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Harlequin syndrome secondary to an extensive vascular malformation in a paediatric patient – case report

Zespół Harlequina wtórny do rozległej malformacji naczyniowej u dziecka – opis przypadku

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Abstract

The paper presents the case of a 4-year-old boy with recurrent, unilateral episodes of facial swelling and erythema, triggered by stress and physical exertion. Initially, an allergic aetiology and angioedema were suspected; however, extensive laboratory and imaging diagnostics ruled out these diagnoses. Magnetic resonance imaging revealed an extensive, infiltrative vascular malformation involving the craniofacial structures. The clinical symptoms resulted from secondary dysfunction of the facial sympathetic fibres, leading to a diagnosis of secondary Harlequin syndrome. Pharmacological treatment with sirolimus led to gradual clinical improvement and significant regression of the lesions on follow-up imaging. The presented case report highlights that recurrent, unilateral facial swelling in a child does not always have an allergic aetiology and may be a manifestation of rare autonomic disorders or vascular pathologies.

Keywords: Harlequin syndrome, recurrent facial oedema, vascular malformation, autonomic nervous system disorders, paediatrics

Streszczenie

W pracy przedstawiono przypadek 4-letniego chłopca z nawracającymi, jednostronnymi epizodami obrzęku i zaczerwienienia twarzy, prowokowanymi stresem oraz wysiłkiem fizycznym. Początkowo podejrzewano etiologię alergiczną oraz obrzęk naczynioruchowy, jednak pogłębiona diagnostyka laboratoryjna i obrazowa nie potwierdziła tych rozpoznań. Badanie rezonansu magnetycznego ujawniło obecność rozległej, naciekającej malformacji naczyniowej w obrębie struktur czaszkowo-twarzowych. Objawy kliniczne wynikały z wtórnej dysfunkcji włókien współczulnych twarzy. Na tej podstawie rozpoznano wtórny zespół Harlequina. Zastosowanie leczenia farmakologicznego sirolimusem doprowadziło do stopniowej poprawy klinicznej oraz istotnej regresji zmian w kontrolnych badaniach obrazowych. Przedstawiony opis przypadku wskazuje, że nawracający, jednostronny obrzęk twarzy u dziecka nie zawsze ma etiologię alergiczną i może być przejawem rzadkich zaburzeń autonomicznych lub patologii naczyniowych.

Słowa kluczowe: zespół Harlequina, nawracające obrzęki twarzy, malformacja naczyniowa, zaburzenia autonomiczne, pediatria

INTRODUCTION

Recurrent facial swelling in children constitutes a significant clinical problem and requires broad differential diagnostics. The most common causes of oedema in paediatric patients include allergy, angioedema (including hereditary angioedema, HAE), infections, inflammatory diseases, salivary gland pathologies, as well as vascular and neurological conditions. In rare cases, symptoms may be associated with disorders of the autonomic nervous system, including Harlequin syndrome (HS)[1].

HS is a disorder of the autonomic nervous system that is rarely described in the paediatric population. It is characterised by unilateral facial flushing and excessive sweating. These symptoms usually occur in response to stimuli such as physical exertion, stress, changes in ambient temperature, or sudden sensory stimuli, and the boundary between the two sides of the face may be clearly demarcated[1,2].

Although idiopathic cases predominate in the scientific literature, reports have also described specific clinical situations leading to the development of HS as a secondary manifestation[1,3].

This article presents the case of a 4-year-old boy with recurrent facial swelling in whom HS was diagnosed secondary to an extensive, infiltrative vascular malformation involving the craniofacial structures.

CASE REPORT

A four-year-old boy was admitted to the Department of Paediatrics for diagnostic evaluation of recurrent swelling and erythema affecting the left side of the face, accompanied by tongue swelling and tearing of the left eye.

The symptoms had been present since the third month of the child's life. Episodes occurred several times a day, most often during crying, agitation, after physical exertion, or after meals, without any relation to the type of food consumed. The changes resolved spontaneously after approximately 10–15 minutes. The episodes were not accompanied by general symptoms, including dyspnoea, hypotension, syncope, or fever. Pregnancy and perinatal history were unremarkable. The patient had neither experienced trauma nor undergone surgical procedures involving the neck or chest. He was not taking any medications. No similar symptoms were reported among family members.

