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Twin reversed arterial perfusion syndrome in historical sources

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SUMMARY

Twin reversed arterial perfusion (TRAP) syndrome is a rare complication of multiple, monozygotic and monochorionic pregnancy. It is a type of chronic twin-to-twin transfusion syndrome, where, next to normally developing donor twin, there is another recipient twin that grows in spite of no heartbeat. The paper is a historical note of twin reversed arterial perfusion syndrome.

Key words: acardius; acardiac fetus; twin pregnancy; history

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INTRODUCTION

Twin reversed arterial perfusion (TRAP) syndrome, also referred to as *chorangiopagus parasiticus* (CAPP) or *fetus acardiacus*, is a rare complication of multiple, monozygotic and monochorionic pregnancy. All cases reported thus far have been related only with this type of pregnancy. It is a form of chronic twin-to-twin transfusion syndrome, where, next to normally developing donor twin, there is another recipient twin that grows in spite of no heartbeat. TRAP is a form of a "life after life" phenomenon. Chorangiopagus, a fetus with no heart or with its only trace form, still lives in spite of the fact that he or she remains biologically dead.

FETUS ACARDIACUS IN HISTORY

Fetus acardiacus is one of the most severe malformations in humans (Fig. 1). These fetuses, mostly deprived of cranial structures, used to be a representation of mythical peoples living somewhere in a very distant world, while superstitions and fear made them a tangible proof of God's wrath. The Inquisition claimed that "headless" fetuses should not be baptized as the soul was said to be located in the brain. In ancient Egypt, anencephalic infants were worshiped as gods with animal heads. The Romans, in turn, ruled that such infants should be killed soon after delivery. In the Middle Ages, the mother was to blame for such a defect. It was usually believed to have been caused by "distorted and abnormal ideas" of the future mothers, e.g. by staring at the guillotine or at an executioner with an axe in his hand or by copulation with animals or devils.

In the fifth century before Christ, the father of historians, Herodotus wrote about the eastern part of Libya (North Africa at the Red Sea): *"In that country in North Africa near the Red Sea coast are the large snakes and the lions, and the elephants and bears and asps, the horned asses, the dog-headed and the headless men that have their eyes in their chests, as the Liby-*

ans say, and the wild men and women besides many other creatures not fabulous." (Fig. 2) [1]. Pliny the Elder, who lived between 24 and 79 AD, placed these mysterious peoples in Ethiopia; he wrote that *"The Blemmyes are reported to have no heads, their mouth and eyes being attached to their chests"* (Fig. 3) [2]. In the Middle Ages, these superstitions were fixed by Thomas Cantipratensis, a Dominican friar, Catholic writer, preacher and theologian, who lived in 1201–1272, in his work from 1263 called *Liber de Natura Rerum* (Fig. 4) [3]. Information found in this work was quoted throughout centuries to come by other authors, for example by Hartmann Schedel in his encyclopedia published in Nuremberg in 1493 [4] or by Conrad Lycosthenes in 1557 [5].

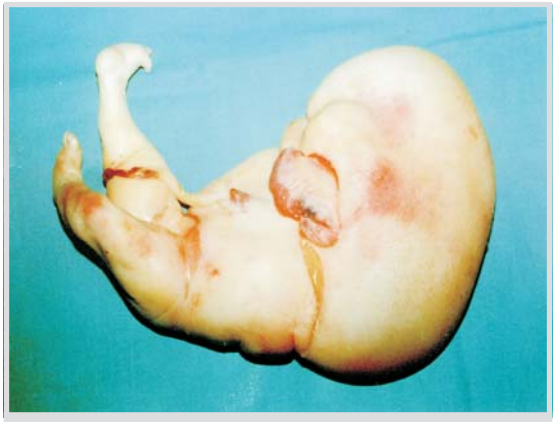

Fig. 1. Heartless fetus

Fig. 2. An acardiac fetus according to Herodotus [1]

