The Natural History of Vincristine-Induced Laryngeal Paralysis in Children

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Objective: To outline the natural history of vincristine-induced laryngeal paralysis (VLP) in children.

Design: Retrospective case series and review of reported cases in the English-language literature.

Setting: Tertiary pediatric center.

Patients: The study included all children with a confirmed diagnosis of VLP by inspection and with complete clinical information. The sources for patient identification were a prospectively kept database and a review of the English-language literature, conducted on PubMed since 1966, as well as a bibliography search.

Main Outcome Measures: Charts and literature were reviewed for demographics, primary diagnosis, other diagnoses, and duration and method of treatment. The prevalence of VLP, locally, was also calculated.

Results: Four children (3 boys and 1 girl) were identified in our database over a 51⁄2-year period, and 10 children (1 girl, 8 boys, and 1 with sex omitted) were described in the English-language literature. Four children had unilateral vocal fold paralysis only, all left-sided. The median age was 2.6 years. Acute lymphoblastic leukemia was the underlying diagnosis in 8 patients. Two patients had Down syndrome, and 1 patient had Charcot-Marie-Tooth disease, type 1. Only 2 patients required tracheotomies, and 1 patient was treated temporarily with bilevel positive-pressure ventilation. The median duration of paralysis was 6.8 weeks. The prevalence of VLP was 1.36%.

Conclusions: The data suggest that VLP is probably underreported and possibly underdiagnosed. Endoscopic inspection is a must in all patients with airway symptoms who are receiving vincristine therapy. Early recognition of VLP is mandatory, as it is reversible, has a good prognosis, and usually needs only interruption of vincristine therapy and conservative treatment.


INCA ALKALOIDS WERE FIRST introduced as antineoplastic agents in early 1960. They are derived from the periwinkle plant (Vinca rosea). Vincristine has a well-established role in the treatment of hematologic malignant neoplasms and solid tumors.1 Vinca alkaloids act as mitotic inhibitors by binding to the protein component of microtubules. Their neurotoxicity is thought to occur because of the binding with tubulin,2,3 where it interferes with microtubule assembly, axonal transport, and secretory functions, thereby causing primary axonal degeneration. This process has been documented by nerve biopsy and electron microscopy.3 The most common clinical manifestations of neurologic toxicity are peripheral neuropathy, autonomic dysfunction (eg, constipation, abdominal pain, paralytic ileus, bladder atony with urinary retention, and orthostatic hypotension), cranial neuropathy, and encephalopathy. Colicky abdominal pain and constipation are often among the earliest manifestations of vincristine neurotoxicity, occurring within days of drug administration and antedating paresthesia or reflex depression.4 The first sign of peripheral neuropathy is loss of deep-tendon reflexes, which is followed by paresthesia, ataxia, foot drop, and muscle wasting.2,5 Cranial neuropathy is less common than autonomic or peripheral neuropathy but is associated with more morbidity. Neurotoxicity has been reported to involve nearly all cranial nerves. It mostly manifests as transient cortical blindness, ocu-lomotor nerve dysfunction with ptosis, diplopia, ophthalmoplegia, jaw pain, facial palsy, sensorineural hearing loss, and vocal cord paralysis. Jaw pain, which represents trigeminal nerve toxicity, can oc-
cur suddenly within a few hours of vincristine administration. V vincristine treatment can also be associated with encephalopathy seizures and a syndrome of inappropriate antidiuretic hormone secretion. However, these forms of central neurotoxicity are very uncommon.

It appeared to us that there are very few reports in the literature that discuss vincristine-induced laryngeal paralysis (VLP), especially in children. The goal of our study was to review our institutional experience and the documented cases from the English-language literature in order to better understand the natural course of the disease.

