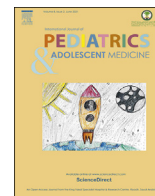


HOSTED BY



Contents lists available at ScienceDirect

International Journal of Pediatrics and Adolescent Medicine

journal homepage: <http://www.elsevier.com/locate/ijpam>

Acute Autonomic Neuropathy as a Rare Cause of Severe Arterial Hypertension in a Child

Halszka Kamińska^a, Anna Kostera-Pruszczyk^b, Anna Potulska-Chromik^b,
Bożena Werner^{a,*}

^a Dept. of Pediatric Cardiology and General Pediatrics, Medical University of Warsaw, Poland

^b Dept. of Neurology, Medical University of Warsaw, Poland

ARTICLE INFO

Article history:

Received 17 January 2020

Received in revised form

29 April 2020

Accepted 28 June 2020

Available online 8 July 2020

Keywords:

Hypertension

Neuropathic pain

Acute autonomic neuropathy

ABSTRACT

A 7-year-old boy was admitted to the Pediatric Cardiology Department with blood pressure of 160/120 mmHg accompanied by burning pain in his hands and feet and tachycardia, followed by a seizure attack for the first time in his life, which presented shortly after admission. The child underwent a widespread diagnostic process – including laboratory tests and imaging – showing inconclusive results. Acute autonomic neuropathy was eventually diagnosed and successfully treated with intravenous immunoglobulin. The described case illustrates the need for a careful and open-minded approach to patients with hypertension.

© 2020 Publishing services provided by Elsevier B.V. on behalf of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

In the pediatric population, particularly in younger children (<6 years old), severe arterial hypertension is mostly secondary to an underlying pathology [1,2]. Among the most common causes of hypertension, renal, endocrine, and vascular diseases can be listed and some of them, if properly attended, may be treated successfully [3]. The aim of presenting the following case report was to illustrate dilemmas and traps on the way to diagnose the rare cause of hypertension in a child.

2. Case report

A 7-year-old boy, previously healthy, was referred to pediatric

care because of recurrent burning pain in his palms and feet lasting for a week. Symptoms started gradually, mild at first, aggravating at times, and the boy could not sleep at night. Only bathing the hands and feet in cold water eased the pain to some extent; painkillers were not effective at all. No skin lesions in parasthetic area were observed. The boy showed no additional symptoms. While he was seen by his family physician, his blood pressure (BP) was recorded as abnormally high. Repetitive readings showed the results of 160/120 mm Hg, for that reason the child was referred to a hospital.

The boy was admitted to the Pediatric Cardiology Department in quite a good general condition. He was alert and in good contact, but evidently suffering and irritated. BP recordings on all extremities continued to be abnormally high both for systolic and diastolic values: 160/120 mm Hg (>99th percentile for gender, age, and height). His skin was unchanged with normal turgor, no lesions, rashes, or edema were observed on palms and feet. His peripheral pulses were strong. He presented tachycardia of 120 bpm, which was interpreted as a result of pain and stress. No signs of infection and no abnormalities were found during neurological examination, no sensory-motor deficit was detected, and his deep tendon reflexes were preserved. There was no anhidrosis.

The detailed history taken from the parents revealed no viral infections, toxic exposure, drugs, or trauma in the imminent past. No headaches or nose bleeding suggestive of symptomatic

Abbreviations: CT, computer tomography; MRI, magnetic resonance imaging; ACEI, angiotensin converting enzyme inhibitor; BP, blood pressure; ABPM, ambulatory blood pressure monitoring; ECG, electrocardiogram; EEG, electroencephalography; HR, heart rate; AAN, acute autonomic neuropathy; and AN, autonomic neuropathy.

* Corresponding author. Head of Department of Pediatric Cardiology and General Pediatrics, Medical University of Warsaw, 63A Żwirki i Wigury Street, 02-091, Warsaw, Poland.

E-mail address: bozena.werner@wum.edu.pl (B. Werner).

Peer review under responsibility of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia.

<https://doi.org/10.1016/j.ijpam.2020.06.006>

2352-6467/© 2020 Publishing services provided by Elsevier B.V. on behalf of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

hypertension were observed. He experienced no symptoms from gastrointestinal or urinary tract – no diarrhea, constipation, and dysuria. The boy was under regular pediatric care and his blood pressure readings so far were within normal limits. The family history was irrelevant.