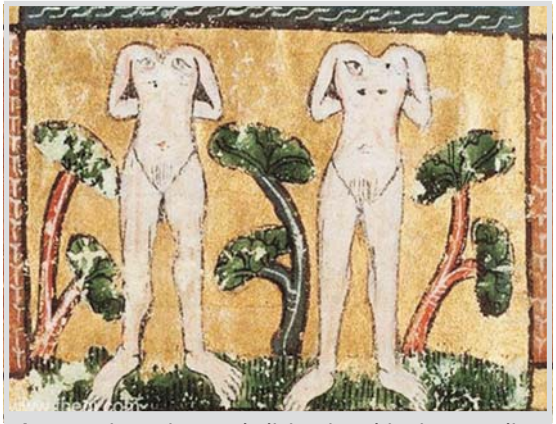

Fig. 3. Enigmatic people living in Ethiopia according to Pliny the Elder [2]

The oldest description of acardia was made by Benedetti in 1533 [6]. He reported a pathological, formless creation and misinterpreted it as a pregnancy mole. The next physician was Benedicta in 1539. In 1832, Gurlt introduced the term *fetus amorphus* to denote defects occurring in cattle, while Geoffrey Saint Hilaire used the term *acardia* for the first time in 1836 [7].

In the 19th century, the term "headless monster" was common in academic publications. In Europe, however, the term "mooncalf" was more common. It was coined in the 16th century by Philip Melanchthon, the closest collaborator of Martin Luther, a co-initiator of the Reformation and a professor at the University of Wittenberg. The term *mooncalf* was used to refer to severe congenital defects that caused miscarriages in cattle or other domestic animals. It was also sometimes used to denote human fetuses with multiple malformations. The term derives from superstitions spread earlier and prevalent in various European folklore traditions, stating that such misshaped creatures were a product of the hostile effect of the moon on fetal development. Mauriceau, a physician who made obstetrics a science, wrote in his treaty that *"The moon-calves are nourished in the womb, to which they nearly always adhere at some place, and are maintained by the blood of which they are perfused like plants watered from the earth. Frequently besides the moon-calf there is another infant, of which it may be separated."*(Fig. 5) [8].

The observation that a "headless monster" was always accompanied by a normally shaped fetus was made many years ago. The fact that it was surely a deformed fetus rather than a mole or polyp was documented on two 16th century leaflets (popular press at that time) (Fig. 6) [9]. One of them describes a case that occurred on the Polish land: *"On the fourth of December, 1551, the Friday after St. Andrew's day, three children were born in the new hospital at Breslaw named All Saints', to a butcher's wife named Ursula Walter Hosperg. One was a small boy who died soon after the baptism. The*

other two were girls and one was imperfect [immature] and stillborn. The third, which is depicted here, was of wondrously rare and frightening shape. For it had neither head nor hands and arms, only the trunk and the feet could be discerned. But it was imperfect [immature] and stillborn. Because such frightening miracles and monsters usually without doubt indicate God's wrath, all Christian souls should sigh and pray to God, our dear Lord Jesus Christ's eternal father, to avert his penalty and anger." Even more fantastic descriptions appeared in another leaflet: [10]"*Around Christmas of 1569 Caspar Hugen's wife, from Matzingen/Thurgau, gave birth to two infants in one delivery. One had no deficiency or blemish, while the other had no head. Instead of a head it had a great black hole out of which it cried; it also had two goose feet and expired when it had emitted one or two cries."*

In the Catholic church, it was theologically important and contrary to prior beliefs of Saint Augustine that the soul was located in the human head. François-Emmanuel Cangiamila, a theologian and a medicine and law graduate, was charged with solving dilemmas associated with baptism upon being appointed a legal advisor of the Archbishop's Curia in Montreale in Sicily. His opinion was that "*therefore, the acranius, how many relicts of the human body he might have, should under no circumstances be baptized: because the head is missing, undoubtedly the primary seat of soul and reason*" [11]. He was also a fervent supporter of cesarean sections during difficult births, both in dead and living women, in order to baptize the fetus. In 1736, in Plama, he conducted the first cesarean section on a dead woman that resulted in retrieving and baptizing a living fetus. As he himself admitted in his work, entitled "*l'Embriologia sacra,*" the principal goal of his activity, which, as he said, was not scientific, but emerged from his ministerial needs and experiences, was to spread the practice of cesarean section in order to guarantee eternal salvation to the unborn child. He was an indirect propagator of more modern obstetric techniques. Further medical studies and observations led to subsequent conclusions, reported in "*Medicina sacra,*" that the drowned could live for longer periods of time under water and they needed to be helped and revived when retrieved.

