

## Hypothermia and Hodgkin lymphoma in children

### Çocuklarda hipotermi ve Hodgkin lenfoma

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#### Abstract

Hypothermia associated with Hodgkin lymphoma is defined rarely. This may be caused by a dysfunction that shall occur in hypothalamus, central and peripheral vascular system, skin and muscles. In this study, two Hodgkin lymphoma cases with developed hypothermia are presented.

Case 1: A 7-year-old girl who applied to the hospital with complaints such as fever, weight loss and night sweating was diagnosed with "Hodgkin lymphoma, mixed cellular type" by a biopsy conducted due to lesions found in her spleen. While diagnostic works continued, the patient was administered paracetamol regularly for fever. The ABVD (adriamycin, bleomycin, vincristine, dacarbazine) therapy protocol was started to be applied on the patient. After chemotherapy was applied in the first day, hypothermia developed on the patient, but this healed spontaneously approximately 5 days later without requiring a further therapy.

Case 2: A 9-year-old girl who applied to the hospital with complaints such as fever, itching and swelling on neck was diagnosed with "Hodgkin lymphoma, nodular sclerosing type" by a biopsy conducted by cervical lymph node.

While diagnostic works continued, the patient was administered paracetamol regularly for fever. At this stage, hypothermia developed on the patient before the chemotherapy was applied. The ABVD therapy protocol was started to be applied on the patient. Hypothermia healed spontaneously approximately 3 days later without requiring a further therapy.

Hypothermia in Hodgkin lymphoma depends probably on the amount of generated endogen pyrogens and accordingly on personally changeable negative feedback threshold of the sensitized hypothalamus.

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**Key words:** Child, Hodgkin, hypothermia, lymphoma.

#### Özet

Hodgkin lenfoma ilişkili hipotermi nadiren tanımlanmıştır. Bu duruma; hipotalamus, santral ve periferik vasküler sistem, deri ve kaslarda meydana gelecek olan bir disfonksiyon neden olabilir. Bu yazıda hipotermi gelişen iki Hodgkin lenfoma vakası sunulmuştur.

Olgu 1: Ateş, kilo kaybı ve gece terlemesi yakınmaları ile başvuran yedi yaşındaki kız hastaya, dalağında tespit edilen lezyonlardan yapılan biyopsi ile "Hodgkin lenfoma, mikst selüler tip" tanısı konuldu. Tanı çalışmaları sürerken ateş için hastaya düzenli olarak parasetamol veriliyordu. Hastaya ABVD (adriyamin, bleomisin, vinkristin, dakarbazin) tedavi protokolü başlandı. İlk gün kemoterapisini aldıktan sonra hastada hipotermi gelişti ancak bu durum ek bir tedaviye ihtiyaç olmadan yaklaşık 5 gün sonra kendiliğinden düzeldi.

Olgu 2: Ateş, kaşıntı ve boyunda şişlik yakınması ile başvuran dokuz yaşındaki kız hastaya, servikal lenf nodundan yapılan biyopsi ile "Hodgkin lenfoma, nodüler sklerozan tip" tanısı konuldu. Tanı çalışmaları sürerken ateş için hastaya düzenli olarak parasetamol veriliyordu. Bu süreçte (kemoterapi almadan önce) hastada hipotermi gelişti. Hastaya ABVD tedavi protokolü başlandı. Hipotermi ek bir tedaviye ihtiyaç olmadan yaklaşık 3 gün sonra kendiliğinden düzeldi.

Hodgkin lenfomada oluşan hipotermi muhtemelen üretilen endojen pirojenlerin miktarına ve buna bağlı olarak duyarlılaşmış olan hipotalamusun kişisel olarak değişebilen negatif geri bildirim eşliğine bağlıdır.

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**Anahtar sözcükler:** Çocuk, Hodgkin, hipotermi, lenfoma.