The 24-h monitoring (ABPM) was started. The ECG monitoring was showing “stiffly” elevated heart rate 120 bpm (sinus rhythm).

During the blood pressure monitoring, the boy presented for the first time in his life a tonic-clonic seizure attack lasting for 5 min, he responded well to midazolam. Urgent CT scan of the brain was performed showing no bleeding or pathological masses, just mild cerebral edema. The patient was started on mannitol and furose-mide. His cerebrospinal fluid was collected and showed no abnormalities.

An analysis of monitored parameters showed both blood pressure and heart rate to be constantly elevated (165/125 mmHg and 125 bpm, respectively) with no variability for 24 h – including the time before, during, and after seizures (Fig. 1). After antiedematous treatment was introduced, the blood pressure had not changed, but HR was elevated to 160 bpm, and sinus rhythm was the same as before (Fig. 2).

The neuroimaging diagnostics were extended: the MRI of the brain (4th day after seizures) and spinal cord (eighth day after seizures) showed no pathologies including no pathological late gadolinium enhancement. EEG was performed (5 days after seizures) and proved to be normal.

The ophthalmological examination and echocardiography showed no changes characteristic of chronic hypertension.

The child was started on calcium blocker (Amlodipine), which

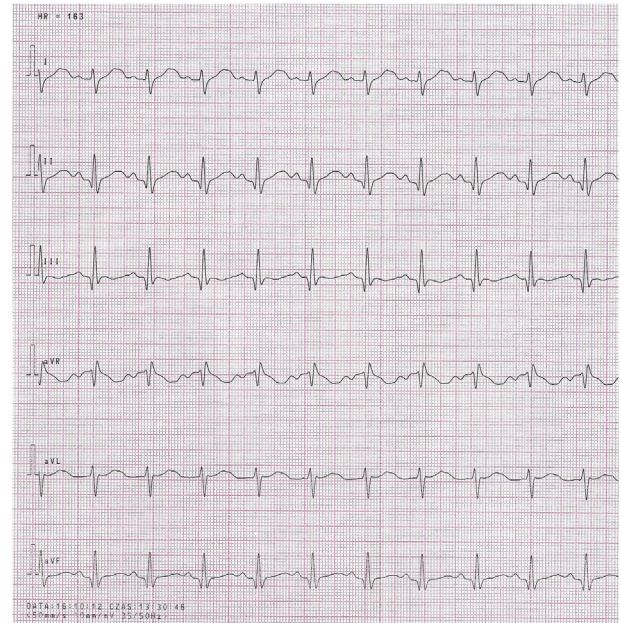


Fig. 2. Patients ECG – sinus tachycardia.

reduced blood pressure to 125–130/85–90 mmHg, still with no variability, HR continued to be elevated up to 150–160 bpm.