Alexis Littre, an anatomist, was of a different opinion. On April 6 1701, he sent an article reporting a case of an acranic fetus and two anencephalic fetuses to the Parisian Medi-

Fig. 4. Headless men according to Dominican friar Thomas Cantipratensis of 1263 [3]

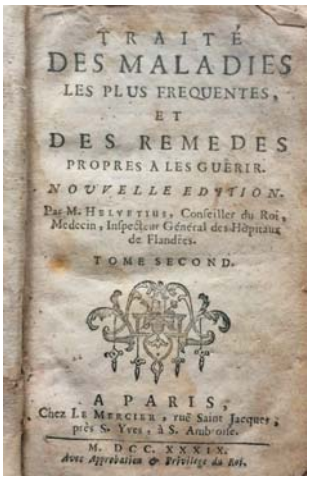

Fig. 5. A title page of the Mauriceau treaty of 1739 [8]

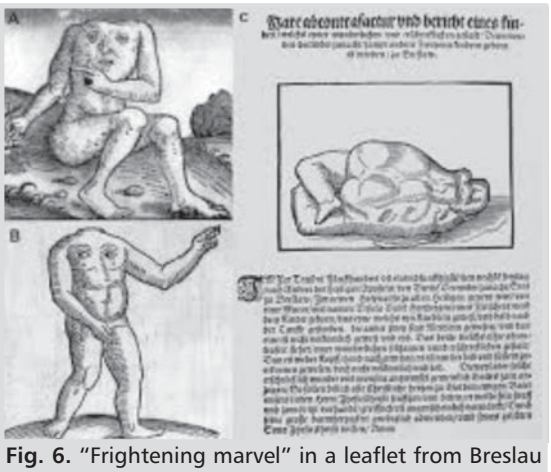

Fig. 6. "Frightening marvel" in a leaflet from Breslau from 1551 [9]

cal Department [12]. In his work, he also wondered about the function of the brain: *"The first two male fetuses, of seven and eight months gestation, were both large and fat hydropic. That of seven months had neither head nor neck, and the upper part of the trunk was covered with skin. This observation sheds doubt on the purpose ascribed to the brain or at least to make it suspect, that the spirits which its glands separate from the blood are as necessary as assumed for movement, nutrition, and other functions of the body. Concerning the functions of the soul, it was barely apparent that this fetus, deprived entirely of the brain, exercised any imagination, judgment, or reasoning, even in an imperfect way. The larger a human's brain, the more the functions of his soul are perfect, and the more he is able to carry them out."*

ETIOLOGY

Acardia was not linked with twin pregnancy until the publications of Mery and Winslow appeared [13,14]. In 1720, Parisian surgeon Jean Mery sent the following description of birth to the Science Academy: "*Marie Guerlin, aged 30 years and pregnant for 6 months, delivered two little girls on September 10 of last year. Nothing was missing to the perfect body of the firstborn infant who lived for half an hour. But the dead second born had a severely deformed trunk whose upper part ended with the first dorsal vertebra. This trunk had no head, neck, scapula, clavicula, nor arms. For the two little girls there was only one placenta the membranes of which formed but one pouch enclosing them both, which is very rare. Of this fused placenta sorted but one cord, which in the middle of its length divided in two, which separately ended at their navels. Having opened the body, we found no lungs nor heart, but in front of the spine there were two vessels in addition to those already described."* Dr. Mery commissioned Chatillon, a drawer of de l'Acadámie, to make drawings during the autopsy. Unfortunately, to date, they have not been retrieved. In 1740, Danish Jacob Benignus Winslow, a Parisian professor of anatomy, provided a detailed description of another malformed fetus: *"After the delivery of a well-formed male infant there came another, but without head. Before I started to dissect the body, I should have had the idea to inject the blood vessels through the umbilical cord"* [14]. Unfortunately, Winslow found no explanation for the circulation in the heartless fetus. Despite this, he wrote: *"Perhaps the mechanism is so simple that, after more experience and further research one will be surprised not to have understood it earlier."* Sulsman recollected how he had informed Winslow about the birth of another headless fetus on April 14 1726 in Strasbourg. Winslow invited him to publish this observation in *Journal des Savans*. When searching for the cause of this pathology, other than merely twin pregnancy, he conducted a detailed interview with the mother. He asked her if she had witnessed any execution during pregnancy. Despite a negative response, Winslow still believed that she must have witnessed a criminal being beheaded.