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## Introduction

Body temperature is normally  $36.8 \pm 0.4^{\circ}\text{C}$ . Changes of  $0.5$  to  $1^{\circ}\text{C}$  in the day are deemed normally [1]. Hypothermia means that the body temperature falls under  $35^{\circ}\text{C}$ . If the body temperature is between  $32$  and  $35^{\circ}\text{C}$ , it is classified as light, if the body temperature is between  $28$  and  $32^{\circ}\text{C}$ , it is classified as moderate, and if the body temperature is lower than  $28^{\circ}\text{C}$ , it is classified as heavy hypothermia [2]. Hypothermia is critical especially in children, elders and disabled patients.

In a clinic, Hodgkin lymphoma (HL) is encountered mostly by a painless swelling in the lymph node. Other critical symptoms include fever, itching, night sweating and weight loss. However, hypothermia is identified rarely in HL [3]. This may be caused by a dysfunction that shall occur in hypothalamus, central and peripheral vascular system, skin and muscles, which play a role in thermoregulation [1].

We present two children with HL diagnosis, who have a hypothermia problem.

## Cases report

**Case 1:** A 7-year-old girl applied to the hospital complaining with fever, weight loss and night sweating available for last one month. There was no significant characteristic in her background and family history. Her physical examination was normal except fever ( $38.9^{\circ}\text{C}$ ) and hepatosplenomegaly. Erythrocyte sedimentation rate (ESR) of the patient was  $67$  m/h (Normal value:  $0$  to  $15$  m/h). In abdomen tomography (CT), there were multiple hypodense areas, where biggest one was  $12$  mm in spleen, and there was a hypodense lesion in paraortic area approximately in a size of  $4.5 \times 2.5$  cm. In thorax CT, conglomerate lymph nodes that fill all mediastinal and bilateral hilar compartments were observed. In PET CT, there were lymph nodes that show an increase in the metabolic activity of lower right cervical, bilateral supraclavicular, mediastinal and intraabdominal areas. Bone marrow was evaluated normally. An "HL, mixed cellular type" was diagnosed by a trucutt biopsy conducted in hypochoic areas in her spleen on the patient. The ABVD therapy protocol was started on the patient. After the patient took each four medicine needed to be taken following the protocol in the first day of the chemotherapy (approximately 9.5 hours after administration of first medicine) hypothermia

(min.  $33^{\circ}\text{C}$ ) developed on the patient. All surveys conducted for the purpose of clarifying the hypothermia etiology were normal. The patient was also regularly administered paracetamol available in pre-therapy period. The developed hypothermia healed approximately 5 days later without requiring a further therapy.

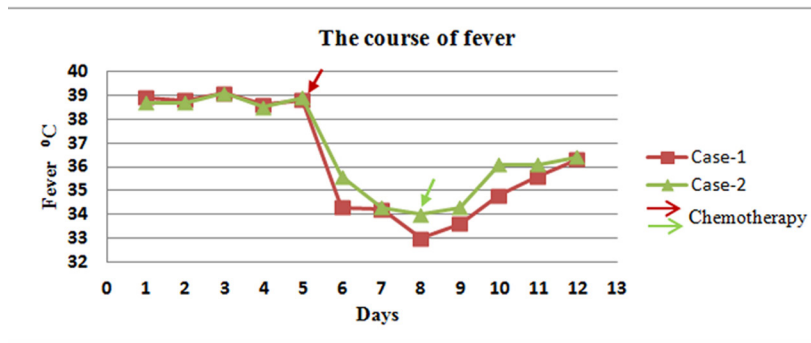
**Case 2:** A 9 year-old-age girl applied to the hospital complaining with fever, itching and swelling in neck available for the last 20 days. There was no critical characteristic in the background and family history of the patient. Her physical examination was normal except fever ( $38,7^{\circ}\text{C}$ ) and left cervical lymph node. ESR of the patient was  $120$  m/h (Normal value:  $0$  to  $15$  m/h). In abdomen CT, there were lymph nodes approximately in a size of  $4.5 \times 5.5$  cm, biggest one of which was at left renal hilus level. In thorax CT, there were lymph nodes, biggest one of which have a small diameter of  $2$  cm, were observed in left axial area. In neck CT, there were conglomerate lymph nodes in left cervical and submandibular area. Bone marrow was evaluated normally. An "HL, nodular sclerosing type" was diagnosed by an exterior biopsy conducted by cervical lymph node. While diagnostic works continued, the patient was administered paracetamol regularly for fever. At this stage, hypothermia developed on the patient (before the chemotherapy was applied) (min.  $34^{\circ}\text{C}$ ). All surveys conducted for the purpose of clarifying the hypothermia etiology were normal. The developed hypothermia healed approximately 3 days later without requiring any further therapy (Figure 1).