The child’s blood and urine samples showed normal renal

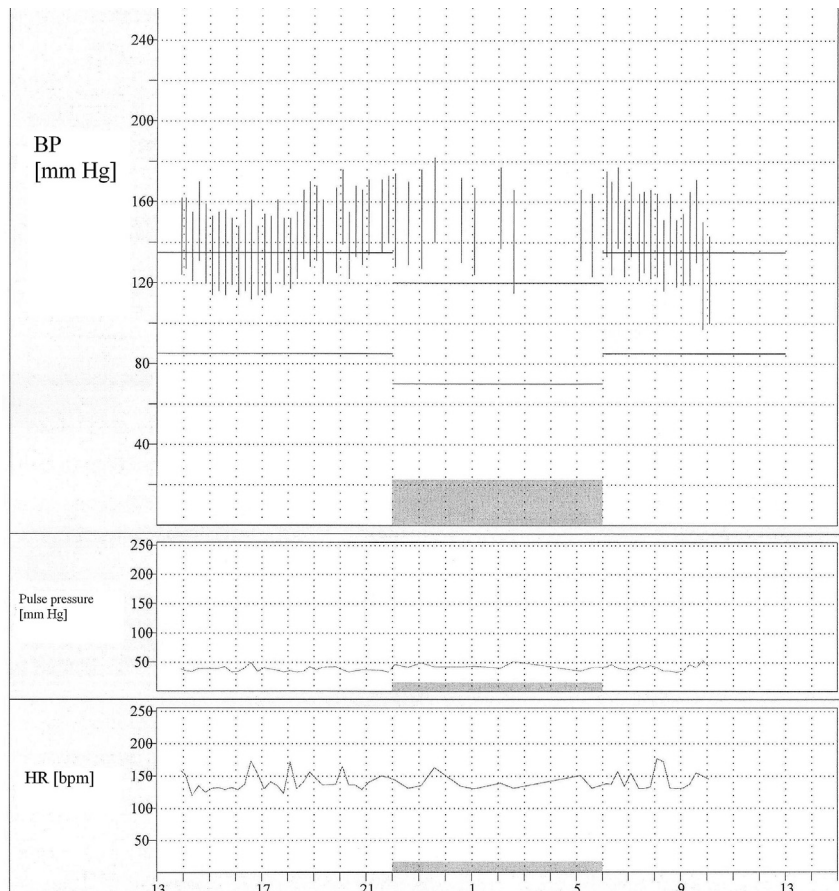


Fig. 1. ABPM results – “stiffly” elevated blood pressure and heart rate.

function and proved negative in a toxic scan; inflammatory agents, antiplasmatic and antinuclear antibodies were not elevated, anti-ganglioside antibodies were negative, porphyrin test negative, abdominal ultrasound, and angio-CT of renal arteries proved normal; and magnetic resonance of abdomen showed no tumors or other pathological masses.

Based on clinical presentation, the conception of mercury poisoning was considered. The patient's blood, urine, and hair samples were sent for mercury testing, returning negative.

Further laboratory tests showed elevated 24-h urine levels of adrenaline (33,3 µg/24h; reference range: 4–20 µg) and noradrenaline (147,6 µg/24h; reference range: 15–80 µg), abnormally high plasma aldosterone level in vertical position (>100 ng/dl – above the scale of the test), and elevated plasma renin activity (>30 ng/ml/h; reference range: 1,5–5,7).

The presented constellation of symptoms: the constant and fixed elevation of blood pressure and heart rate, paresthetic pains, and elevated levels of adrenergic substrates in plasma and urine pointed to constant sympathetic nervous system hyperactivity as the potential source of all the clinical manifestations. The suspicion of acute autonomic neuropathy (AAN) was put forward.

Results of the nerve conduction study of his sensory and motor nerves (performed 10 days after the admission and around 17 days after first symptoms) were within normal limits including preserved F-wave with normal value of latency, somatosensory potentials of medial and peroneal nerve was also within normal limits but a sympathetic skin response test confirmed severe dysfunction of his small nerve fibers (a lack of response). This led to presumptive diagnosis of acquired inflammatory acute neuropathy and the boy was started on intravenous immunoglobulin (in total dose of 2 g/kg) on the eighth day since the onset of the disease. Symptomatic treatment with enalapril and metoprolol led to the normalization of his blood pressure and heart rate (100/55 mmHg and 85–90 bpm, respectively); however, still with no physiological variability. Gabapentin significantly reduced neuropathic pain.

During the next 3 months, the gradual return of blood pressure and heart rate variability was observed.

Pharmacotherapy was slowly reduced and withdrawn after 12 months. After 17 months from diagnosis, the boy made complete recovery. No pharmacological treatment was used. His blood pressure and heart rate were within normal values and physiological rhythm. He felt no pain. The control SSR quantitative nerve conduction study of his sensory and motor nerves (performed 2, 6, and 12 months after the diagnosis) showed results within normal limits; however, sympathetic skin response was still abnormal, probably due to inadequate sympathetic fibers regeneration.

3. Discussion

The presented case report proves how challenging it is to diagnose the cause of secondary hypertension in a child.

In the case of our patient, two parallel lines of diagnostics had to be addressed and interconnected. The first one was related to cardiovascular problem manifested by fixed arterial systolic and diastolic hypertension and sinus tachycardia, the second focused on pains experienced by the child.

Out of the long list of pathologies possible to cause secondary systemic arterial hypertension, not one seemed to be plausible considering the abnormal “stiffness” of the vitals. However, among the most probable were renal pathology, pheochromocytoma, vascular inflammation, tumor in central nervous system or adrenal glands, and toxic etiology [3].

