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CASE REPORT

Central hyperthermia control after propranolol therapy in an infant with septo-optic dysplasia

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Abstract

Introduction: Septo-optic dysplasia (SOD) is a congenital midline brain malformation syndrome involving the hypothalamus-pituitary axis with hypopituitarism and thermal instability. The treatment of central hyperthermia in children with propranolol has already been described. **Case report:** We report the case of a nine-month-old boy with SOD with prolonged fever and increased urinary output. The physical examination was unremarkable, and a thorough etiological investigation was inconclusive. After adjusting the desmopressin dosage to control the central diabetes insipidus and ruling out infectious, inflammatory, and neoplastic etiologies, the diagnosis of central hyperthermia was established and therapy with propranolol was initiated, with sustained normothermia. **Discussion:** Although a definite causal relationship could not be proven, this paper is the first to report the successful management of central hyperthermia in an infant with SOD using propranolol. Further trials are needed to evaluate its efficacy and safety in the management of central hyperthermia in children with SOD.

Keywords: Central hyperthermia. Propranolol. Septo-optic dysplasia plus.

Utilização de propranolol num caso de hipertermia de causa central num lactante com displasia septo-óptica

Resumo

Introdução: A displasia septo-óptica (DSO) corresponde a uma malformação congénita do eixo hipotálamo-hipofisário, conduzindo a hipopituitarismo e instabilidade térmica. Já foi descrito o tratamento da hipertermia central em crianças com propranolol. **Relato do caso:** Lactente do sexo masculino, 9 meses, seguido por DSO. Recorre ao hospital por febre prolongada e aumento da diurese. Exame objetivo não apresentava alterações. Após ajuste da dose de desmopressina para melhorar o controlo da diabetes insipidus e exclusão de causas infeciosas, inflamatórias e neoplásicas, foi assumido o diagnóstico de hipertermia central e iniciada terapêutica com propranolol, verificando-se normotermia nos meses subsequentes. **Discussão:** Ainda que uma relação causal definitiva não possa ser comprovada, este é o primeiro caso reportado de controlo com sucesso de hipertermia utilizando propranolol em lactente com malformações da linha média. São necessários mais estudos para avaliar a sua eficácia e segurança na hipertermia central em crianças com DSO.

Palavras-chave: Hipertermia de causa central. Propranolol. Displasia septo-óptica plus.

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Keypoints

What is known

- Septo-optic dysplasia is a congenital midline brain malformation syndrome associated with hypopituitarism and thermal instability.
- Central hyperthermia should not be overlooked in the pediatric population, especially after ruling out more common causes.
- There are no evidence-based guidelines on the management of central hyperthermia in patients with midline brain malformations.

What is added

- This is the first report of the successful management of central hyperthermia in a SOD infant patient using propranolol.
- In this case, the administration of propranolol was associated with thermic regulation.
- Close monitoring is required during propranolol therapy due to its potential side effects, namely hypothermia, hypoglycemia, and bradycardia.

Introduction

Septo-optic dysplasia (SOD) is a rare congenital midline brain malformation syndrome, originally described by Georges de Morsier in 1956[1]. A diagnosis of SOD requires the presence of at least two features from the triad: optic nerve hypoplasia, agenesis of midline structures, and hypoplasia of hypothalamus-pituitary axis with hypopituitarism[2,3]. SOD "plus" also encompasses associated malformations of cortical development[2,4]. The spectrum of clinical manifestations is broad and only 30-47% of patients display all the elements of the triad[5]. The etiology of SOD is diverse and its estimated prevalence among European countries is 1.9-2.5/100,000 births[6].

