

Peer Review File

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Reviewer A

Comment 1: I propose to include pictures of echocardiography with a left ventricle in systole. Was left ventricular ejection fraction assessed in addition to the shortening fraction?

Reply 1: Thank you for this valuable suggestion. More detailed findings of the initial echocardiography in the emergency department have been added within a new table, summarizing all diagnostic investigations and their findings (see additional files, table 2).

Comment 2: Has there been an evolution of ischemic ECG changes, negative T waves, and QTc prolongation?

Reply 2: We have added a further description of the evolution of ischemic ECG changes within the new table, summarizing all diagnostic investigations and their findings, too (see additional files, Table 2).

Comment 3: The patient underwent cardiac catheterization. What did it involve? Coronary angiography and ventriculography?

Reply 3: The cardiac catheterization involved coronary angiography, ventriculography and the retrieval of myocardial biopsies. These investigations and their results have been added to the new table showing all diagnostic investigations (see additional files, Table 2).

Comment 4: I suggest adding the maximum values of NT-proBNP and troponin in the case presentation.

Reply 4: Thank you for this very useful addition, we have amended the manuscript as follows (see page 6, lines 136-38):

Changes in the text: “Blood gases normalized after one day and cardiac enzymes decreased to normal after one week (Troponin T (hs) max. 1,46 ng/ml one day after admission, NT-proBNP max. 26,833 pg/ml three days after admission, see Figure 2b).”

Comment 5: What medications were used besides catecholamines during hospitalization, which were recommended at discharge?

Reply 5: Thank you for this critical inquiry. We have now listed all cardiologically relevant medication (Adrenaline, Noradrenaline, Milrinone and Levosimendan) including maximum dosages in the manuscript (see page 6, lines 132-35). Of course the patient received further medication like sedation, antibiotics, heparine and antacids. As the idea of this manuscript being a brief case report from a cardiological point of view, we didn't list all these medications in detail.

Changes in the text: “Within the subsequent days, the boy's cardiac function steadily stabilized under medical therapy (Adrenaline max. 0,2 µg/kg/min, Noradrenaline max. 0,1 µg/kg/min, Milrinone max. 1 µg/kg/min, one cycle of Levosimendan),

catecholamine therapy could be reduced and terminated after a few days.”

Comment 6: Too short discussion, limited mainly to the causes of takotsubo. I believe that in this case cardiomyocyte damage should be discussed in patients with non-traumatic subarachnoid haemorrhage (SAH).

Reply 6: Thank you very much for this valuable suggestion. As the manuscript was designed as a brief case report, we didn't plan to elaborate the pathophysiology of Takotsubo cardiomyopathy extensively. We have however added a brief overview about the pathophysiological mechanisms (see page 8, lines 166-78)

Changes in the text: “Takotsubo cardiomyopathy is extremely rare in children and like in our case often initially mistaken for myocarditis or dilated cardiomyopathy. Previously described triggering conditions range from emotional stressors to physical conditions. While the exact pathophysiological mechanisms of Takotsubo cardiomyopathy remain unclear, the most distributed hypothesis implicates myocardial stunning. Sympathetic dysregulation and subsequent catecholamine excess supposedly cause direct toxic cardiomyocyte damage as well as coronary spasms in face of higher cardiac workload. Neurological and neurosurgical disorders as causes of Takotsubo cardiomyopathy seem less common in children than in adult patients and include intracerebral hemorrhage, in some cases due to AVMs and fistulas. Like in our case, especially lesions affecting the medulla, home to important regulators of the autonomic function, can furthermore cause dysregulation of blood pressure and heart rate due to baroreflex failure resulting in cardiogenic shock.”

Reviewer B

Comment 1: Throughout the manuscript, the use of English language needs improvement. There are several sentences that are phrased erroneously, and this will disallow an international reader to fully comprehend what the authors are trying to express.

Reply 1: Thank you for this valuable feedback. The whole manuscript has undergone language editing. The examples especially pointed out have been addressed as follows:

Comment 2: In the abstract section: "A 12-year-old boy suddenly collapsed in severe cardiogenic shock on the verge of requiring extracorporeal life support due to dramatically impaired left ventricular function resulting in ventilation and high catecholamine support. Whilst cardiac function normalized within days and no cardiac pathology was found, hemiparesis and the absence of protective reflexes appeared during the weaning process." This would have been easier to understand if authors worded as, "This case describes a previously well 12-year-old boy who presented acutely with severe cardiogenic shock requiring significant inotropic support and invasive mechanical ventilatory support. Interestingly, cardiac catheterization, myocardial tissue histology, along with biochemical laboratory tests did not yield a definitive diagnosis. As his cardiac function improved gradually within days, he was then found to have hemiparesis and absence of protective airway reflexes on neurological examination."

