JOUR UMRANIYE PEDIATR
2024;4(3):129–132 doi: 10.14744/upd.2025.85047

CASE REPORT
*Pediatric Hematology and Oncology*

# A rare finding in vincristine neuropathy: Pediatric vocal cord paralysis

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## ABSTRACT

Vincristine is a cell cycle-specific vinca alkaloid that affects mitosis and is frequently included in chemotherapy protocols. The most frequent side effect of vincristine, neurotoxicity, requires dose restriction. Vincristine neuropathy is characterized by four different forms: peripheral neuropathy, autonomic neuropathy, cranial nerve palsies, and encephalopathy. Compared to other neuropathies, vocal cord paralysis is rarely observed in vincristine-associated neuropathy. In this article, we present a case of unilateral vocal cord paralysis in a patient who developed hoarseness during treatment for acute lymphoblastic leukemia (ALL). In our case, hoarseness and snoring occurred after four doses of vincristine treatment in the chemotherapy protocol. After the patient with stridor did not respond to inhaler treatments, an examination revealed paresis of the left vocal cord. Pregabalin and B vitamin complexes were administered, and a response was observed in the fourth week. The hoarseness gradually disappeared. Thus, we emphasize that, although rare, unilateral vocal cord paralysis may develop in vincristine neuropathy and may be reversible.

**Keywords:** Neurotoxicity; neuropathy; vocal cord paralysis.

**Cite this article as:** Sümen E, Dursun S, Büyükavcı M, Kara B, Tokgöz H. A rare finding in vincristine neuropathy: Pediatric vocal cord paralysis. Jour Umraniye Pediatr 2024;4(3):129–132.

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**Received (Başvuru):** 22.01.2025 **Revised (Revizyon):** 31.01.2025 **Accepted (Kabul):** 15.02.2025 **Online (Online yayınlanma):** 25.02.2025

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# Çocuklarda vinkristine bağlı nöropatinin nadir bir formu: Vokal kord paralizisi

**ÖZET**

Vinkristin, kemoterapi protokollerinde sıklıkla yer alan ve mitoza etki ederek hücre siklusunu durduran vinka alkaloidlerinden biridir. En sık görülen yan etkisi olan nörotoksisite, tedavide doz kısıtlamasını gerektirir. Vinkristin nöropatisi; periferal nöropati, otonomik nöropati, kraniyal sinir paralizileri ve ensefalopati olmak üzere dört farklı şekilde görülmektedir. Vinkristin ilişkili nöropatide vokal kord paralizisi ise diğer nöropatilere göre nadir olarak gözlenmektedir. Bu yazıda, Akut Lenfoblastik Lösemi (ALL) tanısı ile tedavi almaktayken ses kısıklığı gelişen bir çocukta saptanan tek taraflı vokal kord paralizisini bildiriyoruz. Olgumuzda, kemoterapi protokolünde yer alan dört doz vinkristin tedavisi sonrası ses kısıklığı ve horlama ortaya çıktı. Stridoru olan hastada inhaler tedavilere yanıt alınamayınca yapılan muayenede sol vokal kord paralizisi saptandı. Pregabalin ve B vitamin kompleksleri uygulanan hastada, dördüncü haftada ses kısıklığının tamamen düzeldiği gözlendi. Bu vaka ile, nadir olsa da vinkristine bağlı nöropatide tek taraflı vokal kord paralizisinin gelişebileceğini ve bunun geri dönüşümlü olabileceğini vurgulamak istedik.

**Anahtar Kelimeler:** Nöropati; nörotoksisite; vokal kord paralizisi.

## INTRODUCTION

Vincristine is one of the chemotherapeutic agents in the group of vinca alkaloids that inhibit microtubule polymerization and prevent mitosis (1). It is used in various hematological malignancies and solid organ tumors. The most common side effect of vincristine is neuropathy, which requires dose restriction. Sensory and motor peripheral neuropathy is frequently reported in cases. Symptoms include paresthesia, numbness, foot drop, weakness in the extremities, impairment of reflexes and fine motor skills, and impaired balance.

Autonomic neuropathy has been reported as the second most frequent form after peripheral neuropathy and includes constipation, paralytic ileus, incontinence, urinary retention, orthostatic hypotension, and unexplained tachycardia or bradycardia. In rare cases, cranial nerve toxicity has been reported. Cranial nerve toxicity may manifest as unilateral hearing loss, bilateral ptosis, and vocal cord paralysis due to recurrent laryngeal nerve involvement. Vocal cord paralysis caused by laryngeal nerve involvement may present as life-threatening cranial nerve involvement (2, 3).

