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CASE REPORT
Inherited cardiac conditions/cardiomyopathies

Unexpected high troponin T and I values in a child with hypertrophic cardiomyopathy and acute chest pain: a case report

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Background Elevated troponin T (cTnT) and/or troponin I (cTnI) can be ascribed to multiple causes, mostly resulting from cardiac tissue damage and in lesser numbers resulting from non-cardiac related causes. The presence of macrotroponins is easily overlooked, with potentially negative consequences.

Case summary This case report presents a case study of a 12-year-old child known to have MYH7 gene–associated hypertrophic cardiomyopathy with acute chest pain combined with an unexpected high cTnT and cTnI. A cardiac cause was deemed unlikely after additional investigation, as these showed no abnormalities. After consulting a laboratory specialist, it could be concluded that the high cTnT and cTnI were a result of macrotroponin complexes, a protein complex consisting of circulating protein and endogenous autoantibodies against that protein, resulting in elevated values with misguiding and uncertain clinical significance.

Discussion Awareness of the existence of macrotroponins could have prevented costly diagnostics and prolonged hospital admission with grave psychological impact, especially in children.

Keywords Troponin I • Troponin T • Macrotroponin • Hypertrophic cardiomyopathy • Chest pain • Child • Case report

ESC Curriculum 2.1 Imaging modalities • 2.2 Echocardiography • 2.3 Cardiac magnetic resonance • 2.4 Cardiac computed tomography • 6.5 Cardiomyopathy

Learning points

- When high troponin values cannot be explained clinically, one should investigate the presence of macrotroponins.
- Although macrotroponins have been demonstrated mainly in adults, these proteins can occur in children.
- Both macrotroponin T and I can coexist in the same patient.
- The demonstration of macrotroponins is a relatively simple laboratory procedure that may prevent unnecessary diagnostic investigations and prolonged hospital stays.

