Cardiology in the Young

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Transient left bundle branch block and left ventricular dysfunction in a patient with NLRP1-associated autoinflammation with arthritis and dyskeratosis syndrome

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Brief Report

Cite this article: Garrelfs MR, Hoppenreijs E, Tanke RB. (2019) Transient left bundle branch block and left ventricular dysfunction in a patient with NLRP1-associated autoinflammation with arthritis and dyskeratosis syndrome. *Cardiology in the Young* **29**: 435–438. doi: 10.1017/S1047951118002342

Received: 30 June 2018
Accepted: 26 November 2018
First published online: 25 January 2019

Key words:
NLRP1-associated autoinflammation with arthritis and dyskeratosis; autoinflammation; autoimmune; cardiac involvement; cardiac dysfunction; left bundle branch block

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Abstract

The NLRP1-associated autoinflammation with arthritis and dyskeratosis syndrome is a rare novel autoinflammatory disorder. Cardiac involvement has not been previously reported. We present a 12-year-old girl with NLRP1-associated autoinflammation with arthritis and dyskeratosis syndrome who was diagnosed with severely impaired left ventricular function and complete left bundle branch block during an exacerbation of the disease. Cardiac dysfunction proved to be rapidly reversible after initiation of high-dose methylprednisolone.

The NLRP1-associated autoinflammation with arthritis and dyskeratosis syndrome is a novel autoinflammatory disorder characterised by dyskeratosis, arthritis, recurrent fever, and elevated acute phase reactants.[1] Till date, only three patients have been described in the literature. Cardiac involvement has not been previously reported. We present a 12-year-old girl with NLRP1-associated autoinflammation with arthritis and dyskeratosis syndrome, who was diagnosed with severely impaired left ventricular function and complete left bundle branch block during an exacerbation of the disease. This proved to be rapidly reversible after initiation of high-dose methylprednisolone.

Case report

We report the case of a 12-year-old girl with NLRP1-associated autoinflammation with arthritis and dyskeratosis syndrome, who was seen at the emergency department with headache, abdominal pain, vomiting, diarrhoea, malaise, and fluctuating fever. There was no history of recent infections. Her history revealed a splenectomy years before and an ongoing tubulo-interstitial nephritis. At that time, the patient was treated with amlodipine 2.5 mg twice daily, leflunomide 10 mg once daily, prednisone 3.5 mg once daily, which was being tapered since July 2017, and canakinumab 150 mg once every 4 weeks. The patient was considered immunocompromised due to her medication and a chronic T-lymphocytopenia.

Physical examination showed a pale, tachypnoeic child with a normal oxygen saturation while breathing ambient air. She had a tachycardia of 135 beats per minute and a blood pressure of 98/73 mmHg. Auscultation of the lungs, heart, and abdomen revealed no abnormalities. Her abdomen was diffusely painful on palpation and the liver was palpable 1 cm below the ribs. Her temperature was 36.6°C. Besides the known dyskeratosis, there were no other skin lesions.

Laboratory studies (Table 1) revealed elevated acute phase reactants, including ferritin elevation of liver enzymes and creatinine. She was hyponatraemic, hyperkalaemic, and hypomagnesiemic. Blood gas evaluation showed a metabolic acidosis, with elevated lactate levels. An elevated creatine kinase was noted but other cardiac biomarkers were not tested. Cytokine profiling revealed elevated IL-6, IL-10, and IL-18.

A chest X-ray showed no abnormalities. Her ECG revealed a complete left bundle branch block (Fig 1a). Echocardiography showed a decreased left ventricular function, with a shortening fraction of 16.7% – reference value >26% – and ejection fraction of 34.8% – reference range 56–78% (Fig 2a; Supplementary Video 1).[2]

Suspecting a viral infection with a secondary severe exacerbation of her autoinflammatory disorder complicated by multi-organ failure, the patient was started on high-dose methylprednisolone (30 mg/kg/day) after a fluid challenge with isotonic saline. Because a bacterial infection could not be ruled out at the time, she was started on intravenous ceftriaxone.

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Table 1. Laboratory results.

Measurement	Units	Reference range	Day 0	Day 1	Day 3
Haematology					
Hb	mmol/L	7.5–9.2	8.6	7.6	7.6
WBC	10^9^e^/L	4.0–10.0	10.8	8.0	6.0
Thrombocytes	10^9^e^/L	170–430	66	74	24
PT	seconds	11–15	35		
APT	seconds	24–36	95		
Fibrinogen	mg/L	2000–4000	1.930		
Chemistry					
Ionised calcium	mmol/L	2.2–2.65	0.92	0.87	0.97
Phosphate	mmol/L	0.8–1.4	1.99	2.30	3.32
Sodium	mmol/L	135–145	126	130	129
Magnesium	mmol/L	0.70–1.10	1.12	0.89	1.17
Potassium	mmol/L	3.5–4.7	5.8		5.6
Chloride	mmol/L	97–107	98	101	95
BUN	mmol/L	2.5–7.0	12.9	18.6	41.0
Creatinine	µmol/L	40–80	279	395	669
Immunology					
BSE	mm/hour	3–13	5		17
CRP	mg/L	<10	134	321	81
Ferritin	µg/L	10–150	9.459		
sIL2R	pg/ml	<3000	17255		
IL-1b	pg/ml	0–10	275		
IL-6	pg/ml	0–10	3997		
IL-10	pg/ml	0–23	394		
IL-18	pg/ml	0–34	9398		
IFN-g	pg/ml	0–18	453		
MIG	pg/ml	28–1772	1869		