**METHODS**

This retrospective study was based on a prospectively kept database of surgical and endoscopic procedures (Microsoft Access Database version 2000), which was created and updated by one of us (H.E.-H.) on an ongoing basis since June 2002. Other sources of patient identification were hospital and practice medical charts. All data collected from the surgical database and the hospital and practice medical charts were confirmed and cross-checked across at least 2 of these 3 sources. All patients were treated in the same pediatric center (The Stollery Children’s Hospital, Edmonton, Alberta, Canada), which serves a population of 1.7 million in North and Northwestern Canada, including the provinces of Alberta, British Columbia, and Saskatchewan and the Yukon and Northwest territories. We included only children younger than 17 years who developed respiratory symptoms after vincristine therapy for their primary malignant neoplasm and who received a diagnosis of laryngeal paralysis confirmed by endoscopy. The laryngeal mobility was ascertained using a 2.2-mm flexible endoscope (LF-P Pediatric Intubation Fiberscope; Olympus America Inc, Center Valley, Pennsylvania) with the patient under spontaneous ventilation using intravenous propofol and remifentanil hydrochloride. Bronchoscopy was performed using a rigid bronchoscope (Karl Storz GmbH & Co KG, Tuttlingen, Germany) to visualize the subglottis, trachea, and bronchi. Arytenoid fixation, subglottic lesions, and lesions that could affect cord mobility were ruled out. The diagnosis was, by definition, confirmed in children who had no airway-, voice-, or swallowing-related symptoms before the initiation of vincristine therapy.

**VARIABLES**

The patient’s sex was recorded along with age at the time of the first airway endoscopic procedure. The underlying oncological diagnosis, other associated neuropathy (which included peripheral, cranial, or autonomic dysfunctions), airway symptoms (stridor and voice change), and/or feeding and swallowing dysfunction manifestations (repeated coughing or choking) were also documented. Endoscopic findings (unilateral or bilateral laryngeal paralysis, arytenoid fixation, subglottic lesions, and postcricoid growth) were documented. The duration of VLP was calculated by noting the interval between onset and resolution as confirmed on endoscopic inspection. The airway interventions performed in the affected population (tracheostomy, alternate route of feeding, continuous or bilevel positive airway pressure, and nasal trumpet), as well as other relevant diagnoses, were documented along with relevant complications. The prevalence of pediatric VLP in our center was calculated by collecting a list of the total number of children who underwent vincristine therapy from June 2002 to December 2007 from the regional pharmacy services.

**LITERATURE SEARCH**

An English-language literature search of indexed articles published between 1966 and 2007 was conducted. PubMed was searched using the following MeSH terms: vincristine, vocal cord paralysis, stridor, acute lymphoblastic leukemia, neuropathy, Charcot-Marie-Tooth disease (CMT), hereditary motor, and sensory neuropathy. We also checked the bibliographies of pertinent articles for other articles that might be relevant to our study.

Of the 293 children who received vincristine therapy in our center in the last 5½ years, 4 developed VLP. Therefore, the prevalence of the condition, locally, is 1.36%. The characteristics of these children are reported in Table 1. Three were boys. The median age was 3.5 years (range, 2.0-5.0 years). Two children had underlying acute lymphoblastic leukemia (ALL), and one of them also had Down syndrome. The other 2 children had underlying Ewing sarcoma and rhabdomyosarcoma of the testicles, respectively. Bilateral VLP was noted in 3 children, and 1 child had unilateral left-sided paralysis. The median duration of paralysis was 13.8 weeks (range, 4.0 to 37.3 weeks). One boy required bilevel intermittent positive airway pressure, and 1 girl needed a tracheostomy, whereas the other 2 children were treated conservatively. Swallowing dysfunction was noted in 3 children, and all 4 children were assessed by a speech and language pathologist (S.P.). Because of the increased risk of aspiration, the 3 children with bilateral VLP required periods of nasogastric, nasojejunal, and gastrostomy tube feeding. The boy with unilateral VLP required pacing of thin fluid intake. In 3 patients, vincristine therapy was discontinued when paralysis was diagnosed; however, in

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**Table 1. Children Diagnosed as Having Vincristine-Induced Laryngeal Paralysis (VLP) in Our Institution**