On admission, physical examination revealed slight asymmetry of the face and tongue (Fig. 1), as well as transient erythema and swelling affecting the left side of the face (Fig. 2). No signs of infection or focal neurological deficits were observed.

Peripheral blood count revealed eosinophilia. Renal and hepatic function parameters were within normal limits (Tab. 1). Elevated total IgE levels were detected, along with specific IgE antibodies: class 6 for cat and dog allergens, class 5 for cow's milk, and class 3 for egg white and birch pollen (Tabs. 2–4).

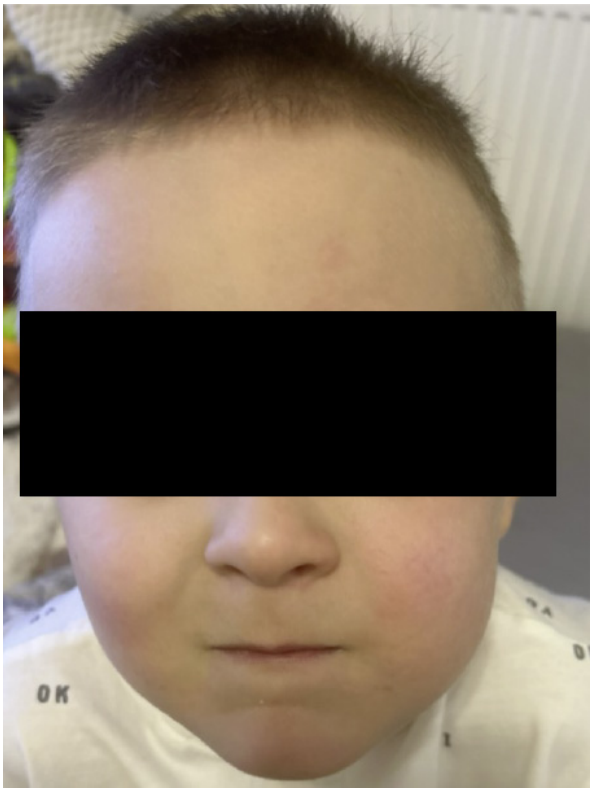

Fig. 1. Facial asymmetry observed in the child

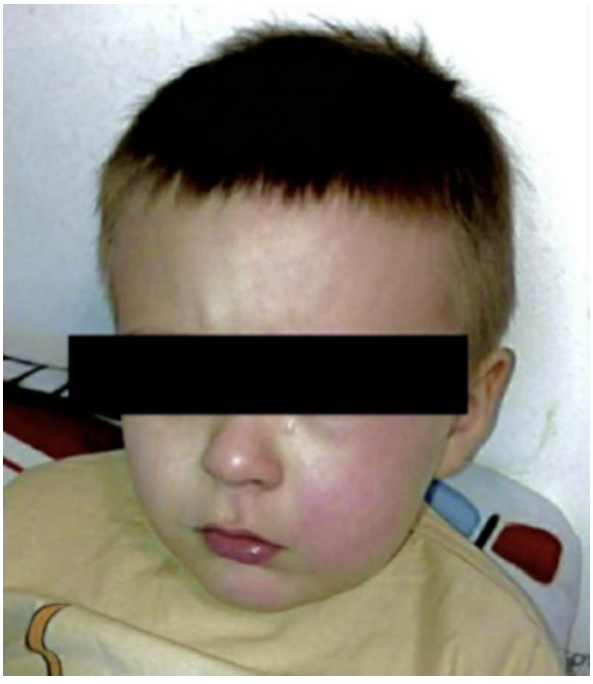

Fig. 2. Unilateral facial flushing observed in the child

Diagnostic evaluation for angioedema was performed, including assessment of C1 esterase inhibitor concentration and activity, as well as complement component C4; all results remained within reference ranges (Tab. 1).