IFN-g = interferon gamma; MIG = monokine induced by interferon gamma; sIL2R = soluble interleukin 2 receptor

Within 24 hours after initiation of therapy, the patient felt markedly better and we repeated our cardiologic evaluation. Strikingly, repeat ECG showed no signs of a conduction disturbance (Fig 1b) and echocardiography revealed a normalised left ventricular function with a shortening fraction of 34.7% and an ejection fraction of 63.6% (Fig 2b; Supplementary Video 2). Two days later, further improvement of cardiac function with a shortening fraction of 41.2% and an ejection fraction of 72.2% was noted (Fig 2c; Supplementary Video 3). At this point, her electrolytes had not been corrected (Table 1).

Blood cultures remained negative and thus antibiotics were ceased after 48 hours. There was a marked improvement of liver function tests but due to persistent oliguria the patient was started on chronic venovenous haemodialysis. Because of clinical improvement, the patient could be discharged from the paediatric intensive care unit to the ward where cardiac function remained unremarkable.

Discussion

Cardiac involvement in autoimmune or autoinflammatory disorders can manifest as pericarditis, myocarditis, endocarditis, and coronary artery disease.[3]The NLRP1-associated autoinflammation with arthritis and dyskeratosis syndrome is a rare autoinflammatory disorder, characterised by diffuse skin dyskeratosis, arthritis, and recurrent fever. This girl has a de novo heterozygous mutation (c.3641C > G, p.Pro1214Arg) in the NLRP1 gene (1).

https://doi.org/10.1017/S1047951118002342 Published online by Cambridge University Press