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Introduction

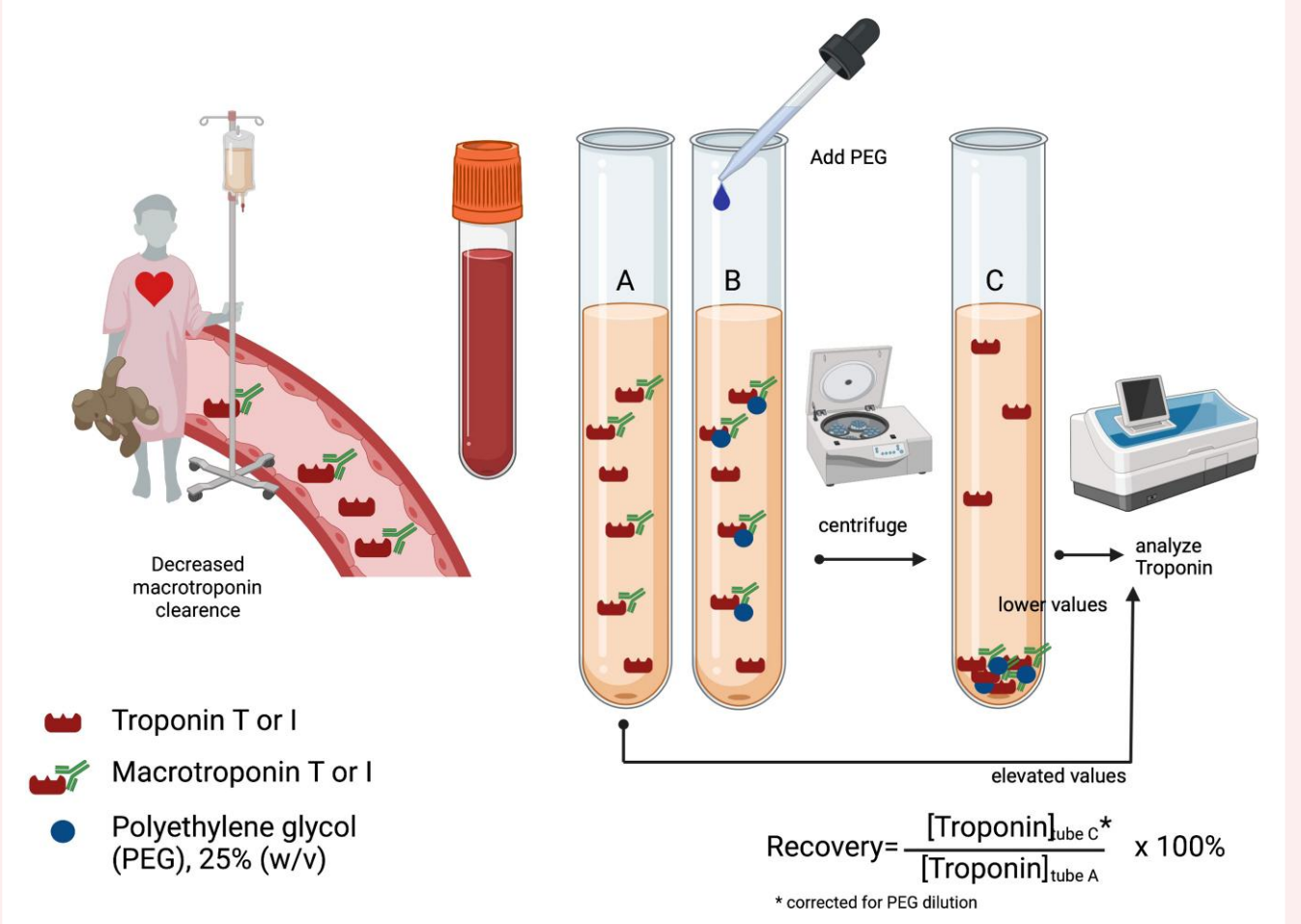
Troponin T (cTnT) is a commonly used biomarker within diagnostics of cardiac cell damage. Both cTnT and troponin I (cTnI) are used to demonstrate cardiac injury quickly and accurately. In adults, elevated troponins (cTn) usually indicate myocardial ischaemia as a result of coronary artery disease but may occur in several other cardiac diseases, such as myocardial inflammation, heart failure, and general inflammation. In children and adolescents, frequent cardiac causes of elevated cTn include myocarditis and perimyocarditis.[1] This case report describes the unexpected finding of a very high cTnI and subsequently very high cTnT value in a child without any evidence of acute cardiac tissue damage, which resulted in unnecessary and prolonged hospital stay and how this could have been prevented. These very high cTn values could later be explained by the demonstration in the laboratory of a harmless anomaly, known as macrotroponins.

Case presentation

A 12-year-old girl, known to have MYH7 gene–associated hypertrophic cardiomyopathy, presented in the emergency room with acute onset of chest pain. The pain was situated at the centre and left side of the thorax and was described as intermittent piercing pain, increased by movement, inspiration, and expiration. The patient had not been ill, and no trauma had occurred prior to the onset of symptoms. Furthermore, signs of hyperventilation and palpitations were absent. The patient was on verapamil and carvedilol. Sublingually administered nitroglycerine had no effect, but after paracetamol 500 mg, the pain slightly improved. At presentation, the heart rate was 70 b.p.m., blood pressure 110/70 mmHg, breathing frequency 17/min, and transcutaneous saturation 97%. Upon heart auscultation, a previously documented grade 2–3/6 systolic ejection murmur was heard, loudest at the left sternal border. The chest pain could be provoked by palpating the sternum.

Transthoracic echocardiography was performed and was similar to earlier transthoracic echocardiography (*Figure 1*; see Supplementary material online, *Movie S1*): significant hypertrophy of both ventricles

Summary figure



A schematic representation of macrotroponin investigation using polyethylene glycol (PEG). The presence of macrotroponin in patients often results in unexpected high troponin (cTn) results due to decreased clearance of macrotroponins from the circulation. Macroproteins, such as macrotroponin, precipitate by the addition of PEG and can after centrifugation be separated from free, unbound cTn in the sample. When macrotroponins are present, subsequent analysis of the PEG-treated sample results in lower cTn results compared with the untreated sample. Created with BioRender.com.