During blood sampling, a stress-related episode occurred, during which transient flushing of the left side of the face

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Parameter	Result	Age-appropriate reference range
WBC (white blood cells)	8.93×10^9/L	$4.0–12.0 \times 10^9$/L
RBC (red blood cells)	4.69×10^{12}/L	$3.9–5.4 \times 10^{12}$/L
HGB (haemoglobin)	12.3 g/dL	11.2–13.8 g/dL
PLT (platelets)	295×10^9/L	$140.0–420.0 \times 10^9$/L
LYM (lymphocytes)	1.92×10^3/L	$2.0–8.0 \times 10^3$/L
NEUT (neutrophils)	5.38×10^3/L	$1.5–8.5 \times 10^3$/L
NEUT% (neutrophils)	60.3%	30–55%
EO (eosinophils)	10.3%	0–8%
Cr (creatinine)	0.3 mg/dL	0.3–1.0 mg/dL
ALT (alanine aminotransferase)	12 U/L	0–35 U/L
AST (aspartate aminotransferase)	36 U/L	15–50 U/L
C1 esterase inhibitor level	36	35,168–69,100 mg/L
C1 esterase inhibitor function	>100%	>68%
Complement component C4	14 mg/dL	10–40 mg/dL
IgE (total IgE)	2,629 IU/mL	30.0–50.0 IU/mL

Tab. 1. Selected morphological, biochemical, and immunological blood parameters with age-appropriate reference ranges for the examined patient

Food allergen	Result	Class
Cow's milk	74 kU/L	5
Baker's yeast	<0.15 kU/L	0
Rye flour	0.24 kU/L	0
Almond	2.4 kU/L	0
Kiwi	<0.15 kU/L	0
Apricot	<0.15 kU/L	0
Tomato	<0.15 kU/L	0
Celery	0.20 kU/L	0
Egg white	4.2 kU/L	3
Egg yolk	0.27 kU/L	0
Potato	1.3 kU/L	2
Rice	0.25 kU/L	0

Tab. 2. Concentrations of specific immunoglobulin E (sIgE) [kU/L] against selected food allergens in the examined patient

Allergen	Result	Class
Sweet vernal grass	0.40 kU/L	1
Timothy grass	0.22 kU/L	0
Meadow fescue	0.32 kU/L	0
Rye	0.47 kU/L	1
Alder	<0.15 kU/L	0
Hazel	0.23 kU/L	0
Oak	0.50 kU/L	1
Ragweed	<0.15 kU/L	0
Narrowleaf plantain	0.17 kU/L	0
Cat	>100 kU/L	6
Dog	>100 kU/L	6
Horse	>100 kU/L	6
Birch	10.4 kU/L	3
Dermatophagoides pteronyssinus (mites)	<0.15 kU/L	0

Tab. 3. Concentrations of specific immunoglobulin E (sIgE) [kU/L] against selected inhalant allergens in the examined patient

Concentration [kU/L]	Class	Description
$0 \leq$ sIgE < 0.35	0	No specific antibodies detected
$0.35 \leq$ sIgE < 0.7	1	Very low antibody titre, often without clinical symptoms
$0.7 \leq$ sIgE < 3.5	2	Very low antibody titre, often without clinical symptoms
$3.5 \leq$ sIgE < 17.5	3	Specific antibodies detected, often with clinical symptoms
$17.5 \leq$ sIgE < 50	4	Strong antibody response, almost always with accompanying clinical symptoms
$50 \leq$ sIgE < 100	5	Very high antibody titre
sIgE > 100	6	Very high antibody titre

Tab. 4. Interpretation of serum specific immunoglobulin E (sIgE) concentrations in relation to panels of inhalant and food allergens

was observed; this reaction was considered a positive provocation test.

Ophthalmological consultation was conducted and revealed no abnormalities, including no features of Horner syndrome. Contrast-enhanced magnetic resonance imaging of the head demonstrated enlargement of the left pterygopalatine fossa with a focal vascular lesion showing moderate post-contrast enhancement. The lesion involved the orbital apex with associated proptosis of the left globe and thickening of the extraocular muscles (Figs. 3, 4), affected the soft tissues of the lacrimal gland region, penetrated the nasal cavity, and infiltrated the wall of the left maxillary sinus (Fig. 5). Laterally and superiorly, it extended to the cavernous sinus, with possible spread along the lateral pterygoid muscle toward the skull base.