Reply 2: The wording has been amended as follows (see page 3, lines 63-69).

Changes in the text: “In our case a previously well 12-year-old boy presented with severe cardiogenic shock due to dramatically impaired left ventricular function requiring significant inotropic support and invasive mechanical ventilation. Interestingly, cardiac catheterization, myocardial tissue histology and biochemical laboratory tests did not yield a definitive diagnosis. As his cardiac function improved gradually within several days and deep sedation could be weaned, he was then found to suffer from hemiparesis and absence of protective airway reflexes on neurological examination during the weaning process.”

Comment 3: Another example would be in Section 2.2: “Despite similar clinical presentation and diagnostic findings as in adults, in childhood however, it is often mistaken not for acute myocardial infarction but for dilated cardiomyopathy or myocarditis.” This statement needs revision, as it is difficult to comprehend author's point here. Based on current literature, Takotsubo cardiomyopathy has been reported in <50 cases in paediatrics, therefore compared to dilated cardiomyopathy or acute viral myocarditis, it is certainly less common. Therefore, this diagnosis is not readily considered in the differential diagnoses when a previously well child presents with cardiogenic shock. I'm unsure why the authors mentioned about acute myocardial infarction. Other differential diagnoses which should be considered in paediatric age group should be: previous untreated Kawasaki's disease resulting in coronary aneurysm, undiagnosed congenital anomalous coronary artery origins - both of which can lead to acute myocardial infarction but the patient would present differently compared to Takotsubo cardiomyopathy.

Reply 3: We agree that the wording of this statement is misleading. Acute myocardial infarction is mentioned, because in adult patients Takotsubo cardiomyopathy is initially often mistaken for acute myocardial infarction whereas pediatric patients are more likely to be initially misdiagnosed as dilated cardiomyopathy or myocarditis. The wording has been amended as follows (see page 4, lines 93-99).

Changes in the text: “While most common among adults, especially elderly women, stress-induced cardiomyopathy has very rarely been described in children, presenting similar clinical symptoms and diagnostic findings as adults. In childhood however, it is often initially mistaken for much more common diagnoses like dilated cardiomyopathy or myocarditis or even rare differential diagnoses like previous untreated Kawasaki's disease, undiagnosed congenital anomalous coronary artery origin or permanent junctional reentry tachycardia.”

Comment 4: In Section 3.2: medical history and clinical presentation, these statements: "During evaluation in the ED he suddenly developed muscular hypotonia, oral leaking of bloody, foamy saliva and pulmonary wheezing. Drastically deteriorating cardiovascular parameters and decreasing saturation of 50% under oxygen therapy resulted in a collapse to somnolence." need revision/amendment. Again, the use of English language and the lack of detail in the clinical case description makes this case report not entirely useful in terms of application to the reader. The utility of a case report

lies in clear and detailed description of the clinical presentation. There is no complete vital signs listed on presentation in the emergency department; blood pressure and heart rate is important in describing the state of shock and why cardiogenic shock was considered. There is no detailed physical examination described here as well. What does "Muscular hypotonia" mean? How about the other parts of neurological examination such as reflexes and Babinski reflexes and pupillary changes? There is also no cardiac physical examination findings described here.

Reply 4: Vital signs and physical examination (as detailed as assessed in the emergency room) are presented in a table format now (see additional files, table 1). Unfortunately there was no detailed neurological examination done within the emergency examination.

Comment 5: Also, for this case report to be useful and applicable to international readers, data such as chest radiographic findings and blood gases will be useful as not every centre will have 2D-echocardiogram available so readily. Chest radiographic findings should be suggestive of acute pulmonary edema.

Reply 5: The boys chest x-ray at admission showing pulmonary oedema has been included as a separate figure and the development of bloodgases is now briefly summarized within the text (see additional files, figure 3 and page 6, lines 125-26 and 136-38).

Changes in the text: "Blood gases showed lactate acidosis (lactate max. 8 mmol/l, pH min. 7,22) and cardiac enzymes were highly increased."

"Blood gases normalized after one day and cardiac enzymes decreased to normal after one week (Troponin T (hs) max. 1,46 ng/ml one day after admission, NT-proBNP max. 26,833 pg/ml three days after admission)."

Comment 6: 2D-echocardiogram findings also needs to be more elaborate and complete. There is no mention of the right ventricular function, coronary origins, as well as LA dilatation. Also, I'm curious to know if there specific findings suggestive of Takotsubo cardiomyopathy.