Burning pain can be caused by a number of metabolic disorders including porphyria and Fabry's disease, heavy metal poisoning, but also autoimmune neuropathies [4–6].

Review of literature delivered a promising lead. Burning pains of palms and feet with constant severe systolic and diastolic hypertension, tachycardia, and even seizures were found out to be caused by mercury poisoning. Presented cases were limited in number but identical to our patient's case, and furthermore, offered hope for successful treatment as all described children presented full recovery after the introduction of chelating therapy [4,5]. The idea of mercury poisoning was additionally consolidated by the boy's parents admitting to the fact that about a month ago they fully equipped and opened a gym at their home, being valuable potential source of toxic agents.

After receiving negative results of blood, urine, and hair tests for mercury, the revision of the diagnostic approach was necessary. Constantly and “stiffly” elevated blood pressure and heart rate, burning paresthetic pains in the extremities and elevated levels of adrenergic substrates in plasma and urine pointed to constant sympathetic nervous system hyperactivity as the source of all the clinical manifestations presented by our patient (Fig. 3).

Autonomic neuropathy (AN), also known as autonomic ganglionopathy or acute pandysautonomia is often autoimmune and in some cases can be considered as an autonomic variant of the Guillain-Barre syndrome [6–9]. Considering the fact that the wide use of mercury-filled thermometers in the past and extremely small number of reported cases of poisoning manifested with sustained hypertension, tachycardia, and paresthesia, we may not be able to rule out AAN in those children or the possibility of mercury being simply its trigger, particularly when reported patients were treated not only with chelating agents, but also with drugs reducing the sympathetic nervous system activity through the suppression of renin-angiotensin-aldosterone system and β-receptors blockade. It is worth noting that apart from standard antihypertensive pharmacotherapy (ACEI and β-blockers), all children received different lines of causal treatment: chelating therapy (in cases of mercury poisoning), intravenous immunoglobulins for suspected autoimmune etiology or even the lack of treatment with the spontaneous regression of symptoms [4,5,8,9].

AN targets small nerve fibers, mostly those unmyelinated or covered by thin layer of myelin (autonomic nervous system) [7]. As the disease does not affect larger nerves, the results of conduction studies for motor and sensory function show no abnormalities [7].

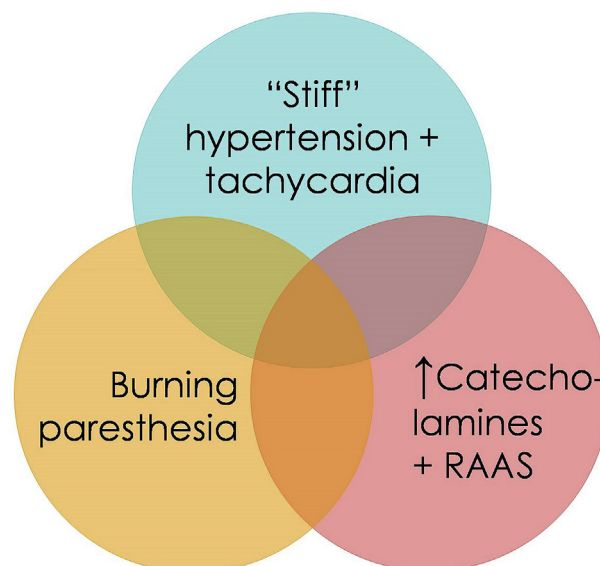


Fig. 3. Pathophysiological constellation illustrating autonomic neuropathy.

Small nerves damage may be caused by infectious, metabolic, or genetic causes; however, in acute forms immune or toxic factors seem to be the most common causes.

It is still unclear if autonomic dysfunction manifested by sustained arterial hypertension, tachycardia, and neuropathic pain in the extremities is a result of hyperactivity of the sympathetic nervous system or rather the inactivation of its parasympathetic counterpart. However, the first alternative seems to be more probable, particularly considering elevated levels of plasma and urine noradrenaline (the most common neurotransmitter in sympathetic fibers), the presence of typical sympathetic pain and good reaction for pharmacological sympathetic blockade [10].