The imaging findings were consulted with the paediatric surgery department at another centre. The overall radiological presentation was consistent with a low-flow vascular malformation involving branches of the trigeminal nerve (V).

In the context of the clinical presentation, secondary dysfunction of the sympathetic fibres supplying the face was suspected, which could explain the features of HS.

The patient was referred for further management to a tertiary paediatric surgery reference centre. Due to the extent and nature of the lesion, which was not amenable to surgical treatment, the case was also consulted with international centres. Based on expert opinions, it was concluded that, at the current stage, the most appropriate therapeutic approach was the initiation of immunosuppressive therapy with sirolimus.

The patient has now been treated with sirolimus for one year at a dose of 0.5 mg daily. The first signs of clinical improvement were observed approximately 2–3 months after initiation of therapy. During the one-year treatment period, temporary discontinuation of the medication was required several times due to infections (mainly respiratory), which correlated with transient exacerbation of clinical symptoms. Follow-up magnetic resonance imaging examinations were performed at six-month intervals, demonstrating a significant reduction in the size of the lesion compared with baseline imaging.

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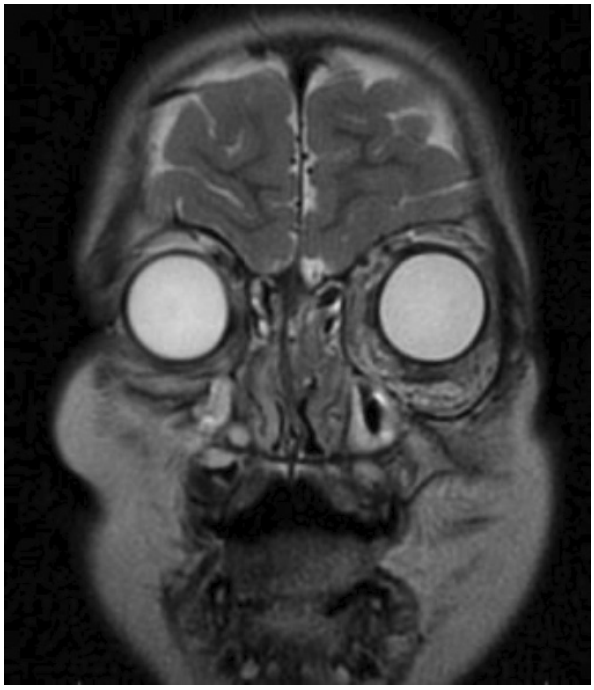

Fig. 3. Magnetic resonance image, T2-weighted sequence with PROPELLER reconstruction, coronal plane, showing a lesion involving the orbital apex

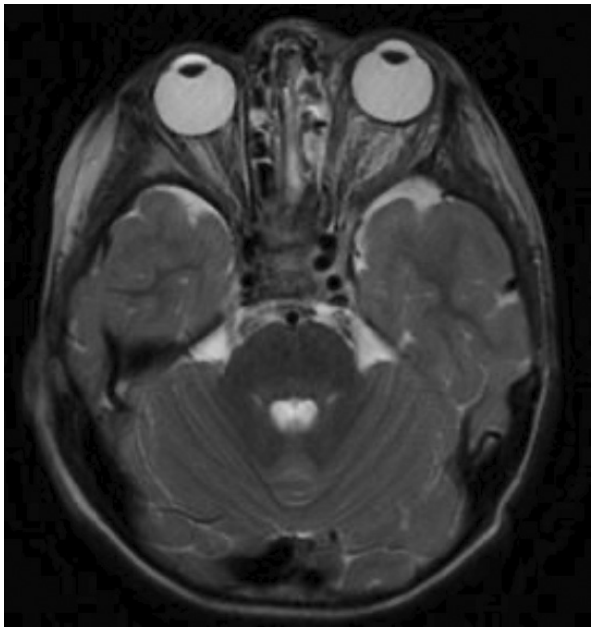

Fig. 4. Magnetic resonance image, T2-weighted sequence with PROPELLER reconstruction, axial plane. The arrow indicates the area of retrobulbar infiltration

DISCUSSION

The presented case highlights the importance of clinical vigilance and the need to extend diagnostic evaluation in children with symptoms of an atypical course and recurrent nature.

