	Male	Not present	27-year-old, G1P0	Not present	Not present	Acrania, exencephaly
		Female	Not present	32-year-old, G2P1	Not present	Not present	Acrania, exencephaly
Ruggieri et al, 2007 [20]	1	Female	Not present	Not mentioned	Not present	Abruptio placenta and fetal distress detected at 38-week-old of gestation	Bilateral periventricula nodular heterotopia
Purandare et al, 2008 [19]	3	Female	Not present	30-year-old, G7P5	Not present	Not present	Encephalocele, agenesis the corpus callosum, an fused thalami

		Male	Not mentioned	22-year-old, G7P3	Present (Developmental delay in 2 siblings, and 1 sibling has brain hamartoma)	Chlamydia infection, smoking, alcohol and marijuana use	Encephalocele, periventricular leukomalacia, agenesis the corpus callosum, aqueductal atresia, cereb and cerebellar leptomeningeal heterotop and focal cerebellar corti dysplasia
		Female	Not mentioned	20-year-old, G1P0	Not present	Not present	Holoprosencephaly, hypothalamic hamartoblastoma, abser falx cerebri, abnormal sk base, shallow sella turcic and ectopic pituitary pres in the nasopharyngeal submucosa
Hyun Lee et al, 2011 [13]	1	Not mentioned	Not present	26-year-old, G1P0	Not present	Not present	Constricted head and bra dilatation of bilateral late ventricles

Barros et al, 2014 [1]	2	Not mentioned	Not mentioned	32-year-old, not mentioned	Not mentioned	This pregnancy was a result of Assisted Reproductive Technology (ART)	Meroacrania
		Not mentioned	Not mentioned	23-year-old, not mentioned	Not mentioned	Not present	Encephalocele, cranial cl
Li et al., 2017 [15]	2	Male	Not present	22-year-old, G1P0	Present	Not present	Acrania
		Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not present	Encephalocele
Amiji et al, 2019 [4]	1	Male	Not mentioned	Age not mentioned, G1P0	Not present	Not present	Optic nerve hypoplasia midline brain abnormalit (agenesis of corpus callosum or absence of septum pellucidum), an pituitary hypoplasia wit consequent hypopituitari

da Silva AJF, 2019 [18]	1	Female	Not mentioned	35-year-old, G1P0	Not mentioned	Consanguineous marriage	Exencephaly with parti absence of the cranial bones, including frontal, temporal, and left pariet bones
Yengo-Kahn et al, 2020 [16]	1	Female	Not mentioned	Not mentioned	Not mentioned	Not present	Encephalocele
Chatterjee et al, 2021 [5]	1	Male	Not mentioned	Age not mentioned, G1P0	Not mentioned	Severe respiratory infection at the second trimester related to severe bouts and coughing	Limited dorsal myeloschisis, and dyspla of cervical laminae at vertebrae C3-C7
Yazawa et al, 2021 [17]	1	Male	None	24-year-old, G1P0	None	None	Occipital encephalocel

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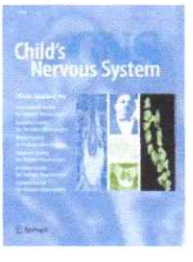

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