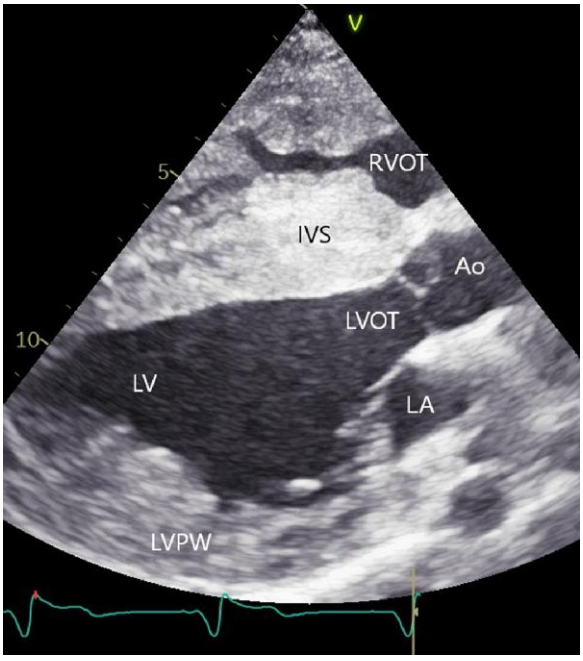


Figure 1 Transthoracic echocardiography, showing a parasternal long-axis view with a hypertrophic myocardium without left ventricular outflow tract obstruction. Ao, aorta; IVS, interventricular septum; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; LVPW, left ventricle peripheral wall; RVOT, right ventricular outflow tract.

(left ventricle peripheral wall thickness in diastole of 14.7 mm and interventricular septal thickness in diastole of 17.3 mm), decreased systolic function (fractional shortening of 10%, tricuspid annular plane systolic excursion 1.1 cm), diastolic dysfunction, no regional wall movement disorders, and no pericardial effusion.

Blood tests revealed elevated cardiac enzymes (reference values in brackets): cTnT 558 ng/L (<14 ng/L), N-terminal brain natriuretic propeptide (NT-pro-BNP) 1322 ng/L (<125 ng/L), creatinine kinase (CK) 285 U/L (<145 U/L), creatinine kinase muscle/brain isoenzyme (CK-MB) activity 199 U/L (<25 U/L), CK-MB mass 15.53 µg/L (<3 U/L), lactate dehydrogenase (LDH) 1198 U/L (<247 U/L), blood urea nitrogen 5.6 mmol/L (2.5–7.5 mmol/L), creatinine 56 µg/L (in women 50–90 µmol/L), and estimated glomerular giltration rate 121 mL/min/1.73 m^2, all measured on cobas CE modules (Roche Diagnostics, Mannheim, Germany). In addition to cTnT, cTnI, a similar but biochemically different cardiac marker, was also elevated (36 823 pg/mL; reference value for adults: 25.1–34.4 pg/mL; measured on the Lumipulse immunoanalyzer, Fujirebio Inc., Tokyo, Japan). C-reactive protein was low at 0.6 mg/L (<10 mg/L). *Table 1* shows the laboratory findings over the course of time.

Anamnesis and physical examination led to a low suspicion of a heart-related cause. However, the high cardiac enzymes seemed unfitting for such a diagnosis. The patient was not on any medication, such as checkpoint inhibitors or monoclonal antibodies, which could interfere in cTn analysis. Due to this discrepancy, the patient was admitted for observation and additional investigations were performed.

Viral serology was negative, and C-reactive protein remained low. Thoracic X-ray showed no abnormalities besides cardiomegaly. Computed tomography angiography showed a normal origin and course of the coronary arteries and no pulmonary embolism.

Table 1 Laboratory findings over the course of time

Date	cTnT (ng/L)	CK (U/L)	CK-MB activity (µg/L)	CK-MB mass (U/L)	LDH (U/L)
Admission	558	285	199	15.53	1198
Day 2	769	203	64	16.44	617
Day 3	1005		31	19.48	423
Day 4	1224				
Day 5	1608	232	45	31.66	488
Day 8	905	137		14.66	
Day 11	698	144	27		347
5 months later	803	111	22		

Magnetic resonance imaging shows hypertrophy (*Figure 2*) and no signs of myocarditis and a normal pericardium. Myocardial perfusion scintigraphy did not show signs of ischaemia.