Reply 6: In short: RV-function was normal, coronary origins orthotope, LA not relecantly dilated. Findings of the emergency echocardiography have been removed from the text, but added in detail to a new table, summarizing all diagnostic investigations (see additional files, table 2 and page 5, lines 116-17)

Changes in the text: "Emergency echocardiography showed massive acute left ventricular functional restriction."

Comment 7: "Catecholamine therapy (Suprarenin and Milrinone)" - trade names should be avoided, generic drug names should be used so that the international reader can better understand therapies used.

Reply 7: We totally agree, that only generic drug names should be used! The term "Suprarenin" has been switched to the generic drug name ("Adrenaline") (page 5, line 118-20).

Changes in the text: "Catecholamine therapy (Adrenaline and Milrinone) was initiated and after intubation the boy was transferred to pediatric intensive care for further

evaluation and potential extracorporeal life support (ECLS) therapy.”

Comment 8: In Section 3.3, authors need to specify what other investigations were done. This is again useful for readers to understand authors' thought processes and how they reached the final diagnosis of Takotsubo cardiomyopathy later. "As all other investigations were negative (i.e. intoxications, substance abuse, etc.)" - this statement is too vague, and needs more details. A table format of all investigations done would be useful to present.

Reply 8: Thank you for this valuable suggestion. A table summarizing all diagnostic investigation has been added (see additional file, table 2).

Comment 9: In section 3.4, authors need to provide more details and information on the clinical neurological findings. This statement "mild left hemiparesis and the absence of protective gagging, coughing and swallowing reflexes" is again too vague, and does not help reader learn how to piece these neurological findings with the MRI brain scan findings later.

Reply 9: As the primary focus of our manuscript is a brief case description, we tried to condense the extensive existing information. However, the neurological clinical findings are now described more in detail and correlated with the MRI findings (see page 6, lines 141-49).

Changes in the text: “During the weaning process and while preparing extubation with reduction of analgo-sedation the boy presented with the absence of protective gagging, coughing and swallowing reflexes (no reaction to endotracheal and oral suction) and mild left hemiparesis (left-sided motor weakness when compared to the right side, like pressing doctors hand or pushing with feet).

Subsequent cerebral MRI revealed a hematoma in the dorsolateral caudal medulla oblongata with intraventricular blood accumulation that was judged only few days old and sufficiently explained the lack of brainstem reflexes as well as the motor weakness.”

Comment 10: In Section 4, Discussion: "In retrospect, after initially suspecting acute viral myocarditis, we could identify the brainstem bleeding based on the fistulous AVM as precipitating cause of this acute ventricular impairment only with a few days delay when the neurologic symptoms got obvious after the patient's improvement." This statement needs revision and amendment. English language use here is erroneous and makes it difficult to understand. This is the summary paragraph by authors about the entire case and how all the parts piece together, therefore it needs to show clarity despite the diagnosis not being clear during the management of the case itself. It needs to be a clear and succinct summary of all the pertinent points and data and why eventually the authors think it is Takotsubo cardiomyopathy secondary to a brainstem hemorrhage secondary to an AVM.

Reply 10: Thank you for this helpful advice. We have clarified and specified the cases summary as follows (see page 8, lines 159-65)

Changes in the text: “Our patient presented in severe cardiogenic shock with drastically

impaired left ventricular function. Initially suspecting dilated cardiomyopathy or myocarditis, specific cardiologic diagnostics did not show pathological findings yielding to a diagnosis. When additional neurological symptoms got obvious during the weaning process, a brainstem bleeding due to a fistulous AVM was identified. Thus only in retrospect, the neurological condition was interpreted as precipitating cause of the acute ventricular impairment yielding to the diagnosis of Takotsubo cardiomyopathy.”

Comment 11: Overall the discussion section needs to crystallize the learning points and then use current medical literature to support the case learning points. Discrepancy can also be pointed out and therefore suggestion for improvement. These can benefit the reader if elaborated well.

Reply 11: We have amended and crystallized the discussion as a whole and specified the case learning points in the conclusion (see page 8, lines 181-87).

Changes in the text: “Conclusion and learning points:

- Acute myocarditis and dilated cardiomyopathy are the most common diagnoses in severe pediatric heart failure, but
- Takotsubo cardiomyopathy as a rare but possible cause for secondary acute left ventricular dysfunction and cardiogenic shock should not be disregarded
- Precipitating etiological factors such as intracranial processes should be ruled out on a regular basis.”

Reviewer C

Comment 1: Title and Abstract: I recommended the title "Takotsubo cardiomyopathy in a 12-year-old boy caused by acute brainstem bleeding".