Central hyperthermia is characterized by an elevation in body temperature secondary to a thermoregulation defect, devoid of any infectious or inflammatory cause. It is often linked with intracranial injury such as traumatic brain injury (TBI), subarachnoid hemorrhage, and hypothalamic damage as the hypothalamus plays a pivotal role in body temperature regulation[7,8]. Central hyperthermia is frequently resistant to typical antipyretic drugs such as paracetamol, requiring non-pharmacological interventions or drugs with notable side effects, such as bromocriptine[9]. Propranolol has also been utilized in treating central hyperthermia in adults due to its comparatively milder side-effect profile, although its precise mechanism of action is not fully understood[10].

Midline brain malformations are most commonly associated with hypothermia[11]. SOD induces dysfunction in the hypothalamus-pituitary axis with hypopituitarism and thermal instability. The cause of thermal instability in SOD is still not fully understood but is presumed manifold.

We report a case of persistent central hyperthermia in a nine-month-old male patient with SOD plus and its management using propranolol. This case report describes a potential new indication for an extensively-studied drug and, to our knowledge, is the first paper describing the use of propranolol and the successful management of central hyperthermia possibly caused by hypothalamic dysfunction in a pediatric patient with SOD.

Case report

Following the onset of hypoglycemia, bilateral nystagmus, and axial hypotonia during the first days of life, along with laboratory findings consistent with panhypopituitarism encompassing central hypothyroidism, adrenal insufficiency, and diabetes insipidus, a diagnosis of SOD was suggested. The brain MRI confirmed the diagnosis of SOD "plus" as a broad spectrum of abnormalities of the midline structures and associated malformations of cortical development were present. The brain MRI abnormalities included complete agenesis of the pituitary stalk, involving both the anterior and posterior pituitary and olfactory bulbs, optic nerve hypoplasia, bilateral subependymal heterotopia, and perisylvian polymicrogyria. Genetic testing yielded negative results for pathogenic mutations. After the neonatal diagnosis of SOD, a multidisciplinary follow-up was established. He was prescribed levothyroxine, hydrocortisone, and desmopressin. The patient was admitted to the pediatric emergency department (PED) with fever and increased urinary output, with no other symptoms.

The fever had started 19 days before admission to the PED. Before being admitted to our hospital, he was observed twice at a regional hospital and discharged home with conservative measures. The temperature rise, measured by a digital thermometer, occurred two to three times a day, reaching 39.7°C in the evening and was associated with polyuria (daily urine output estimated at 7-8 mL/Kg/h), with no other associated symptoms. No recent respiratory or gastrointestinal disorders were reported, nor had the patient travelled to any rural or exotic areas, been in contact with sick people or animals, or had any other notable exposures.