After additional investigation, doubts were raised concerning the unexpectedly and disproportionally high cTnT and subsequent cTnI values. Therefore, a laboratory specialist was consulted, and it was concluded that these results could be explained by the following: (i) an analytical error, (ii) an interference of endogenous antibodies like human anti-mouse antibodies (HAMA) and/or heterophilic antibodies in immunoassays, or (iii) the presence of macrotroponins.[2]

The first hypothesis was rejected since both cTn assays were increased, even after reanalysis. For the second hypothesis, the presence of these antibodies was investigated using heterophilic blocking tubes (Scantibodies Laboratory Inc., CA, USA) and dilution with a negative plasma sample. Percentage recovery of cTnI and cTnT appeared unaffected (recovery of 104 and 109%, respectively). Therefore, the influence of endogenous interfering antibodies was excluded. Finally, the third hypothesis was investigated by using a 25% (w/v) polyethylene glycol (PEG) pre-treatment.[3] The summary figure is a schematic representation of the macrotroponin investigation using PEG. In a sample drawn on Day 4, a total cTnT of 1224 ng/L was found with a recovery of 21.7% after PEG precipitation; in addition, a total cTnI of 44 175 ng/L with a recovery of 0.2% was found. To be able to interpret these recovery percentages, 10 different randomly chosen residual anonymized samples with different cTnT and cTnI values were similarly pre-treated with PEG. Recovery rates for cTnT and cTnI ranged from 96–136% to 74.5–109.5%, respectively (*Table 2*). From these data, it can be concluded that the markedly elevated cTnT and cTnI values from our patient can be explained by the presence of macrotroponin T as well as macrotroponin I.

Since no alternative diagnosis other than musculoskeletal pain could be ascertained and the chest pain spontaneously subsided after 7 days, the patient was discharged from the hospital after 9 days with declining but still elevated cardiac enzymes. In the months following the patient's hospital discharge, cTnT values remained high. Again, macrotroponin T was investigated in a sample drawn 5 months after hospital admission. The cTnT concentration was 803 ng/L, whereas after PEG precipitation, only 15% of the initial cTn could be recovered.

Discussion

Troponin is a biomarker with high sensitivity for myocardial injury and as such is often used for diagnosing acute coronary syndrome.[4] However, elevated values can be found in several other clinical circumstances related to our case. For example, MYH7 gene mutation (with which the patient was known) can lead to myopathy.[5] In patients

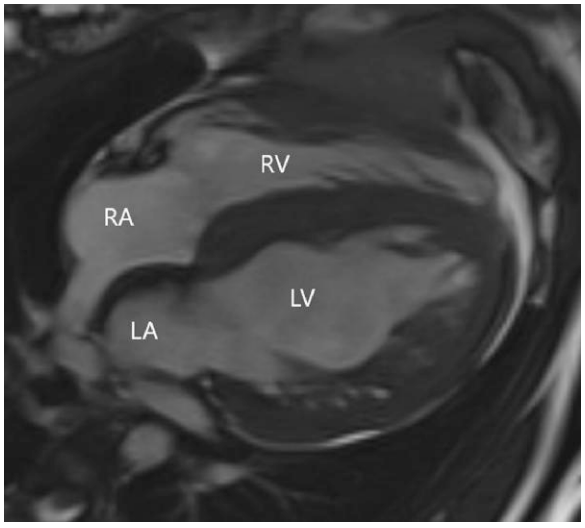


Figure 2 Cardiac magnetic resonance imaging, showing a four-chamber view with severe hypertrophic cardiomyopathy in the left and right ventricles. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Table 2 Free troponin T and I after polyethylene glycol precipitation of macroproteins in 10 randomly selected samples, reported as a percentage of total troponin, median values and 95% confidence intervals (95% CI)