Literature and knowledge about autonomic disorders in children, particularly cases with acute presentation, are extremely limited [11,12]. Analyzing the symptoms, diagnostic findings, and lines of treatment, it seems that whatever the reason for pathological sympathetic hyperactivity, acute forms are connected with good prognosis. All patients described in literature with symptoms similar to our case presented full recovery over time.

4. Conclusion

As the reported case shows that dealing with a child presenting acute, severe, and sustained arterial hypertension, particularly in a wider constellation of unspecific symptoms, we need a careful and open-minded approach. It is worth to remember about AAN as a potential cause of hypertension.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical statement

Hereby, I, Bożena Werner, consciously assure that for the manuscript “Acute Autonomic Neuropathy as a Rare Cause of Severe Arterial Hypertension in a Child” the following is fulfilled:

- 1) This material is the authors' own original work, which has not been previously published elsewhere.
- 2) The paper is not currently being considered for publication elsewhere.
- 3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
- 4) The paper properly credits the meaningful contributions of co-authors and coresearchers.

- 5) The results are appropriately placed in the context of prior and existing research.
- 6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.
- 7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

Declaration of competing interest

The authors have indicated that they have no potential conflicts of interest to disclose.

References

- [1] Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* 2017;140(3):e20171904. <https://doi.org/10.1542/peds.2017-1904>.
- [2] Gupta-Malhotra M, Banker A, Shete S, Hashmi SS, Tyson JE, Barratt MS, et al. Essential hypertension vs. secondary hypertension among children. *Am J Hypertens* 2015;28:73–80. <https://doi.org/10.1093/ajh/hpu083>.
- [3] Bajracharya P, Olivera MR, Kapur G. Epidemiology of secondary hypertension in children. *Curr Cardiovasc Risk Rep* 2014;8:388. <https://doi.org/10.1007/s12170-014-0388-3>.
- [4] Torres AD, Rai AN, Hardiek ML. Mercury intoxication and arterial hypertension: report of two patients and review of the literature. *Pediatrics* 2000;105(3):e34. <https://doi.org/10.1542/peds.105.3.e34>.
- [5] Brannan EH, Su S, Alverson BK. Elemental mercury poisoning presenting as hypertension in a young child. *Pediatr Emerg Care* 2012;28:812–4. <https://doi.org/10.1097/PEC.0b013e3182628a05>.
- [6] Ishitobi M, Haginoya K, Kitamura T, Munakata M, Yokoyama H, Iinuma K. Acute dysautonomia: complete recovery after two courses of IVIg. *Brain Dev* 2004 Dec;26(8):542–4. <https://doi.org/10.1016/j.braindev.2004.02.012>.
- [7] Hoeijmakers JGJ, Faber CG, Miedema CJ, Merkies ISJ, Vles JSH. Small fiber neuropathy in children: two case reports illustrating the importance of recognition. *Pediatrics* 2016;138(4):e20161215. <https://doi.org/10.1542/peds.2016-1215>.
- [8] Abdel-Salam F, Basu AP, Johnson S, Devlin AM. Suspected pheochromocytoma in a patient with Guillain-Barré syndrome. *Pediatrics* 2013;131(3):e955–8. <https://doi.org/10.1542/peds.2012-1445>.
- [9] Nass R, Chutorian A. Dysaesthesias and dysautonomia: a self-limited syndrome of painful dysaesthesias and autonomic dysfunction in childhood. *J Neurol Neurosurg Psychiatry* 1982;45(2):162–5. <https://doi.org/10.1136/jnnp.45.2.162>.
- [10] McDougall AJ, McLeod JG. Autonomic neuropathy. I. Clinical features, investigation, pathophysiology, and treatment. *J Neurol Sci* 1996;137(2):79–88. [https://doi.org/10.1016/0022-510X\(95\)00355-6](https://doi.org/10.1016/0022-510X(95)00355-6).
- [11] Freeman R. Autonomic peripheral neuropathy. *Lancet* 2005;365:1259–70. [https://doi.org/10.1016/S0140-6736\(05\)74815-7](https://doi.org/10.1016/S0140-6736(05)74815-7).
- [12] Axelrod FB, Chelimsky GG, Weese-Mayer DE. Pediatric autonomic disorders. *Pediatrics* 2006;118(1):e309–21. <https://doi.org/10.1542/peds.2005-3032>.