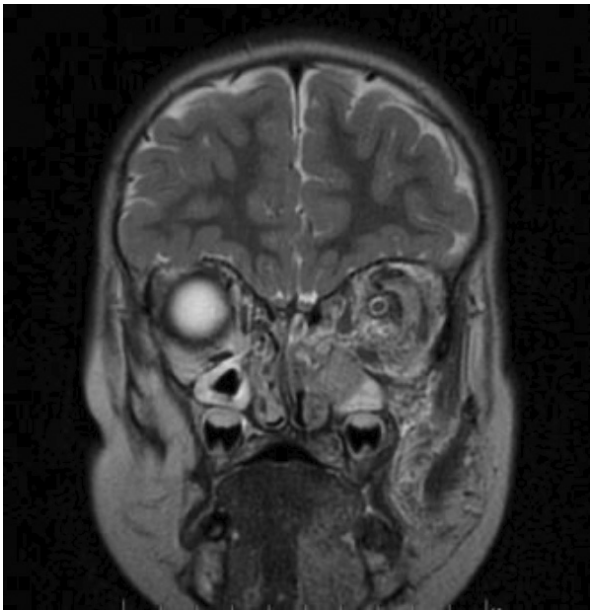

Fig. 5. Magnetic resonance image, T2-weighted sequence with PROPELLER reconstruction, coronal plane, showing a lesion penetrating into the nasal cavity and infiltrating the wall of the left maxillary sinus

In the described boy, the first and predominant clinical manifestation consisted of recurrent, unilateral facial swelling, initially suggesting an allergic aetiology or HAE. However, the absence of any correlation between symptom occurrence and potential food allergens or exposure to airborne allergens, as well as normal results of investigations for HAE, argued against these diagnoses. Therefore, HS was considered in the differential diagnosis.

A characteristic feature of HS is the unilateral nature of symptoms and their clear provocation by emotional stimuli and physical exertion, which was distinctly observed in the presented patient.

In most reported cases, HS is idiopathic (up to 54.6% of cases), and follows a mild course, without significant neurological symptoms or detectable abnormalities on imaging studies[4–7].

However, an increasing number of publications emphasise that HS should be regarded as a diagnosis of exclusion, owing to the growing body of evidence indicating that HS may represent a secondary manifestation associated with damage to or compression of sympathetic structures during vascular, neoplastic, or iatrogenic processes[4,7,8].

Sousa Dias et al. highlight that, in the paediatric population, every case of HS requires thorough diagnostic evaluation for structural, vascular, or neoplastic lesions until their presence has been unequivocally excluded[7].

The occurrence of HS symptoms results from unilateral dysfunction of sympathetic fibres innervating the cutaneous vessels and sweat glands of the face.

The sympathetic pathway supplying the face originates in the hypothalamus, with fibres descending through the brainstem to the ciliospinal centres in the spinal cord at

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No.	Age	Sex	Primary/ Secondary HS	Diagnostic evaluation	Treatment	Author	Year
1.	6 years	Male paediatric patient	Primary idiopathic	Exercise provocation test; ophthalmological examination	No treatment implemented	Kim et al.	2016[15]
2.	4 years	Female paediatric patient	Primary idiopathic	Exercise provocation test combined with exposure to intense sunlight	No treatment implemented	Beullens et al.	2021[8]
3.	2 years	Male paediatric patient	Primary idiopathic	Exercise provocation test combined with exposure to intense sunlight; pharmacological pupillary test	No information available	Beullens et al.	2021[8]
4.	9 years	Female paediatric patient	Primary idiopathic	Exercise provocation test	No information available	Breunig et al.	2012[12]
5.	4 years	Male paediatric patient	Primary idiopathic	Ophthalmological examination; exercise provocation test	No treatment implemented	Rkiek et al.	2025[16]
6.	4 months	Male paediatric patient	Primary idiopathic	Ophthalmological examination	No information available	Elnahry et al.	2021[17]
7.	6 months	Female paediatric patient	Primary idiopathic	Symptom provocation test during wakefulness	No treatment implemented	Kang et al.	2018[18]
8.	6 years	Female paediatric patient	Secondary	Exercise provocation test combined with heat exposure	No information available	Beullens et al.	2021[8]
9.	9 years	Male paediatric patient	Secondary	Exercise provocation test; chest magnetic resonance imaging; neurophysiological examination	No treatment implemented	Butragueño Laiseca et al.	2018[19]
10.	3 years	Male paediatric patient	Secondary	Laboratory tests; chest computed tomography; tumour biopsy	Thoracoscopic resection of mediastinal tumour	Czapla et al.	2024[20]