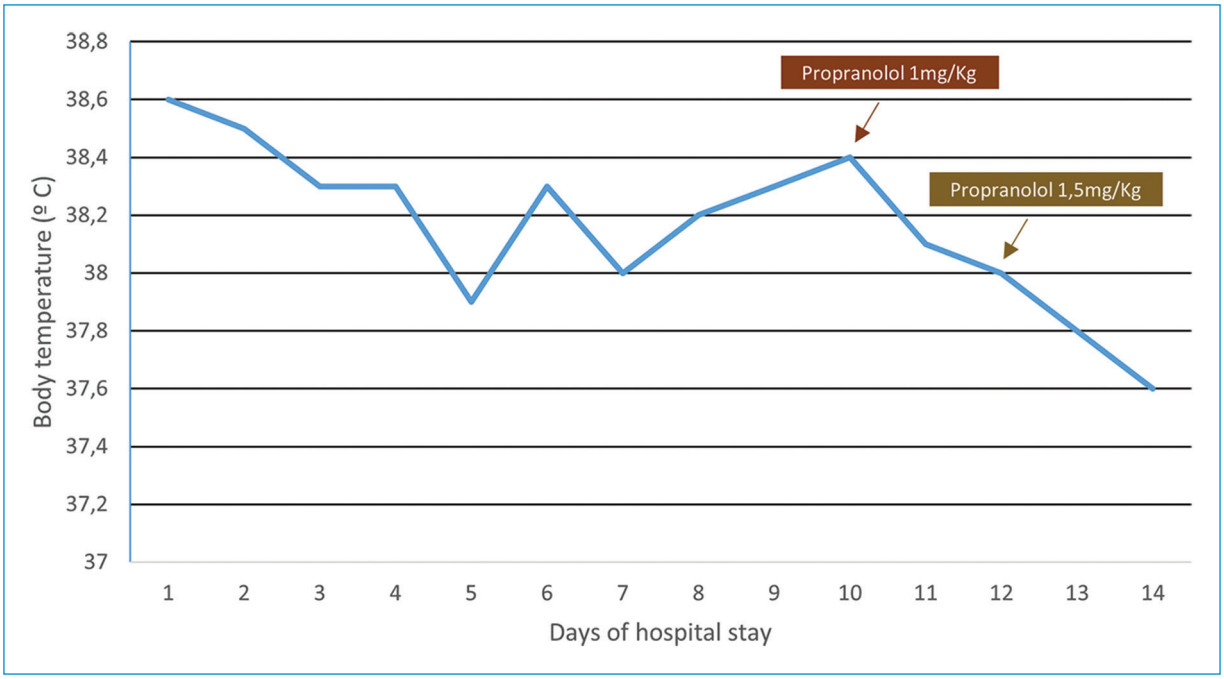

Figure 1. Evolution of the highest daily body temperature during the hospital stay. Propranolol therapy was initiated on day 10 (red) at 1 mg/Kg/day and adjusted to 1.5 mg/kg/day 48 hours later (yellow) as hyperthermia persisted.

Involuntary weight loss, night sweats, or other constitutional symptoms were also not present. The patient had had no prior episodes of fever of unknown origin. Air temperature during this period peaked at 24°C, with average daily values of 14°C, and there was no family history of autoimmune disorders.

The physical examination was unremarkable except for the high body temperature measured in the tympanic membrane. The patient was admitted. Initial laboratory results revealed the presence of hypernatremia (Na^+ 158 mEq/L), with no other electrolyte disturbances. Both C-reactive protein and procalcitonin were negative, and all other laboratory results were unremarkable. Blood and urine cultures showed no pathogen growth. The desmopressin dosage was increased to correct the high urinary output and hypernatremia, and the hydrocortisone dosage was adjusted to the stress dose (40 mg/m2). A watchful waiting approach was adopted, and no broad-spectrum empiric antibiotic therapy was initiated as all the inflammatory markers were within the normal range and the patient did not appear septic.

During the hospital stay, a thorough etiological investigation was performed, including blood, urine, and stool cultures, IGRA and SARS-CoV-2 RT-PCR tests, all of which were consistently negative. Other serological tests for infectious agents, including the Epstein-Barr virus (EBV) and cytomegalovirus (CMV) were also negative. Inflammatory markers were repeated and remained within the normal range throughout. Imaging tests were also performed: the chest radiograph was normal, as was the abdominal, renal, and bladder ultrasound. A record of the infant's daily body temperature during his hospital stay is shown in figure 1.

A neoplastic etiology was also considered but deemed unlikely, as the patient showed no cytopenia and had normal blood levels of uric acid and lactate dehydrogenase and a normal erythrocyte sedimentation rate. Moreover, imaging studies did not support this diagnosis.

As an infectious cause was excluded and recurrent hyperthermia (on average, two to three times a day, in a predominant evening pattern) persisted despite the normalization of serum sodium levels and urinary output achieved after increasing the daily doses of desmopressin and the use of paracetamol, the hypothesis of central hyperthermia was considered.