In 1789, physician Sommerfeld Kähler was the first to combine the presence of an acardiac fetus with abnormal umbilical vascular connections in one of triplets [15]. After an autopsy, he wrote: "*The midwife, after delivery of two stillborn infants at seven months gestation in June 1777, found that something was left in the uterus, which did not feel like a properly formed fruit. It was larger and heavier than the twins, with imperfect genitalia, cleft lip, and a bundle of empty and thin vessels around the umbilicus. The skull contained a rudimentary and imperfect brain, the chest abnormal remnants of the lung. The eyes, the heart with the large vessels, the trachea and the esophagus were entirely absent. Likewise all abdominal viscera lacked except small intestines, which by size and position were abnormal. Lacking a good artist, I could only obtain a rough drawing (Figure 2A)*" [15].

In 1812, anatomist Johann Friedrich Meckel (Junior) from Halle collected approximately 50 cases of acranic fetuses from the global literature, including four of his own [16]. He concluded that the defect was specific for twin pregnancy, but was unable to elucidate the pathogenesis. In June 1826, Étienne Geoffroy St. Hilaire [17] from the Faculty of Medicine in Paris addressed his colleagues with a sarcastic remark, saying: *"Mr. Moreau gave me the honor of informing me that he is going to present a human monster born this morning, a complete acephalus. Will you also present, I answered, his firstborn twin and the placenta in common between the two individuals?The presence of a twin is necessarily linked with development of an acephalic monster. Mr. Moreau was stricken by the unequal distribution of the amniotic fluid in the two pouches; abundant to the excess in the pouch containing the regular fetus, and scarce or nearly absent in that of the monstrous fetus."* Geoffroy often criticized Winslow due to his general convictions and erroneous obse-

rvations concerning the causes of the malformations.

Lengthy reports on acardiac fetuses were also published by Tiedemann in 1813 [18], Be'clard in 1817 [19], Vrolik in 1834 [20] and Otto in 1841 [21]. They classified different types of malformations and symptoms that distinguished them from the anencephalic fetuses. However, the development of an acardiac fetus was interpreted as developmental restriction and the proper explanation of its cause was not attempted. In 1836, Thomas Hodgkin and Astley Cooper from the Guys hospital described anastomoses on the surface of the placenta and concluded that "*the heart of the normal fetus impelled the blood into the arteries of the placenta and funis.*"

Based on the first experimental embryonic tests, Heinrich Meckel (1850) [16] and Schultz (1854) concluded that human monochorionic twins are always monozygotic, and thus they may share common circulation. However, Meckel and his predecessors misinterpreted the course of fetal development in twin pregnancy with an acardiac fetus as they underestimated the vascular relationships in the placenta. They devoted too little attention to the capillary system and too great attention to the hypercapillary and large vessels that usually joined two umbilical cords on the fetal aspect of the placenta [16].

Preliminary observations of Johann Friedrich Meckel on the relationship of this pathology with twin pregnancy were ultimately confirmed 38 years later by his nephew and foster son Heinrich Meckel [22]. In 1850, he defined the pathomechanism of the syndrome as retrograde blood flow dependent on large arterio-arterial and veno-venous anastomoses. He believed that the heart of this fetus developed abnormally from the very beginning and finally stopped. Afterwards, the acardiac fetus could receive secondary nutrition via arterial perfusion from his normally developing twin (so-called "pump twin"). In 1859, Claudius [23] published a monograph on acardia in which he suggested another theory. He believed that primarily normal cardiac development was followed by secondary degeneration due to retrograde aortic flow, which led to vascular thrombosis and cardiac arrest followed by subsequent cardiac atrophy. Both of these mechanisms are believed to exist independently.