In this article, we present a patient who was followed and treated for acute lymphoblastic leukemia and developed vocal cord paralysis after vincristine treatment.

## CASE REPORT

A 14-year-old male patient was referred to Türkiye from Syria for treatment due to fever, weight loss, pain and swelling in the ankles, wrists, and the dorsum of the left foot, as well as pancytopenia detected in examinations.

On physical examination, the liver was palpable at 3 cm, the spleen at 1 cm, and bilateral cervical millimetric lymphadenopathy was detected. The dorsum of the left foot and the right wrist were edematous and painful on palpation. Laboratory values were as follows: white blood cell: 3900/mm$^3$; neutrophil: 700/mm$^3$; hemoglobin: 8.3 g/dL; platelet: 24,000/mm$^3$; aspartate aminotransferase: 23 U/L; alanine aminotransferase: 18 U/L; uric acid: 4.5 mg/dL; lactate dehydrogenase: 1239 U/L.

Bone marrow aspiration was performed after 25% lymphoblasts were observed in the peripheral smear. Bone marrow smear showed 60% L1-type lymphoblasts. Flow cytometry studies were compatible with CALLA+ (Common Leukemia-Associated Antigen) pre-pre B-ALL, showing CD19: 30%, CD10: 30%, CD20: 5%, CD22: 60%, and CD79a: 69%. No cells were observed in the cerebrospinal fluid at the time of diagnosis. The patient was considered at intermediate risk, and chemotherapy was started according to the ALLIC BFM 2009 protocol.

On the 15$^{th}$ day of the protocol, 50% L1-type lymphoblasts were observed in bone marrow aspiration, and the patient was evaluated as high-risk B-ALL. On the 33$^{rd}$ day of the protocol, diffuse leg pain started. On physical examination during this period, muscle strength was intact, and deep tendon reflexes of the lower extremities were hypoactive. On the 35$^{th}$ day, lower extremity muscle strength was 4/5 bilaterally, and lower extremity deep tendon reflexes were absent.

Vincristine-associated neuropathy was considered in the patient who had received four doses of 1.5 mg/m$^2$/day vincristine intravenously throughout the protocol. Electromyography was compatible with diffuse peripheral motor neuropathy. The patient with vincristine-associated neuropathy was started on pregabalin 5 mg/kg/day, which was increased to 10 mg/kg/day after one week. In addition, B1, B6, and B12 vitamin complexes were added to the treatment.

On the 45$^{th}$ follow-up day of treatment, the patient developed cough, hoarseness, and snoring, in addition to pain and muscle weakness. Physical examination revealed stridor. No acute phase increase was observed in laboratory tests. No infiltration was observed on chest X-ray, and cold vapor adrenaline inhaler treatment was initiated for croup. However, since hoarseness

persisted, snoring increased during sleep, and there was no response to treatment, a video-laryngoscopy examination was performed. The examination showed that laryngeal and rima glottidis patency was adequate, right vocal cord movement was normal, and the left vocal cord was immobilized.

Vincristine neuropathy-related unilateral vocal cord paresis was considered in the patient based on clinical findings and laryngoscopic examination results. Pregabalin and vitamin B complexes were continued in the patient's current treatment. No respiratory distress developed during follow-up. Furthermore, since vincristine was not included in the Protocol 1 Phase 1B of the patient's current chemotherapy regimen, treatment was continued without modification.

In the second week of pregabalin and vitamin B treatment, neuropathic pain decreased, and hoarseness completely resolved by the fourth week. A follow-up video-laryngoscopic examination revealed that bilateral vocal cord movements were normal.

## DISCUSSION

Vincristine is effective in the M phase of the cell cycle and stops cell division by inhibiting the polymerization of microtubules (4). However, this effective mechanism also causes neurotoxicity in peripheral, autonomic, and cranial nerves. Vincristine neurotoxicity may present in four different forms: peripheral neuropathy, autonomic neuropathy, cranial nerve palsies, and encephalopathy. These side effects are limiting factors in the use of vincristine (5).