Sample	cTnT (ng/L)		cTnI (ng/L)	
	Plasma	Free cTnT (%)	Plasma	Free cTnI (%)
1	42.8	117	80.4	83
2	250.2	116	1563.5	95
3	659.6	112	3150.5	95
4	279.9	121	29.1	91
5	113.1	125	1277.2	95
6	354.7	109	4891.8	92
7	718.8	102	10 930.6	85
8	51.2	125	105.9	79
9	2783.0	104	45 069.2	89
10	1022.0	121	15 343.1	104
Median	317.3	116	2357.0	92
95% CI		**96–136**		**74.5–109.5**

Median values and 95% confidence intervals of these 10 randomly selected samples.

with skeletal myopathies, elevated cTnT can be found, in addition to elevated CK. Myopathy might also explain the musculoskeletal pain and elevated CK in our patient. In myopathy patients, however, cTnI is lower,[6] which made the likelihood of myopathy in our patient smaller as this marker was high. In 25–50% of patients with hypertrophic cardiomyopathy without acute coronary syndrome, increased levels of cTn can be found[7] and cTnT values up to 140 ng/L have been described.[4] In our patient, cTnT and cTnI were elevated to a level highly suspicious for acute coronary syndrome, leading to extensive diagnostics and prolonged hospital admission. During admission, the presence of macrotroponins was demonstrated as the cause of the disproportionately high cTnT and cTnI.

A macroprotein is a protein complex consisting of circulating protein and endogenous autoantibodies against that protein,[8] resulting in elevated values due to decreased clearance with misguiding and uncertain clinical significance. The incidence of macrotroponins is estimated to be 0.065–6.5%, but a higher incidence is also reported.[9] Previously published cases[3,10–12] describe the discovery of a single macrotroponin T or I in adult patients, with increasing incidence over the age of 50.[9] Literature about macrotroponin in children, however, is scarce.[13,14] One case report is worth mentioning, namely a macrotroponin found in a newborn of which autoantibodies against cTn were hypothesized to be passively transferred from the mother. Our case report however describes the simultaneous presence of two different macrotroponin complexes, namely macrotroponin T and macrotroponin I, as an explanation for discrepantly elevated cTnT and cTnI. The discovery of both macroproteins in the same 12-year-old patient makes this case remarkable.

In 25–50% of patients with hypertrophic cardiomyopathy, increased levels of cTn can be found, especially those with a thicker myocardium,[7] which might be a result of continuous leakage of cTn caused by insufficient oxygenation of cardiac cells due to abnormal thickening of the cardiac wall.[15] This might trigger the immune system to form autoantibodies against both cTn, resulting in macrotroponin complex formation. Why our patient had both macrotroponins for cTnT and cTnI, we can only speculate; cTnT and cTnI are different molecules with different genetic characteristics, transcribed from different genes,[16,17] which makes it likely that both macrotroponins are formed by different autoantibodies. The observed fluctuation of cardiac markers during admission in our patient was probably the net result of cTn release from chronically injured myocardial tissue, autoantibody titres, and (macro)troponin clearance.

Conclusions

This case report describes a child with a markedly elevated cTnT as well as cTnI without a clear pathological aetiology. After PEG precipitation, the elevated cTnT and cTnI could only be explained by the presence of macrotroponin T and I. In the future, elevated cardiac cTn in this patient should be interpreted in line with these described findings.

Since cTn is a commonly used biomarker to diagnose cardiac injury accurately, cardiac paediatricians and cardiologists should be aware of the possible existence of macrotroponins. Establishing the presence of macrotroponins can aid in preventing costly diagnostics and prolonged hospital admission with grave psychological impact, especially in children.

Lead author biography

Dr Anneke C. Muller Kobold (1967) is since 2005 a clinical chemist at the Department of Laboratory Medicine at the University Medical Center Groningen (UMCG) and the head of the Laboratory of Binding Analysis. Her main focus as a clinical chemist and immunologist is on improving and innovating biomarker-based diagnostics in the fields of inflammation and immunology, inflammatory bowel diseases, and endocrinology.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Consent: Full approval was obtained from the patient and her legal representatives in accordance with COPE guidelines.

Conflict of interest: None declared.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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