Tab. 5. Comparative analysis of reported cases of HS in the paediatric population

the C8–Th2 levels. Subsequently, preganglionic fibres travel through the sympathetic trunk to the superior cervical ganglion, and postganglionic fibres accompany the internal and external carotid arteries, innervating the facial blood vessels and sweat glands[2]. Damage to this pathway at any level results in unilateral loss of sympathetic activity, which clinically manifests as absence of flushing and sweating on the affected side, with compensatory enhancement of vasomotor and sudomotor responses on the contralateral side. Any disturbance along this pathway may constitute a cause of secondary HS[1,3].

The most frequently described causes of secondary HS include trauma and complications following surgical procedures in the thoracic region or vascular interventions involving the carotid arteries, aorta, or major vascular trunks. Other causes include proliferative lesions compressing sympathetic structures, such as tumours of the superior mediastinum, including Pancoast tumours. A significant etiological group also comprises vascular pathologies, including carotid artery dissection, carotid or vertebral artery aneurysms, vascular malformations, and infarctions of the brainstem or lateral medulla[1,2,9,10].

Additionally, the literature describes cases in which potential etiological factors included infections with neurotropic viruses such as human herpesvirus 6, cytomegalovirus, parvovirus B19, and varicella-zoster virus, which exhibit tropism for structures of the autonomic nervous system[2].

In the present case, magnetic resonance imaging revealed an extensive, infiltrative vascular malformation. Similar mechanisms of secondary HS related to compression or infiltration of sympathetic structures by vascular or proliferative lesions have been described in the literature; however, they remain rare in the paediatric population[4,5,11].

In most idiopathic cases, HS does not require treatment. Indications for the management of secondary cases largely depend on the underlying aetiology of the syndrome[5,12]. When symptoms cause significant psychological or social distress, symptomatic treatment, clinical observation, patient and caregiver education, and avoidance of triggering factors are recommended. To mitigate the aesthetic aspects of the disease, periodic injections of botulinum toxin on the unaffected side may be used[6], representing the least invasive therapeutic option compared with ipsilateral sympathectomy or repeated stellate ganglion blocks[11].

Depending on the aetiology of the secondary form, various therapeutic strategies have been described, including surgical treatment, endovascular procedures, conservative management, or pharmacological therapy[8].

Recently, increasing attention has been paid to the role of mTOR pathway inhibitors, such as sirolimus, in the treatment of extensive vascular malformations in children, although data regarding patients with concomitant HS remain limited[12–14].

In the present case, this treatment appears to be effective, although further clinical follow-up and cautious assessment of long-term safety are required. It also cannot be excluded that, at a later stage of the disease, appropriate surgical intervention may become necessary.

A summary of paediatric cases of idiopathic and secondary HS reported in the English-language literature is presented in Tab. 5.

CONCLUSIONS

The presented case report highlights that recurrent, unilateral facial swelling in a child does not always have an allergic aetiology and may represent a manifestation of rare

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autonomic disorders or vascular pathologies. HS should be considered in the differential diagnosis of such symptoms, particularly when they are unilateral and triggered by emotional or physical stimuli.

In secondary cases, early and comprehensive imaging of the central nervous system and cervicofacial structures is of key importance, as it enables identification of the underlying disease and facilitates appropriate, multidisciplinary management.

Additionally, this case suggests that pharmacological treatment targeting the underlying pathology, including therapy with mTOR pathway inhibitors, may lead to clinical and radiological improvement and may represent a potential therapeutic option in selected cases of secondary HS.