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Underlying Oncological Diagnosis</th>
<th>Duration of Paralysis, wk</th>
<th>VLP</th>
<th>Airway Intervention</th>
<th>Associated Neuropathy</th>
<th>Swallowing Dysfunction</th>
<th>Alternate Feeding Route</th>
<th>Chemotherapy Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/2</td>
<td>ALL</td>
<td>37.3</td>
<td>B</td>
<td>T</td>
<td>No</td>
<td>Yes</td>
<td>NJT</td>
<td>No</td>
</tr>
<tr>
<td>2/M/4</td>
<td>ALL + Down syndrome</td>
<td>20.0</td>
<td>B</td>
<td>IPAP</td>
<td>Yes</td>
<td>Yes</td>
<td>GT</td>
<td>No</td>
</tr>
<tr>
<td>3/M/5</td>
<td>Ewing sarcoma (patient died)</td>
<td>7.5</td>
<td>B</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NGT</td>
<td>No</td>
</tr>
<tr>
<td>4/M/3</td>
<td>Rhabdomyosarcoma of the testicles</td>
<td>4.0</td>
<td>L</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphoblastic leukemia; B, bilateral; GT, gastrostomy tube; IPAP, intermittent positive airway pressure; L, left-sided; NGT, nasogastric tube; NJT, nasojejunal tube; T, tracheostomy.
the child with Ewing sarcoma, the vincristine course had already been completed at the time of VLP diagnosis. Resolution of the paralysis was endoscopically confirmed in all patients, and after complete recovery, the vincristine therapy was restarted in 2 patients. The first patient was the child with rhabdomyosarcoma of the testicles and unilateral VLP in whom vincristine therapy was restarted at 50% of the original dosage and subsequently increased to the regular regimen. The second patient was the child with Down syndrome who developed peripheral neuropathy after restarting vincristine therapy in the form of pain involving the jaw and upper extremities, which lasted for 1 week. The therapy was continued at half the original dosage until course completion. We did not recommend therapy in the girl with ALL after decannulation or in the boy with Ewing sarcoma (who had a relapse and died because of a recurrent primitive neuroectodermal tumor). There was no recurrence of VLP in any of our patients, and none of them developed any other cranial neuropathy.

The literature search produced 448 hits; 28 abstracts were reviewed, 18 of which were used. A total of 10 children with VLP were described in the literature (Table 2): 8 boys, 1 girl, and 1 patient whose sex was not mentioned. Their median age was 2.1 years (range, 0.4 to 15.0 years). Six children had underlying ALL, 1 of whom also had Down syndrome. The other 4 children had underlying lymphoma, embryonal rhabdomyosarcoma of the bladder, brainstem ependymoma, and posterior fossa anaplastic ependymoma. The VLP was identified using indirect laryngoscopy in 2 children (patients 1 and 2 in Table 2), flexible laryngoscopy in 3 children (patients 3, 4, and 5 in Table 2), and direct laryngoscopy in 1 child (patient 6 in Table 2). In the remaining 4 children, the authors performed laryngoscopy without mentioning whether it was direct, indirect, or flexible. Seven children had bilateral VLP, with the remaining 3 exhibiting left-sided paralysis only. Only 1 child in this group required a tracheotomy. One child who had associated CMT, type 1, died after 8 months of therapy (because of infectious complications). Vincristine therapy resulted in a recurrence of VLP in another child 13 months after he had completely recovered from his initial episode of VLP (patient 10 in Table 2). Resolution of the VLP was confirmed with laryngoscopic examination in 7 children but was not mentioned in 3 children (patients 1, 2, and 7 in Table 2). Two children required gastrostomies, and swallowing dysfunction was noted in 4 other children. There was no mention of swallowing dysfunction or modifying route or feeds in the rest of the cases. Peripheral and autonomic neuropathy, which was noted in 4 children, presented as hypotonia, constipation, painful paresthesia, and upper and lower limb motor weakness. No other cranial neuropathy was reported in any of the 10 children who were described in the literature.

When we combined the data from the above-mentioned 2 series, we noted some interesting results. The majority of the children in the combined series were boys (11 of the 14 patients, with 1 patient's sex not documented). The most common underlying malignant neoplasm noted in this combined series was ALL, again predominantly among boys (6 of 8 patients with ALL, with 1 patient's sex not known). The median age was 2.6 years (range, 0.4-15.0 years). Ten cases had bilateral involvement, and the 4 cases of unilateral paralysis were all left-sided. The median duration of paralysis was 6.8 weeks (range, 0.7-38.5 weeks). With the exception of 2 patients who underwent a tracheostomy and 1 patient who needed bilevel intermittent positive airway pressure, none of the patients required any airway intervention. Both children with underlying Down syndrome had airway intervention, either in the form of intermittent positive airway pressure or tracheostomy. Peripheral and autonomic neuropathy was noted in 5 children, and swallowing dysfunction was noted in 7 children. None of the children in the combined series had any other cranial neuropathy.