In 1850, Meckel von Hemsbach were the first to express a clear opinion that an acardiac fetus must be kept alive by the heart of the normally developing "pump twin" [22]. He wrote that *"in fruits, whose own circulation is impossible due to malformation of the heart, a meagre life is supported by the other fetus, while simultaneously general hydrops of the acephalus results from circulatory failure."*

In a brochure issued in 1859, anatomist Claudius [23] was the first to openly question the thesis that the "heartless" twin had a primary defect. He linked the occurrence of this malformation solely with fetal circulation: *"Certain appending or turned-out skin parts occur where organs declined; at the site of the head, the tips of the extremities, the ventral surface of the trunk, never the dorsal. Sometimes a small retraction is found instead of an appendix. One umbilical artery of the healthy twin branches over half of the placenta, the other proceeds towards the second insertion, bends from the surface and enters the umbilical cord of the acardiac; the umbilical vein divides into two larger branches, which accompany both arteries; one of them proceeds towards the second insertion and becomes the acardiac's umbilical vein. In the acardiac's umbilical artery the blood therefore flows in a reversed direction, from the placenta into the body; the flow splits at the hypogastric division, one half goes down towards the art cruralis, the other half up towards the art iliacacommunis, the aorta likewise receives a current in reversed direction, from bottom to top."*

Claudius believed that, considering all the vascular connections between fetuses in monochorionic pregnancies and the hemodynamic conditions in these settings, which cannot be compared with any other cases in the biological world, it can be assumed that the initial development of the acardiac fetus's heart is not necessarily anomalous. He concluded that this defect could be caused by a random connection of the umbilical vessels between fetuses. Buhl in 1861 and Hecker in 1864 confirmed Claudius's observations [24].

In 1860, Spaeth published a paper in which he questioned this randomness. He gathered a high number of twin placentas, including 31 monochorionic placentas, in which vascular anastomoses were found in each case. He realized that the reciprocal circulation must exist in all or nearly all monochorionic pregnancies. His theories were validated by the fact that several pairs of twins had severe complications caused by hemodynamic imbalance in their common circulation [25]. Spaeth perfectly well realized the conclusions emerging from earlier theories,

which he called the *"doctrine of the negative effect of one fetus on the other."* Despite his excessively detailed case descriptions that confirmed this "doctrine," he declared in the conclusions of his publication that this had found no confirmation in his observations. He claimed that as one fetus would sometimes die without a visible effect on the development of the other, despite the existence of common circulation, this meant that each twin's development had to be independent. He also argued that irrespective of the type of the placenta, it might be suspected that each fetus led a separate life, independent of the neighboring twin. Spaeth's publication suggests that Galton obtained an estimated percentage of 24% of monochorionic twins of all twins delivered, and compared it with "other estimates," which, as he stated, usually provided the value of 6%.

Austrian anatomist Joseph Hyrtl published in 1870 a pioneering atlas containing detailed illustrations and descriptions of various placentas that he had examined. By injecting the umbilical vessels, he unquestionably demonstrated that there are vascular anastomoses between monochorionic fetuses [26].