Vincristine-associated neuropathy is generally reported between 2 and 19 weeks after drug exposure in the literature (6). Symptoms usually present as pain in the lower limbs, reluctance to walk, and constipation. In our case, leg pain and reluctance to walk first appeared four weeks after the start of treatment. However, no significant neurotoxicity was observed, and the chemotherapy protocol was continued. During follow-up, increased complaints and absence of deep tendon reflexes led to an electromyography examination, which was consistent with peripheral neuropathy. At this point, the patient had completed four doses of vincristine treatment.

Within 10 days of completing four doses of vincristine, the patient developed hoarseness. Initially, symptoms were evaluated for an infectious process. However, no culture growth was detected, and hoarseness was unresponsive to treatment. Since the patient had vincristine-induced neuropathic pain during this period, hoarseness was also evaluated in this regard. The patient had unilateral vocal cord paralysis. Since other chemotherapy agents do not have such effects, this condition was considered vincristine-associated neuropathy. Upon further investigation, it was observed that cases of vincristine-induced vocal cord paralysis were indeed serious and rarely reported in the pediatric population (7, 8). Although cases of hoarseness and ptosis occurring together in vincristine-related cranial neuropathy have been reported, ptosis was not observed in our patient (9).

Vocal cord paralysis is a life-threatening condition and may require emergency airway management, especially if bilateral cord paralysis is observed. Approximately 55–66% of patients with bilateral vocal cord paresis require tracheostomy to maintain airway patency (10). In our patient, tracheostomy was not required, as the paralysis was unilateral, and respiratory distress was not observed.

It is not possible to predict the neurotoxicity caused by chemotherapeutic agents, and currently, there is no prophylactic drug that is effective for prevention. Additionally, there is no consensus on whether the drug should be re-administered after neurotoxicity develops as a side effect (11). A literature review revealed that symptoms regressed when the drug was discontinued after neuropathy developed, but the recovery process could extend up to years (12). In our case, vincristine was not administered during follow-up, and a response was observed in a short time with symptomatic treatment, leading to regression of complaints.

Vincristine-induced peripheral neuropathies are commonly reported, and despite various treatment modalities, there is no specific treatment for vocal cord paresis. In our case, gabapentin and pyridoxine complexes were continued. With a conservative approach, the patient's symptoms regressed, and recovery was achieved in about four weeks. While cases in the literature have reported vocal cord paralysis persisting for up to three years after vincristine discontinuation, requiring pyridostigmine-pyridoxine treatments, our patient responded to treatment quickly (13). Thus, this case highlights a neurotoxic side effect that is reversible with drug discontinuation and symptomatic management.

## CONCLUSION

Vincristine is a chemotherapeutic agent commonly used to treat leukemia, but it can cause serious side effects such as neurotoxicity. Vocal cord paralysis is a rare side effect and may be reversible. This case demonstrates that vincristine neuropathy can be successfully managed with conservative treatment and that vocal cord paralysis is reversible. Serious complications can be prevented by careful monitoring of patients during treatment and early intervention.

**Authorship Contributions:** Concept – ES, SD; Design – ES, SD, MB, BK, HT; Supervision – MB, BK, HT; Fundings – ES, SD, MB, BK, HT; Data Collection and/or Processing – ES, SD; Analysis and/or Interpretation – ES, SD, MB, BK, HT; Literature Search – ES, SD; Writing – ES, SD; Critical Review – ES, SD, MB.

**Informed Consent:** Written informed consent was obtained from the families of the patients who participated in this study.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Use of AI for Writing Assistance:** Artificial intelligence methods were not used in this study.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Yazarlık Katkıları:** Fikir – ES, SD; Tasarım – ES, SD, MB, BK, HT; Denetleme – MB, BK, HT; Kaynaklar – ES, SD, MB, BK, HT; Veri Toplanması ve/veya İşlemesi – ES, SD; Analiz ve/veya Yorum – ES, SD, MB, BK, HT; Literatür Taraması – ES, SD; Yazıyı Yazan – ES, SD; Eleştirel İnceleme – ES, SD, MB.

**Hasta Onamı:** Yazılı hasta onamı bu çalışmaya katılan hastaların ailelerinden alınmıştır.

**Çıkar Çatışması:** Yazarlar çıkar çatışması bildirmemişlerdir.

**Yazma Yardımı için Yapay Zeka Kullanımı:** Bu çalışmada yapay zeka yöntemleri kullanılmamıştır.

**Mali Destek:** Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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