## Discussion

Hypothermia was reported in hypothalamus tumors such as lipoma, astrocytoma, craniopharyngioma, etc, and in non-Hodgkin lymphoma and carcinoid tumors [4]. But, others are more in HL.

In HL, hypothermia never depends on age and sex and its reason is not clear yet. In cases reported up to now, the authors have talked about different reasons and mechanisms.

Most important ones of them are chemotherapeutic agents: Chlorambucil, prednisolone, procarbazine, doxorubicin, methotrexate, bleomycin, doxorubicin, dacarbazine, mustine, nitrogen mustard, vinca alkaloids, cisplatin, and chlorpromazine [5–7].



**Figure 1.** The course of fever in cases (The arrows indicate the time of the start of chemotherapy)

In some publications, it is asserted that hypothermia developed after antipyretics administered for hyperthermia such as paracetamol, salicylate and metamizol [8,9].

In addition to medicine, the facts that neuropathy, hypoglycemia and chemotherapy reduce generation of the pyrogens released from lymphoid tissues and/or Kupffer cells, and the disease expands to hypothalamus without any clinical and radiologic findings, and any immunological disorder available previously in the patient and surgical invention are considered as factual causes [3,10,11].

Hypothermia is also reported in nodular sclerosant type and types free of lymphocytes, especially in mixed cellular types [3,9–11].

In one of our cases, hypothermia developed upon administration of paracetamol. In one of our cases, hypothermia developed upon administration of both paracetamol and application of chemotherapy. One was mixed cellular type and the other one was nodular sclerosant. Both healed spontaneously without requiring a further therapy.

The facts that hypothermia developed in not all, but a very small part of the patient subject to chemotherapy or antipyretic; any different chemotherapeutic and antipyretic agents are accused as factual causes; and such event never recurred in repeated dosages of the same medicine make us away from effects of the medicine. Also, the fact that hypothermia is encountered in different subsets shows that the only subset context shall not be true.

It is asserted that hypothermia developed respectively within 2 to 3 hours, 12 hours and second day, and healed spontaneously

respectively within one day, three days, four days, seven days, ten and thirty days [5,8,10].

Contrary to in-vitro non-malign lymphoid tissues, spontaneous excessive pyrogen generation is determined on the lymphoid tissues of the HL patients [12]. From our point of view, this is associated with amount of pyrogens released from tumor cells or other reactive cells and personal versions of hypothalamic response given to these pyrogens [13]. Although body of a human is kept constant in a certain range, the fact that such values change both at certain hours of the day and from person to person supports any personal hypothalamic version [13]. In other words, if the amount of the endogen pyrogens is at a level to cause fever and the hypothalamic fever threshold complies with this, a fever reaction occurs in the patient. If amount of the endogen pyrogens is reduced by pharmacological treatment (chemotherapy or antipyretic), hypothalamus that adapts to fever starts the hypothermia by a rebound effect. The fact that hypothermia is observed initially both in patients with hyperthermia and in patients without hyperthermia is not a handicap for this idea [3,5,8,10]. Even if there is not hyperthermia initially, hypothalamus is under a certain pressure due to the endogen pyrogens and as amount of the pyrogens is reduced by therapy, it may cause hypothermia due to excessive negative feedback. That is why thermoregulatory center consists of both heat loss and heat generation centers. Here there is a type of feedback. Heat loss in hypothalamus triggers central heat loss [14].

In conclusion, it is not possible to describe hypothermia occurred in HL for only one reason. Hypothermia depends probably on the amount of the endogen pyrogens and accordingly

individually changeable feedback threshold of the sensitized hypothalamus.

**Conflict of interest:** The authors declare no conflict of interest.

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