However, the greatest merit in the study on vascular anastomoses in twin placentas and in the understanding of the pathomechanisms responsible for this syndrome belongs undoubtedly to Friedrich Schatz (1841–1920), an obstetrician/gynecologist from Rostock [27]. Vascular anastomoses between fetuses had been known since the second half of the 17th century, but their relevance and effects on the development of pregnancy and fetuses still remained unknown, unappreciated and ignored. The breakthrough came when this German physician discovered all types of anastomoses and described various complications to pregnancy and labor that they might induce (Fig. 7). The fundamental method of monochorionic placenta examination used by this physician was injection of fluids with four colors into these vessels. Two of the colors were injected to the venous and arterial system in the part of the placenta belonging to one of the fetuses, while two other colors were administered to the vascular system of the part of the second fetus's placenta. He observed that there was the third, previously unknown, type of anastomosis, namely arteriovenous connection (A-V) in the placenta. He discovered that these connections were located inside the placental tissues within the capillaries and were always of an opposed type, i.e. arterio-venous or veno-arterial. He also stated that blood exchange in these vessels took place with a great force that depended on the blood pressure difference between an artery and a vein. Schatz believed that the amount of blood flowing through these connections can be calculated by measuring the caliber of efferent and afferent vessels, especially in places where the villi of one half of the placenta communicate with those of the other half. As he claimed that vascular anastomoses in the placenta are a part of the circulation of both fetuses, he used the term "third circulation" to underline the unique nature of this phenomenon. He also concluded that, as these vessels run from one twin to the other, there is a possibility of blood transfusion between them. Friedrich Schatz developed Claudius's theory and postulated gradual adoption of both circulations by the stronger fetus of superior location and better nutrition. This process would subsequently lead to the degeneration of the weaker fetus. He demonstrated that intraplacental anastomoses in an acardiac twin can be arterio-arterial and veno-venous, by contrast with arteriovenous anastomoses found in TTTS. Schatz called them the "third circulation" and hypothesized that for flow reversal to occur, the umbilical vein had to be occluded due to umbilical hernia in one of the twins [27]. Schatz claimed that "*arterio-arterial and veno-venous anastomoses probably, in most cases, allow pregnancy continuation to term, but these cases are also the most prone to the development of an acardiac twin. In the case of umbilical cord bending or the occurrence of another type of stenosis, the venous flow (flow of oxygenated*

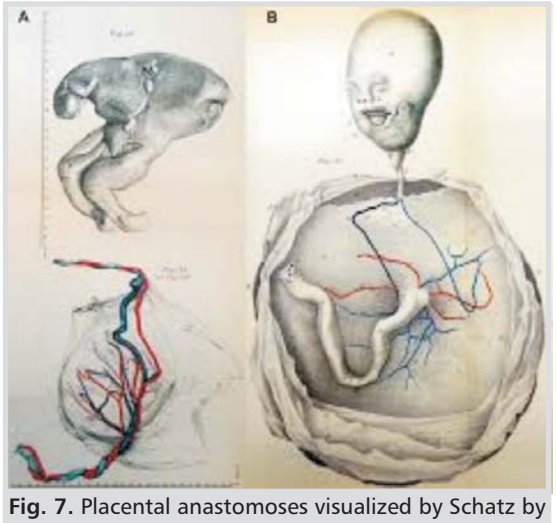

Fig. 7. Placental anastomoses visualized by Schatz by color injection in 1899. (A) Acardius acranius; (B) acardius acormus [37]

blood) to the fetal heart will be blocked in one of the twins, and the blocked blood will be delivered to his twin. In this case, this twin lacks normal supply of oxygenated blood, while the other not only receives too much of it, but also their heart sends out arterial (deoxygenated blood) to the first twin through the arterial anastomosis. Should this condition continue, proper functioning of the vessels in the twin with a narrowed umbilical cord will be drastically altered. The function of their heart will weaken, and then stop completely. In this last case, the circulation will be maintained only thanks to the heartbeat of the other fetus with normal blood flow direction and thanks to retrograde flow in the acardiac twin."

In 1875, several months before the publication of a preliminary report by Schatz, Ahlfeld published his first work on twins [28]. In total, he published four articles, the final in 1879. In the first paper (1875). Ahlfeld criticized Claudius's views, claiming that in the case of acardia, the circulation of the stronger heart indicates blood flow direction in the embryo that first developed the allantois, thereby counteracting the capillary flow direction and reaching the body of the other embryo. Ahlfeld was the first researcher to have paid attention to the role of placental vascularity in the pathogenesis of the defect.

In 1981, Bieber put forward a different hypothesis regarding the mechanism leading to the development of a twin pregnancy with an acardiac fetus. He believed that this could occur if two sperm cells simultaneously fertilize the ovum and its second polar body ("polar body twinning") [29].