### Table 2. Literature Review of Cases of Vincristine-Induced Laryngeal Paralysis (VLP)

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Underlying Oncological Diagnosis</th>
<th>Duration of Paralysis, wk</th>
<th>VLP</th>
<th>Airway Intervention</th>
<th>Associated Neuropathy</th>
<th>Swallowing Dysfunction</th>
<th>Alternate Feeding Route</th>
<th>Chemotherapy Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/5.8</td>
<td>ALL</td>
<td>0.7</td>
<td>L</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>2/F/2.2</td>
<td>T-cell lymphoma</td>
<td>2.0</td>
<td>L</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>3/M/1.5</td>
<td>Embryonal rhabdomyosarcoma (bladder)</td>
<td>6.0</td>
<td>B</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>4/M/1.3</td>
<td>Brainstem ependymoma</td>
<td>2.0</td>
<td>B</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>5/M/3.0</td>
<td>ALL</td>
<td>2.0</td>
<td>L</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>6/0/0.4</td>
<td>ALL</td>
<td>1.0</td>
<td>B</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>7/M/15.0</td>
<td>ALL + CMT (patient died)</td>
<td>34.3</td>
<td>B</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>TLS, sepsis</td>
</tr>
<tr>
<td>8/M/3.0</td>
<td>ALL + Down syndrome</td>
<td>38.5</td>
<td>B</td>
<td>T</td>
<td>No</td>
<td>Yes</td>
<td>GT</td>
<td>No</td>
</tr>
<tr>
<td>9/M/1.8</td>
<td>Posterior fossa anaplastic epedymoma</td>
<td>34.3</td>
<td>B</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>10/M/2.0</td>
<td>ALL</td>
<td>26.0, recurred after 56.0 wk</td>
<td>B</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>GT</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphoblastic leukemia; B, bilateral; CMT, Charcot-Marie-Tooth disease (type 1); GT, gastrostomy tube; L, left-sided; NA, information not available; question mark, sex unknown; T, tracheostomy; TLS, tumor lysis syndrome.
On retrospectively reviewing the 293 cases involving vincristine therapy at our institution from 2002 to 2007, we identified 4 children with VLP, whereas we found a total of only 10 pediatric patients in the English-language literature since 1966, which probably means that VLP is underreported. It is quite possible that some of these fragile patients are missed because they present with seemingly innocuous dysphonia that is attributed to multiple or prolonged intubations. Some patients may even have died because of progressive airway obstruction or sepsis as a result of continued aspiration, without the link to a laryngeal problem being identified.

The most common malignant neoplasm diagnosed in children is ALL, representing nearly one-third of all pediatric cancers,\(^1\) with a peak incidence in children aged 2 to 5 years. T-cell ALL is more frequently seen in boys. However, in reviewing the series of cases in the literature, there was no mention of ALL type; therefore, we are unable to account for the preponderance of boys noted in our study. The majority of VLP cases in the combined series were bilateral, whereas all unilateral cases were left-sided. This may represent a chance finding, but the staff otolaryngologist (H.E.-H) noted that the left side of the larynx recovered later than the right (a finding that was not supported by serial endoscopy or laryngeal electromyography). It is tempting to assume that the left recurrent laryngeal nerve is more prone to neurotoxic process because of its length. In a study on the pathogenesis of vincristine-induced peripheral neuropathy, Sahenk et al\(^9\) concluded that vincristine-exposed microtubules were significantly shortened, and, on cross-section, there was a decrease in the number of microtubules per square micrometer of axonal area compared with controls. Furthermore, the shortened microtubules showed a clear inabilty to maintain their normal longitudinal orientation, which would account for the abnormalities in axoplasmic transport.