Reply 1: Thank you for this suggestion. We are of course willing to omit the words “a case report” in the end of the title, as we had added them only because they were demanded by the CARE reporting guidelines. The title has been amended accordingly (title page 1, line 1)

Changes in the text: "Takotsubo cardiomyopathy in a 12-year-old boy caused by acute brainstem bleeding".

Comment 2: 4.1. As the authors described, Takotsubo cardiomyopathy can be triggered by central nervous system disorders such as stroke or intracranial bleeding. In a recent study regarding Takotsubo cardiomyopathy complicating ischemic stroke, ischemic lesions in the right anterior cerebral arterial circulation, especially the insula cortices and peri-insular area, were found to be associated with Takotsubo cardiomyopathy [Jung JM, Stroke 2016;47:2729-2736]. It has been reported that the insula and medulla play an important role in cardiovascular autonomic function [Oppenheimer SM, Neurology 1992;42:1727–1727, Hong JM, Neurol Sci. 2013;34:1963–1969]. Please explain the relationship between bleeding sites and the occurrence of Takotsubo cardiomyopathy.

Reply 2: We are very thankful for this actually very interesting addition. As the manuscript was designed as a brief case report, we didn’t plan to elaborate the

pathophysiologic mechanisms of Takotsubo cardiomyopathy extensively. We have however added a brief explanation about the importance of bleeding site for autonomic dysregulation in this case (see page 8, lines 166-78)

Changes in the text: “Takotsubo cardiomyopathy is extremely rare in children and like in our case often initially mistaken for myocarditis or dilated cardiomyopathy. Previously described triggering conditions range from emotional stressors to physical conditions. While the exact pathophysiologic mechanisms of Takotsubo cardiomyopathy remain unclear, the most distributed hypothesis implicates myocardial stunning due to sympathetic dysregulation and subsequent catecholamine excess. Neurological and neurosurgical disorders as causes of Takotsubo cardiomyopathy seem less common in children than in adult patients and include intracerebral hemorrhage, in some cases due to AVMs and fistulas. Like in our case, especially lesions affecting the medulla, home to important regulators of the autonomic function, can cause dysregulation of blood pressure and heart rate due to baroreflex failure resulting in cardiogenic shock.”

Comment 3: I feel that English is required to be brushed up in the entire.

Reply 3: Thank you very much for this well advice and the very explicit and thoughtful suggestions. The whole manuscript has undergone language editing especially considering the examples pointed out by the reviewer as follows:

Comment 4: Line1. Please rephrase to "Takotsubo cardiomyopathy is characterized by acute and reversible severe ventricular dysfunction due to intensive emotional or physical stress following catecholamine excess."

Reply 4: The wording has been amended as follows (see page 3, lines 59-60).

Changes in the text: “Takotsubo cardiomyopathy is characterized by acute and reversible severe left ventricular dysfunction due to intensive emotional or physical stress followed by catecholamine excess.”

Comment 5: Line 38. Please rephrase to "Cardiac function normalized within several days, and no underlying cardiac abnormality was found; however, hemiparesis and the absence of protective reflexes appeared during the weaning process."

Reply 5: In accordance with another reviewers comment, the wording has been amended as follows (see page 3, lines 65-69).

Changes in the text: “Interestingly, cardiac catheterization, myocardial tissue histology and biochemical laboratory tests did not yield a definitive diagnosis. As his cardiac function improved gradually within several days he was then found to suffer from hemiparesis and absence of protective airway reflexes on neurological examination during the weaning process.”

Comment 6: Line 41. Please rephrase to "Subsequent brain imaging studies revealed a brainstem bleeding due to a fistulous arteriovenous malformation."

Reply 6: The wording has been amended as follows (see page 3, lines 70-71).

Changes in the text: “Subsequent brain imaging studies revealed a brainstem bleeding

due to a fistulous arteriovenous malformation appearing to be only a few days old.”

Comment 7: Line 44. Please rephrase to "Our present case demonstrated that brain stem bleeding could precipitate Takotsubo cardiomyopathy manifesting hemodynamic collapse."

Reply 7: The wording has been amended as follows (see page 3, lines 73-74).

Changes in the text: “Our present case demonstrated, that brainstem bleeding could precipitate Takotsubo cardiomyopathy manifesting hemodynamic collapse.”

Comment 8: Line 46. Please rephrase to "Severe ventricular impairment has been described in many adults with subarachnoid hemorrhage; however, this condition is extremely rare among children."

Reply 8: The wording has been amended as follows (see page 3, lines 74-76).

