The Harlequin phenomenon after thoracoscopic repair of esophageal atresia and tracheoesophageal fistula: Is there any coincidence?

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The experience and number of endoscopic surgery procedures applied in newborns are constantly growing, showing efficacy in many thoracic and abdominal conditions. However, there is an ongoing debate concerning the safety of this technique and the influence on the developing organism. Due to the relatively recent introduction of these methods in the therapy of congenital anomalies, we still have quite little knowledge about their long-term sequelae. The Harlequin phenomenon is a complex, little known and probably heterogeneous anomaly. It involves episodes of sharply demarcated erythema with the dividing line running exactly along the midline. We observe the appearance of episodes of unilateral flushing and sweating on the left half of the body in children who have been operated on using the thoracoscopic approach in the first days of life, due to esophageal atresia and distal tracheoesophageal fistula (EA/TEF), which are very similar to the Harlequin phenomenon. During long-term follow-up visits, parents of 2 out of 55 children, who had been operated on during the period 2005–2011, turned our attention to these unusual symptoms. To our knowledge, this is the first report of the Harlequin phenomenon following esophageal surgery. The aim of the study is to analyze the possible pathogenesis of the observed anomaly, in the context of the existing congenital defect, and the operative technique used.

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1. Case report

1.1. Case 1

The boy, weighing 1950 g, was born in 35 hbd by caesarean section, as a second twin. The pregnancy was complicated by the premature departure of amniotic fluid and intra-amniotic infection. After delivery he was diagnosed with AE/TEF. The patient had no additional congenital anomalies. A cardiac examination, performed routinely before surgery, showed a small PFO, which closed spontaneously after a few days and was not observed in subsequent echocardiograms. He was operated on the second day of life as a result of AE/TEF. This was the first patient operated on in our center using the thoracoscopic approach. The standard anesthesia, with endotracheal intubation and muscle relaxation, was performed. A central line was placed into the femoral vein. The three-port technique was used. The azygos vein was not divided and served as a landmark of the TEF location. The mediastinal pleura was opened longitudinally just beneath and above the azygos vein. Once found, the fistula was closed with one 5 mm titan clip closest to the trachea and transected. The two esophageal ends were separated by a distance of 2 cm. The upper pouch was mobilized up to the neck to gain accessory length. There was a blind dissection without using diathermy to the level of thorax inlet. The only sharp dissection with scissors was used to divide the fibrous adhesions between upper pouch end and tracheal wall. The esophageal single-layer anastomosis was made with 5 stitches, under moderate tension, and the chest was drained. The direct post-operative course was uneventful.

A long-term follow-up visit was carried out when the boy was 6 years old. The parents stated that the boy had suffered frequent bronchitis in the first years of his life. He had twice had anastomotic dilatations under general anesthesia. At the time of the visit, the patient had no dysphagia, no persistent cough or any other problems common in children with EA/TOF. The parents assessed his general development as not differing from the development of his peers. They were concerned, however, by the presence of unusual symptoms emerging after intense physical effort. There was a
The occurrence of similar symptoms was reported in patients with sympathetic fiber damage resulting from cancer or strokes at the spinal cord, as well as iatrogenic causes such as trauma in the course of paravertebral analgesia in the thoracic segment or during jugular vein cannulation [9–12]. Nevertheless, reports on the Harlequin syndrome following surgical intervention are rare and further investigations. The last time they were in contact was when the boy was 7 years old. According to the parents, the episodes of a color change are becoming less frequent from year to year and are now rarely present.

2. Discussion

Reports on the Harlequin syndrome following surgical intervention are rare. However, a distinction should be made between the two terms existing in the literature that have similar symptoms but occur in a different circumstances and in distinct groups of patients i.e. ‘Harlequin syndrome’ and ‘Harlequin color change.’

Neligan and Strang used the second term for the first time in 1952 to describe an unusual symptom in neonates. It consisted of lateral color change, occurring temporarily and episodically for a short period, with spontaneous resolution within minutes. The line of demarcation was described as strikingly sharp, running along the face, trunk and genitalia, but the pink color had migratory characteristics, with a simultaneous pallor of the other half of the body [1,2]. In the following years, there were several anecdotal reports regarding the occurrence of similar symptoms in a pediatric group of patients in different circumstances, like anesthesia or the presence of ductal dependent heart disease [2,3]. Prematurity and low birth weight were thought to be putative risk factors, but neither of them were finally confirmed [1,4]. Rao and Campbell suggest a more complicated mechanism of Harlequin color change. In two reported newborns, symptoms occurred in temporal relation with the systemic prostaglandin in administration, in order to maintain patency of the ductus arteriosus. It remains, however, unexplained if the color change occurred in response to the drug itself or to the temporary closure of the ductus leading to hypoxia [2]. Moreover, the authors point out specific characteristics of patients, in a number of previous reports, with circulatory or respiratory disorders. Congenital heart defects were found in two patients [3,5]. One of them was an extremely circulatory-compromised newborn who had an inoperative Harlequin color change, during the course of a Nissen fundoplication and gastrostomy. Due to these particularly complex heart defects, the boy had previously undergone a number of cardiac procedures and a tracheostomy [5]. Another newborn had earlier incidents of tachypnoe, which could also indicate the presence of circulatory dysfunction [2,6]. According to the authors, hypoxia could act as a trigger mechanism for vasomotor disorders of the skin; however, suggested pathophysiological mechanisms are not clear [2].