Conflict of interest

The authors declare no conflicts of interest.

Author contribution

Original concept of study: KM, AB. Collection, recording and/or compilation of data; analysis and interpretation of data: JAD, AMK. Writing of manuscript: KM. Critical review of manuscript; final approval of manuscript: BK, AR, AB.

References

1. Lance JW, Drummond PD, Gandevia SC et al.: Harlequin syndrome: the sudden onset of unilateral flushing and sweating. J Neurol Neurosurg Psychiatry 1988; 51: 635–642.
2. Joshi HR, Singh J, Packiasabapathy S: Harlequin syndrome. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL 2026.
3. Willaert WIM, Scheltinga MRM, Steenhuisen SF et al.: Harlequin syndrome: two new cases and a management proposal. Acta Neurol Belg 2009; 109: 214–220.
4. Dróżdż O, Dołęga M, Gacka P et al.: Harlequin syndrome: unraveling the complexities of etiology, clinical presentation, and management: a comprehensive review. EJMO 2024; 8: 245–249.
5. Mavroudis I, Balmus IM, Ciobica A et al.: Mini-review on the Harlequin syndrome – a rare dysautonomic manifestation requiring attention. Medicina (Kaunas) 2022; 58: 938.
6. Elboukhari K, Baybay H, Elloudi S et al.: Idiopathic harlequin syndrome: a case report and literature review. Pan Afr Med J 2019; 33: 141.
7. Sousa Dias M, Meneses M, Barroca Macedo R et al.: Harlequin syndrome in children: secondary until proven otherwise. BMJ Case Rep 2023; 16: e257719.
8. Beullens N, Tourlamain G, Vallaeys L et al.: Harlequin syndrome in a pediatric population: a case series. Acta Neurol Belg 2021; 121: 625–631.
9. Sarikaya H, Georgiadis D, Baumgartner RW: Harlequin syndrome in spontaneous dissection of the cervical carotid artery. Neurology 2008; 71: 1459.
10. Lee DH, Seong JY, Yoon TM et al.: Harlequin syndrome and Horner syndrome after neck schwannoma excision in a pediatric patient: a case report. Medicine (Baltimore) 2017; 96: e8548.
11. Wasner G, Maag R, Ludwig J et al.: Harlequin syndrome – one face of many etiologies. Nat Clin Pract Neurol 2005; 1: 54–59.
12. Breunig JA, Hartmann M, Freire CF et al.: Harlequin syndrome in childhood – case report. An Bras Dermatol 2012; 87: 907–909.
13. Harbers VEM, Rongen GAPJM, van der Vleuten CJM et al.: Patients with congenital low-flow vascular malformation treated with low dose sirolimus. Adv Ther 2021; 38: 3465–3482.
14. Wiegand S, Dietz A, Wichmann G: Efficacy of sirolimus in children with lymphatic malformations of the head and neck. Eur Arch Otorhinolaryngol 2022; 279: 3801–3810.
15. Kim JY, Lee MS, Kim SY et al.: A pediatric case of idiopathic Harlequin syndrome. Korean J Pediatr 2016; 59 (Suppl 1): S125–S128.
16. Rkiek Y, El Jouari O, Gallouj S: A pediatric case of idiopathic harlequin syndrome. Dermatology Online J 2025; 31.
17. Elnahry AG, Gamal Eldin AA, Elnahry AG et al.: Concomitant congenital Horner and Harlequin syndromes: case report and review of literature. J Pediatr Neurol 2021; 19: 177–179.
18. Kang JH, Zafar MS, Werner KGE: Child neurology: an infant with episodic facial flushing: a rare case and review of congenital harlequin syndrome. Neurology 2018; 91: 278–281.
19. Butragueño Laiseca L, Vázquez López M, Polo Arrondo A: Harlequin syndrome in a paediatric patient: a diagnostic challenge. Neurologia (Engl Ed) 2018; 33: 478–480.
20. Czapla A, Ejzak S, Pawelec K et al.: Harlequin syndrome associated with mediastinal ganglioneuroma: a case report. Pediatr Pol 2024; 99: 374–377.

DOI: 10.15557/PiMR.2026.0019