Changes in the text: “Severe ventricular impairment has been described in many adults with subarachnoid hemorrhage; however, this condition is extremely rare among children.”

Reviewer D

Comment 1: This patient had severe and acute ventricular dysfunction, but extracorporeal life support was not required. TC in children is less common and serious cardiogenic shock or mortality is even rarer. But in some cases, LV dysfunction was so severe that the patient needed mechanical circulatory support followed by full recovery of ventricular function.

In this patient, ECLS was not applied as the patient recovered with medical management. However “ECLS” was frequently used in the manuscript even though it was not used. “Severe LV dysfunction with cardiogenic shock” seems to be enough.

J Cardiovasc Med (Hagerstown). 2017;18:262-7; Chonnam Med J. 2019 Sep;55(3):179-180

Reply 1: Thank you for this critical discussion of our wording. We have mentioned ECLS therapy specifically to stress the severity of our patients condition. He was primarily admitted with the intention of implanting ECLS and his parents had already undergone informed consent for both ECLS as well as listing for transplantation, before we realized he might improve with medical treatment only. We have however changed wording and dropped the reference to ECLS in the abstract (see page 3, line 63-65).

Changes in the text: “In our case a previously well 12-year-old boy presented with severe cardiogenic shock due to dramatically impaired left ventricular function requiring significant inotropic support and invasive mechanical ventilation.”

Comment 2: page 2, line 60: Authors defined Takotsubo cardiomyopathy as acute and severe LV dysfunction., however, LV dysfunction severity or cardiac enzyme elevation is not mandatory for the diagnosis of TC. Reversible ventricular function is a key factor for diagnosis, but it is not included in this sentence. Furthermore “Characterized” would be better than “defined”.

Reply 2: Thank you very much for this valuable specification, we have adapted the

wording accordingly and stressed the reversible character of the LV dysfunction in Takotsubo cardiomyopathy (see page 3, lines 59-60).

Changes in the text: “Takotsubo cardiomyopathy is characterized by acute and reversible severe left ventricular dysfunction due to intensive emotional or physical stress followed by catecholamine excess.”

Comment 3: How about regional wall motion abnormality and ejection fraction by biplane? Did you check LV angiogram for the appearance of apical ballooning during catheterization?

Reply 3: The initial echocardiography (and all further ones) showed no localized wall motion abnormalities, ejection fraction assessed in the initial echocardiography in the emergency department was 30 %. The LV angiogram also showed concentric pumping without localized wall motion abnormalities. These informations have been added within a new table summarizing all diagnostic investigations done (see additional files, table 2).

Comment 4: Were muscular hypotonia, decreased consciousness, and respiratory distress fully explained by LV dysfunction? Was there any clue for the neurologic deterioration before respiratory failure? Initial chest X-ray would be needed as a figure.

Reply 4: Obviously in retrospect the mentioned symptoms presented by the patient in our emergency department could have been caused by the brainstem bleeding. Initially and under the diagnosis of acute cardiogenic shock due to suspected myocarditis or dilated cardiomyopathy and potential deterioration caused by arrhythmias, these symptoms were much more likely and sufficiently explained by LV dysfunction. As the patient deteriorated shortly after his arrival in the emergency department no detailed neurologic examination took place before sedation and intubation, thus the first clue for the underlying neurologic condition appeared as hemiparesis and absence of protective reflexes in the weaning process as described.

Initial chest x-ray showing pulmonary oedema has been added as a figure (see additional files, figure 3).

Comment 5: Other cardiac enz. Such as CK, CKMB should be suggested. How about lactic acid level during the acute phase?

Reply 5: Thank you for this valuable additions. CK and CK-MB measures were elevated in our patient. These findings have been included in an additional table summarizing all diagnostic investigations (see additional files, table 2). Information about blood gases are now given in the text (see page 6, lines 125-26 and 136-38)

Changes in the text: “Blood gases showed lactate acidosis (lactate max. 8 mmol/l, pH min. 7,22) and cardiac enzymes were highly increased.”

“Blood gases normalized after one day and cardiac enzymes decreased to normal after one week (Troponin T (hs) max. 1,46 ng/ml one day after admission, NT-proBNP max. 26,833 pg/ml three days after admission).”

Comment 6: Unnecessary abbreviations were used, such as AoVTI and MI, which were

used only once in the manuscript.

Reply 6: All abbreviations, which were only used once, have been deleted from the manuscript (see title page 2, “Abbreviations”, page 5, lines 113-17)

Changes in the text: “Emergency echocardiography showed massive acute left ventricular functional restriction.”