In 1988, Lance noticed the resemblance of the symptoms observed in some adult patients to those described previously in newborns. They complained of the sudden onset of unilateral congestion of the face and ipsilateral excessive sweating following exercise, intense emotion or during times of heat. He labeled the observed clinical picture as the ‘Harlequin syndrome’ [7]. Neurological examination showed reduced response of the pale side to thermal and emotional stimuli. Considering the limitation of the symptoms to the head, damage probably occurred at the level of the third thoracic segment. It is worth noting that the affected side is the pale one, due to inability to mount the correct vasomotor response of cutaneous vessels for sympathetic stimuli as an effect of denervation [7,8]. The term ‘Harlequin syndrome’ is, therefore, reserved for cases associated with damage to the sympathetic nervous system.

1.2. Case 2

The boy, weighing 2800 g, was born in the 37th week of pregnancy, by caesarean section. The pregnancy was complicated by polyhydramnios. He had no additional congenital anomalies. As with the first patient a routine echocardiogram showed hemodynamically insignificant PFO, that was no longer noticed in subsequent studies after several days. The patient was operated on during the first day of life. He was the fourth case treated with the endoscopic technique in our department. Anatomic conditions and the surgical technique did not differ from the above described case. Central venous access was the same, via femoral vein cannulation. The fistula was closed with two clips; the esophagus was anastomosed under slight tension, with 5 sutures, and the drain was left in the pleural cavity.

A long-term follow-up visit was carried out when the boy was 3 years old. By that time, he had frequent tonsillitis and underwent a third tonsil removal. He was diagnosed with immune disorders, i.e. neutrophil dysfunction, but the incidences of infection soon clearly decreased. In the parents’ opinion he developed as a healthy child, although they had recently observed a change in the skin color of the face and body after physical effort, especially during vigorous play. The skin erythema affected the same left side, as in the previous case. Symptoms resolved spontaneously within a few minutes of rest. Parents were not positively disposed to carry out

Fig. 1. Unilateral skin color change.
relate mainly to the neck surgery. In 1996, Turco and Faber described the case of a 2 year old girl, who developed contralateral hemifacial plethora soon after lymphatic malformation removal from the right cervical area. Symptoms lasted for 3 h and intensified during crying and coughing [13]. Three years later, persistent right side Harlequin syndrome with associated left side Horner syndrome was described in a newborn after resection of a sympathetic chain neuroblastoma from the left neck approach and sympathetic interruption was confirmed by examination of the skin conductance response [14]. Similarly, the coexistence of both syndromes was reported nine years later in a two-year-old boy, following a large cervical lymphatic malformation removal. During the operation the mass was found to be strongly adherent to the esophagus and the trachea [8]. Contralateral plethora gradually retreated spontaneously over the course of two months. In these three cases the symptoms were presumably caused by intraoperative sympathetic chain trauma between the superior cervical ganglion and the stellate ganglion beneath [8].

Reports on the Harlequin syndrome following surgical intervention are rare and relate mainly to the neck surgery. Nevertheless, in one study on neonates with esophageal atresia, excessive sweating was noticed in 8 of the 120 evaluable patients. Moreover, in one it concerned only the right half of the body [15]. It was possibly an incomplete form of Harlequin syndrome without concomitant skin color change, or the changes were so faint that was omitted in the clinical examination.

In the light of the cited literature, among potential causes of the skin color change in presented cases, two factors should firstly be taken into account: significant heart defects and mechanical damage to the sympathetic trunks at some stage of the preparation of the upper esophagus. Central venous cannulation, as a potential risk factor, may be fairly ruled out, as both patients had central venous access via the femoral vein. Moreover, the compound of a congenital defect itself cannot be excluded.

3. Conclusion

Our patients and their symptoms differ from the cases referred to as the ‘Harlequin color change’ in several points. None of described boys had a congenital heart disease, apart from PFO that underwent spontaneous closure within a few days of birth. In both cases the defect wasn’t hemodynamically significant. Furthermore, the symptoms were first noticed several years later in the absence of a circulatory compromise and hypoxia. The events were not related to the administration of any drug. It also appears that the change in a skin color had a different and less migratory character. Consequently, some mechanical damage of sympathetic fibers seems to be more probable.

The question of what the causative factor was remains. The circumstances in which symptoms were observed in our patients, i.e. strenuous physical effort, were similar to those in ‘Harlequin syndrome’ following sympathetic fiber injury. One constant element is the lack of any additional signs of respiratory and cardiovascular distress and spontaneous resolution after only minutes without sequelae. What is more, in the first boy, the detailed neurological examination revealed limited autonomic neuropathy on the operated–upon side. It is not known what was the role of a disc protrusion at the cervical spine but, as the spinal cord was normal, the association of this lesion with the occurrence of symptoms seems less probable.

As described above, there are known cases of intraoperative injuries leading to unilateral color change; however, they usually concern neck surgery where the lesions of cervical sympathetic trunk were more evident. In the described cases, the course of the operation did not differ from the procedures performed in 53 other newborns operated upon in our center through to 2011. In both cases the dissection of the pouch was not excessive and there was no unexpected damage to any adjacent structures. However, it should be noted that the symptoms occurred in the very first patients that we operated on using the thoracoscopic approach; an amendment to the learning curve should therefore be taken into account.

Despite many years have passed since the first description of the Harlequin phenomenon, it is still ambiguous, which further refers to its relationship with esophageal atresia. A full understanding of the role of the thoracoscopic surgery in the etiology of the skin color change remains unknown and requires further observation and research.

References