CLASSIFICATION

In 1898, Schatz classified the malformations into two types depending on the heart structure: hemiacardius (incompletely formed heart) and holoacardius (absent heart) [30], while in 1902 Das distinguished four types [31]:

1. Acardius anceps (*paracephalus*) – the least atrophic form characterized by partial development of the head and deformation of the face, trunk and limbs. The base of the skull and partially the brain are developed.
2. Acardius acephalus is the most common type characterized by the absence of the head or by its only fragmentary presence. The shoulder girdle is undeveloped, the upper limbs are absent or aplastic, the organs above the diaphragm are represented in trace amounts, while the bowel and abdominal organs are only primitive.
3. Acardius amorphus is the least developed type. In most cases, it is only a bulk of connective tissue covered by swollen skin. Some traces of visceral tissue may be present.
4. Acadius acormus is the rarest. Only the head with hair is present, but never fully developed.

In 1925, Simonds and Gowen [32] added the fifth type to this classification, namely acardius myelacephalus. In this case, only partially developed head is present with an identifiable upper limb (limbs) and sometimes trace amounts of nervous tissue. The classification of Das as well as Simonds and Gowen still remains valid.

In 1983, Van Allen et al. proposed the current term of *twin reversed arterial perfusion sequence* (TRAP) [33].

WORK-UP AND TREATMENT

In 1953, Gillim and Hendricks calculated the prevalence of TRAP at 1% of monozygotic twins, which translates to one case per 35,000 births [34]. Having analyzed 184 cases of acardia published in years 1960–1991, Healey stated that the risk of perinatal death for the "pump twin" was 35% and 100% for the acardiac twin [35]. The main causes of death were congestive heart failure, polyhydramnios and premature birth.

Since the advent of ultrasonography in obstetrics (1960), prenatal diagnosis and therapy aiming to save the normally developed child have been possible. Lehr and DiRe [36] were the first to present an ultrasound image of an acardiac twin in 1978, while in 1988 Pretorius et al. [37] used color Doppler to visualize the retrograde flow of arterial blood. In 1983, Platt et al. were the first to define ultrasound criteria for the identification of TRAP syndrome [38]. They also expressed an opinion that the normally developing fetuses often exhibited congestive heart failure due to sustaining circulation of the abnormally developing twin.They hypothesized that in this case it would be helpful to conduct a surgical procedure consisting in tightening the acardiac twin's umbilical cord after visualizing it in a small operative laparoscope and ligating or clamping it. Another step was to prepare intrauterine intervention methods aiming to safe the pump twin. In 1989 Robie et al. selectively removed the abnormally developing fetus from the uterus by hystero-

tomy in week 22 of gestation (710 g), and then, in week 33, they extracted a normally developed live male fetus weighing 2130 g in a cesarean section procedure [39]. In the same year, Hamada et al. [40] conducted percutaneous occlusion of the umbilical cord using a coil, while two years later, Porreco et al. performed embolization using an embolic material [41].

In twin reversed arterial perfusion, therapeutic management is not always necessary. If a "fetal parasite" of small size (<25% of the donor mass) is present, the risk to the normal fetus's life is low or absent. Since there are no typical anatomic structures, ultrasonographic determination of the estimated body weight of a "heartless" fetus is very difficult. In these cases, Moore et al. [42] as the first proposed the use of the following formula: body weight = 1.2 L^2 - 1.7 L, later modified by Malinowski [43]: body mass in grams = (1.2 L^2 - 1. 7 W^2): 10; where L is the largest longitudinal dimension, and W is the largest transverse dimension.

In 1994, Quintero et al. noted a successful cord ligation in the fetoscope [44]. In 1987, Seeds et al. [45] conducted an unfortunately unsuccessful fetoscopic closure of the umbilical vessels in an acardiac fetus using laser. This method and the method consisting in the administration of concentrated alcohol directly into the acardiac twin's vessels were successfully used by Sepulved et al. [46] in 1995. In 2002, Tsao et al. published the results of vascular radiofrequency ablation procedures conducted in 1998–2001 [47]. In their material, 12 of 13 pump twins survived.

CONCLUSION

Fortunately, TRAP remains a rare form of this most severe malformation in humans. Thanks to better understanding of its pathogenesis, it has lost its mythical associations, and prenatal diagnosis and interventions have increased the chance for survival of the pump twin. However, there are still numerous unknowns awaiting discovery.

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