In view of this hypothesis, an electrocardiogram was performed and, as no cardiac contraindications were present, a trial therapy with propranolol was initiated on day 10, followed by an improvement in body temperature regulation. The initial propranolol dose of 1 mg/Kg/day was adjusted to 1.5 mg/Kg/day after 48 hours of therapy as hyperthermia persisted, albeit at

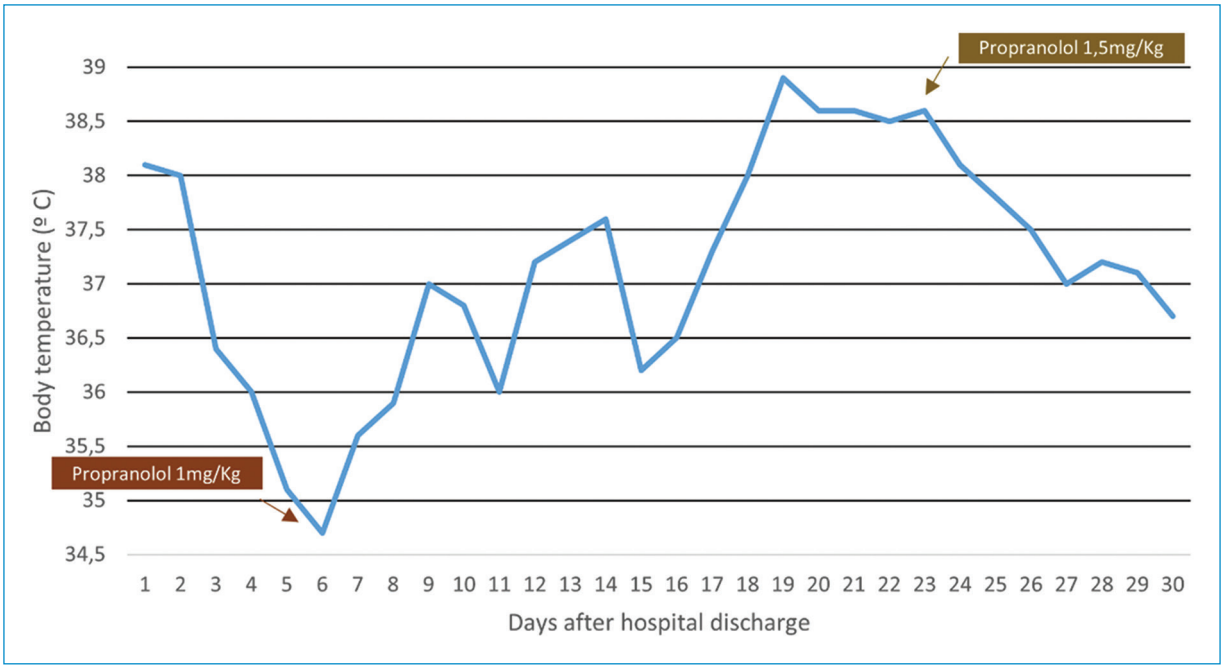

Figure 2. Evolution of body temperature in the first 30 days after hospital discharge. The propranolol dose was reduced to 1 mg/Kg/day on day 5 (red) as the patient presented with hypothermia. A second dose increase was performed on day 23 after hospital discharge hyperthermia reappeared (yellow).

lower levels (Fig. 1). Verbal informed consent was given by the mother for the off-label use of propranolol.

During the infant's hospital stay, no side effects of the propranolol therapy were observed, namely hypothermia, hypoglycemia, hypotension, or bradycardia, and no other electrolyte disturbances were observed. The patient became afebrile on day 12 and was discharged on day 14.

After discharge, the mother continued to monitor body temperature daily with a tympanic membrane device. In the days following discharge, a descending pattern in the body temperature curve was noted with hypothermia, as body temperature reached its nadir at 34.7°C. As a result, the daily doses of propranolol were reduced to 1 mg/Kg/day five days after discharge and there were no further instances of hypothermia during follow-up.

Hyperthermia recurred on day 18 post discharge and a new adjustment of the propranolol dose was needed on day 23. Following this adjustment, a stable temperature within the normal range was maintained, even in the warmer months of summer.