It has been reported that vincristine toxicity has a cumulative effect. Frequent (more than once a week) and higher doses (>2 mg/m\(^2\)/wk) increases the toxicity.\(^11\) All 4 children in our series were given vincristine at a dosage of 1.5 mg/m\(^2\)/wk. Of the 10 pediatric patients described in literature, 6 were given 1.5 mg/m\(^2\) (patients 1, 2, and 7-10 in Table 2). In case 1 (patient 6 in Table 2), the first dose was given at 1 mg/m\(^2\) followed by 1.125 mg/m\(^2\) for doses 2 to 4. In the remaining 3 cases, the exact dosage of the therapy was not reported. Therefore, most children on record developed VLP while receiving a regular dose.

Both children with underlying Down syndrome had airway intervention in the form of intermittent positive airway pressure and tracheostomy. Children with Down syndrome are hypotonic and at increased risk of developing ALL. These factors likely make them prone to acquire the complication and to become severely affected. They probably represent a group that needs close scrutiny and aggressive early interventions.

We are not able to explain the wide range in duration for recovery from paralysis after vincristine withdrawal. However, with a median duration of 1½ months, the parents and children can be assured that the process is relatively short-lived in most instances and that supportive measures will suffice to stave off ill effects. Neurotoxic effects of vincristine therapy may be more severe than usual in patients with preexisting neurologic diseases. There have been reported cases of patients with CMT who developed severe vincristine-associated neuropathy. A genetic myelin defect, as seen in CMT, type 1, predisposes to a severe neuropathy with exposure to an axonal toxin.\(^12\) Patients with other neurologic diseases, such as hereditary motor and sensory neuropathy type I\(^13\) and Guillain-Barré syndrome,\(^14\) have also developed severe diffuse motor and sensory neuropathy after receiving low doses of vincristine.

In hematologic malignant neoplasms, vincristine is used largely because of its relatively low myelotoxic effects and its proved action in cells of lymphocytic lines. The severity of symptoms and the degree of reversibility are important considerations in weighing its risk-to-benefit ratio in the treatment of childhood cancers such as ALL. However, this may not always be feasible, particularly in patients who are receiving urgent chemotherapy, but it may be justified in patients who have clinical signs of neuropathy or a close relative with CMT.

Currently, there are no known methods of preventing or decreasing the toxic effects that are associated with vincristine therapy other than modification of the dosage or discontinuation of the therapy. Folinic acid and pyridoxine have been tried as possible antidotes but gave no protection.\(^15,16\) Recently, oral glutamic acid therapy has been tested, with encouraging results.\(^17\) Results from animal experiments and human observations show that the administration of lithium may counteract vincristine-induced neurotoxic effects.\(^18\) The use of lithium would need to be looked at in a large clinical trial and also in children.

The main solution to dealing with vincristine toxicity is early diagnosis and intervention, through increasing awareness. The assumption that hoarseness is due to an upper airway infection, croup, laryngitis, or a leukemic infiltrate should be avoided, and vincristine should not be given to a child with hoarseness until a laryngoscopy is performed. Children who have Down syndrome and who are receiving vincristine therapy should be closely monitored as they have associated hypotonia and are at a high risk for airway intervention. Because of the complexity of children who are receiving chemotherapy, the potential for misdiagnosis is high; therefore, the decision to visualize and secure the airway should be considered early, as bilateral vocal cord paralysis can be life threatening.

In conclusion, we would like to emphasize that VLP is probably an underreported and possibly underdiagnosed clinical problem. It must be ruled out by endoscopic inspection in all children who are receiving vincristine therapy and who have airway symptoms or swallowing abnormalities. Early recognition of VLP is mandatory, as it is reversible, has a good prognosis, and obviates the need for aggressive airway intervention; it also requires appropriate measures to protect the lower
airway until resolution occurs. It is one example of a containable side effect of successful treatment of childhood cancers. Our study findings are useful for counseling parents and teams that are managing the condition.

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Author Contributions: Dr Kuruvilla had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kuruvilla, Wilson, and El-Hakim. Acquisition of data: Kuruvilla and Wilson. Analysis and interpretation of data: Kuruvilla, Perry, and El-Hakim. Drafting of the manuscript: Kuruvilla and El-Hakim. Critical revision of the manuscript for important intellectual content: Kuruvilla, Perry, Wilson, and El-Hakim. Administrative, technical, and material support: Kuruvilla, Wilson, and El-Hakim. Study supervision: Perry and El-Hakim.

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REFERENCES