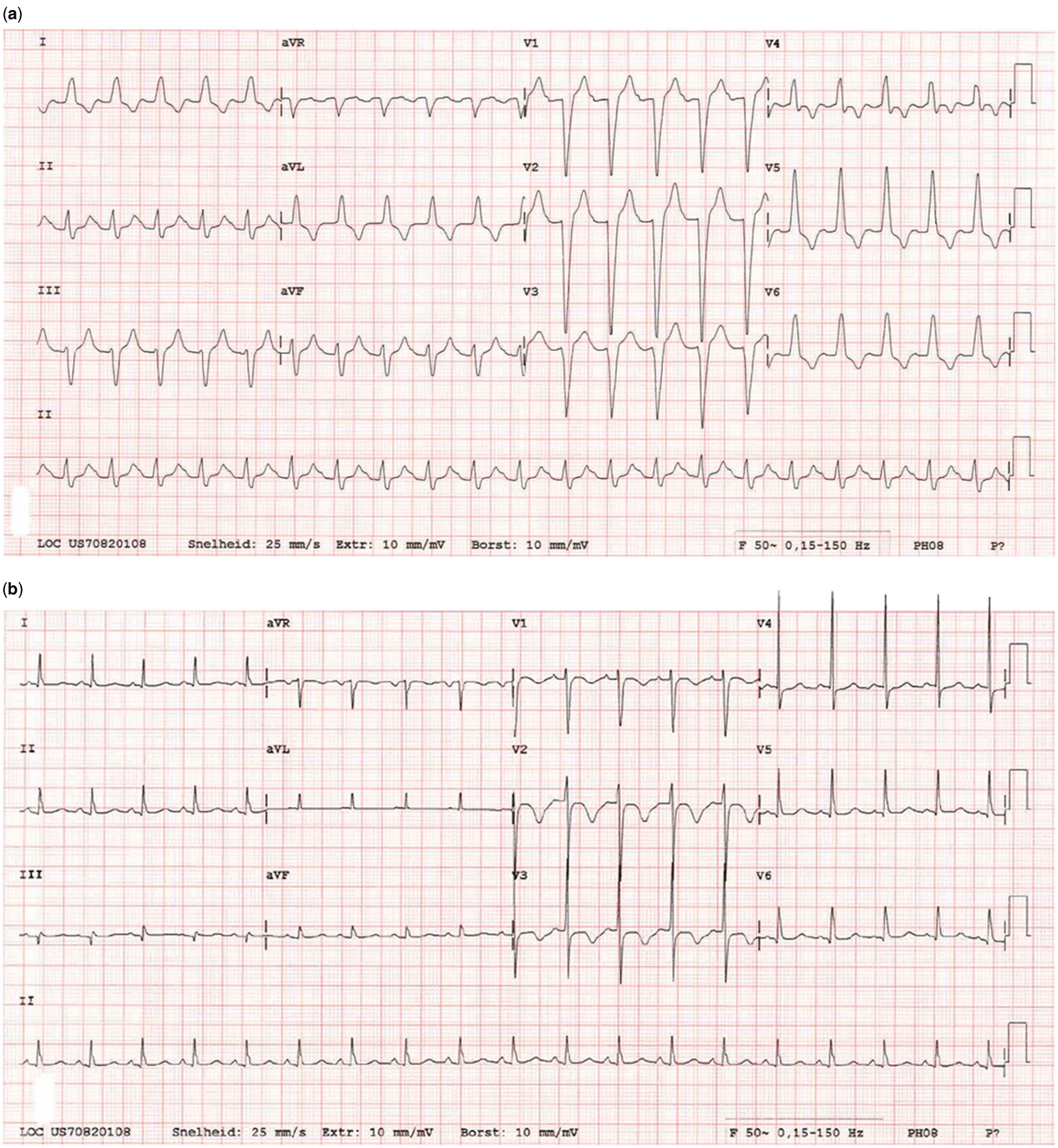

Figure 1. (*a*) ECG made at presentation, before treatment with intravenous methylprednisolone, showing complete left bundle branch block. (*b*) ECG made on day 1, 24 hours after initiation of treatment with intravenous methylprednisolone, showing no signs of a left bundle branch block.

Before this report, cardiac involvement had not been reported in patients with NLRP1-associated autoinflammation with arthritis and dyskeratosis syndrome.

We described a patient that developed left ventricular dysfunction and conduction disturbance during an exacerbation of her autoinflammatory disease. A striking finding was the rapid resolution of these abnormalities after initiation of high-dose intravenous methylprednisolone.

We postulate that the observed exacerbation of our patients disease resulted in massive release of inflammatory mediators which caused myocardial depression and conduction disturbances, similar to those seen in patients with septicemia.[4,5] Primary myocarditis seems less likely due to the striking improvement shortly after initiating immunosuppressive therapy, but cannot be ruled out completely.

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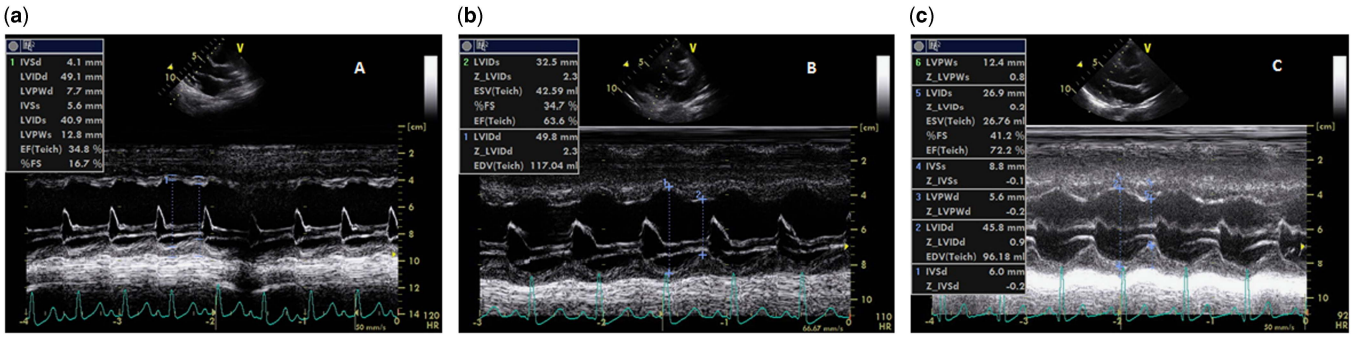

Figure 2. Echocardiography findings. (*a*) M-mode echocardiographic assessment at presentation (day 0). (*b*) M-mode echocardiographic assessment after 24 hours of intravenous methylprednisolone (day 1). (*c*) M-mode echocardiographic assessment after 72 hours of intravenous methylprednisolone (day 3).

Cytokines function as mediators of immune and inflammatory reactions. They are thought to play a crucial role in the early decrease in cardiomyocyte contractility during sepsis.[6] Increased circulating and intracardial cytokines are furthermore associated with chronic heart failure, ischemic myocardial dysfunction, coronary artery disease, left ventricular remodelling, and dysfunction and development of a dilated cardiomyopathy.[5,7–10]

Indeed, several interleukins, including IL-6 and IL-18, were elevated during this exacerbation in our autoinflammatory disorder patients.

The observed co-occurrence of electrolyte disturbances could have exacerbated the cardiac abnormalities. However, we believe this only played a minor role as cardiac function improved promptly after initiation of immunosuppressive therapy, despite persisting electrolyte disturbances (Table 1).

Conclusion

Acute cardiac dysfunction and conduction disturbances can be seen in patients with NLRP1-associated autoinflammation with arthritis and dyskeratosis syndrome. Increased circulating cytokines most likely play a crucial role in the development of the described cardiac abnormalities, although the exact pathophysiologic mechanism remains unclear.

Acknowledgements. The authors thank Ellen J.H. Schatorjé for her review of our manuscript.

Financial support. This research received no specific grant from any funding agency, or from commercial or not-for-profit sectors.

Conflicts of interest. None.

Ethical standards. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent. Informed consent was obtained from all individual participants, or their parents, included in the study. Additional informed consent was obtained from all individual participants, or their parents, for whom identifying information is included in this article.

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