The variation in daily body temperature and propranolol daily doses during the first month is represented in figure 2.

Over the remaining follow-up period of 10 months, no other periods of persistent fever were present, with normothermia, except for short self-limited episodes of acute infection. Since no other periods of hyperthermia were present, therapy was gradually reduced and stopped after 22 months. No further episodes of hyperthermia have occurred since then.

Discussion

Fever is one of the leading reasons for emergency department admissions among the pediatric population, particularly in infants. In most instances, the etiology is an infectious disease, often from the gastrointestinal or upper respiratory tract presenting as a self-limited benign condition[12]. Diagnosis can often be established through a meticulous clinical examination and no further etiological investigation is usually required[12]. Nevertheless, in a minority of cases, the cause of the fever remains uncertain, even after performing a comprehensive medical history, a thorough physical examination, and an initial laboratory assessment. In this case, after ruling out other infections by atypical agents, less prevalent causes such as inflammatory or neoplastic etiologies were considered[13].

Central hyperthermia is rare among the pediatric population and is usually considered a diagnosis of exclusion after ruling out more common infectious or neoplastic causes[14]. This diagnosis should not be overlooked, especially in a patient with midline brain malformations involving the hypothalamus and its temperature-regulating nuclei[14]. Central hyperthermia is primarily associated with TBI, brain neoplasms, and disturbances of the hypothalamic-pituitary axis with thermal instability[15]. Rarely, the use of certain medications, such as halogenated volatile anesthetics and succinylcholine, may trigger a life-threatening temperature rise secondary to a hypermetabolic state known as malignant hyperthermia[15,16].

The use of propranolol is widespread in children, namely in migraine prophylaxis, congenital heart disorders, and infantile hemangiomas, where it is regarded as first-line therapy due to its vasoconstriction, inhibition of angiogenesis, and stimulation of apoptosis effects[17]. Notwithstanding the use of propranolol being considered generally safe, hypothermia is one of its side effects. The explanation behind the thermal instability secondary to its use is thought to be twofold: the nonspecific blockage of β2 and β3 receptors in the central nervous system given its high lipophilicity and capacity to cross the brain-blood barrier and the lowering of the thermogenic effect of brown adipose tissue by inhibiting its β2 adrenergic receptors[18].

There are no evidence-based guidelines on the management of central hyperthermia in infants since there is insufficient data to provide solid recommendations and the use of available therapeutic drugs in the pediatric population is generally an extrapolation from adult trials, with little to no expertise among pediatric teams[9,19].

The use of propranolol for the treatment of central hyperthermia has already been documented in pediatric patients and, on a larger scale, in adults, namely in intracranial hemorrhage secondary to TBI[20-21]. The proposed hypothesis is that the non-specific beta-adrenergic blockage of propranolol within the CNS leads to a reduction of the hyperadrenergic tone, thereby lowering body temperature in cases of a hyperadrenergic state following acute brain injury[22].

In this particular case, the exact pathophysiological mechanism for the persistent fever remains unknown, although dysfunction of the hypothalamus-pituitary axis is presumed to play a leading role. The use of propranolol to treat central hyperthermia in SOD in pediatric patients is considered "off-label" since there is currently insufficient evidence to support its use. Even though a definite causal relationship cannot be proven, this is the first report of the successful management of central hyperthermia in a SOD infant patient using propranolol. Further trials are warranted to assess the efficacy and safety of this therapy, thus providing high-quality evidence that will allow for the successful management of central hyperthermia in pediatric patients.

Previous presentations

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Author contributions

A. Sousa: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Analyisis or interpretation of data either from patients, research studies, or literature; Drafting the article; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. M. João Lage: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Analyisis or interpretation of data either from patients, research studies, or literature; Drafting the article; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. L. Lopes: Acquisition of data either from patients, research studies, or literature; Analyisis or interpretation of data either from patients, research studies, or literature; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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