Vocal cord paralysis secondary to vincristine treatment in children – A case series of seven children and literature review

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Introduction

Vincristine is a vinca alkaloid chemotherapy agent used in the treatment haematological malignancies including acute lymphoblastic leukaemia (ALL) and some lymphomas. Common toxicity includes neuropathy which can be peripheral, autonomic or less commonly central[1]. Vincristine remains an essential chemotherapy agent in modern ALL protocols[1,2,3]. It's mechanism of action is by inhibiting the M phase of mitosis by binding with the protein component of microtubules. Axonal degeneration takes place when axonal transport and secretory functions are impaired thus leading to apoptosis and toxicity in neural tissue. This is typically seen within the extra-ocular muscles and larynx in cranial neuropathy[1].

Recurrent laryngeal nerve palsy resulting in vocal cord paralysis (vcp) in children has been documented in the literature in multiple case reports and small number of case series[4].We present the largest case series to date of seven children who sustained vcp secondary to vincristine chemotherapy for ALL and review the literature.

Ethical considerations

Ethical approval was not required by our hospital trust.

Methods

A retrospective case note review was performed of all patients diagnosed with vcp during or after treatment with vincristine in our centre between 2010 and 2019. Data such as chemotherapy regime, additional medical therapy, other medical conditions, unilateral or bilateral cord involvement, treatment including tracheostomy, complications and symptom resolution were identified. A literature review was then undertaken of all cases of vcp secondary to vincristine.

Results

Seven patients were identified and included, three female, four male.All children were between two years and four years, all had a diagnosis of ALL.None of the patients had any underlying comorbidities prior to their diagnosis of ALL. (table 1)

Symptom onset in five of the patients was during induction chemotherapy after just 2-4 weekly doses of vincristine. In two cases vcp was diagnosed later during blocks of vincristine containing chemotherapy. In both cases vcp was preceded by other signs of neuropathy including very poor mobility, ptosis and a squint. In all patients vocal cord paralysis presented as increased work of breathing and stridor. Six patients sustained bilateral and one patient a left, unilateral vcp.Of the bilateral cases, four required surgical tracheostomy and the remaining three were managed conservatively with no need for airway protection. All patients recovered from vocal cord paralysis despite all but one patient receiving further vincristine. Regimes and doses were

adjusted to a level of vincristine exposure deemed necessary by the treating haematologist to achieve long term leukaemia remission. Chemotherapy regimes were modified in all cases to reduce vincristine exposure and in some cases patients were switched to an alternative chemotherapy regime not containing vincristine for consolidation and interim maintenance phases of treatment. Doses in induction and consolidation phases were omitted from the time of diagnosis of vcp.

Vincristine was reintroduced in all patients with tracheostomies for the intensive phases of chemotherapy. One patient without a tracheostomy was given vinblastine instead of vincristine as the risk of neurotoxicity is felt to be lower with this agent.

No patients were given the usual monthly vincristine doses in the prolonged maintenance phase of treatment.

All children with tracheostomies were eventually decannulated up to one year following the surgery at a point where no further vincristine was planned. One patient developed subglottic stenosis and whilst decannulated may require laryngotracheal reconstruction for impaired exercise tolerance.

There have been no cases of leukaemia relapse in this patient cohort

Discussion

Synopsis of key findings

All cases were in young children under the age of five years despite the centre treating children with ALL up to the age of 17 yrs.

In all seven cases, and similarly to the other cases we identified in the literature, symptoms occurred often during the induction period within a few doses of vincristine [1,4,5], thus suggesting toxicity may not necessarily be dose dependant.

All seven patients had symptoms of hoarse voice, stridor and increased work of breathing. Due to the complex nature of children undergoing chemotherapy, it is therefore important not to attribute these symptoms to more common problemssuch as croup or a lower respiratory tract infection. It is therefore advisable to have a low threshold for referral to an ENT specialist for awakebedside examination of the larynx[4]. Bilateral cord paralysis can be an acutely life threatening condition if missed and prompt diagnosis is essential. Four of seven of the cases had preceding potential signs of neuropathy, (table 1) however, in three children stridor was the first vincristine related symptom therefore vcp should be considered in any child being treated with vincristine who presents with hoarse voice, stridor or breathing difficulties.

None of the patients were on any medications such as azole antifungals that are known to increase the toxicity of vincristine including vcp[6,7].

In our case cohort all patients received some further doses of vincristine yet still had full vocal cord recovery within a year. The risk of further vincristine is of permanent need for tracheostomy but this must be traded against the risk of leukaemia relapse from inadequate therapy.. The aim should be to deliver vinca alkaloids in as close to target dose as possible during the intensive phases of therapy but can be more safely omitted in the continued maintenance phase. We therefore suggest a potential management algorithm in figure 1.

Strengths of the study

To date this is the largest case series of paediatric patients sustaining vcp secondary to vincristine chemotherapy for ALL occurring within one tertiary referral centre within the UK. From this we were able to identify patterns such as laterality, onset of symptoms from commencing chemotherapy and therefore considerations towards management of future planned vincristine doses. Time for recovery and treatment interventions were also identified.

All our patients had no underlying medical conditions prior to being diagnosed with ALL nor where they on any medications known to increase the toxicity. We could therefore deduce our finding from a comparative

selection of paediatric patients and compare our case series to other cases reported in the literature and guide clinicians faced with this clinical situation.

Comparison with other studies

To date there are around twenty case reports and a few small case series of no more than three paediatric patients [4]. Symptom onset mostly occurred during the induction phase of treatment[4]. Similarly in the other cases that were identified symptoms resolved after cessation of vincristine which had variable rates of recovery from weeks to months. It is known that drugs such as itraconazole, ,erythromycin, isoniazid, phenytoin and mitomycin c may increase the toxicity of vincristine thus making neurotoxicity more likely [5,7]. Further to this, hepatic impairment may also contribute as vincristine is metabolised by the cytochrome p450 enzymes. L-asparaginase, often concomitantly administered with vincristine impairs the hepatic clearance of vincristine thus increasing the chances of toxicity [5]. A genetic predisposition to vincristine toxicity has also been suggested via a polymorphism of a promotor region of one of the genes that encodes microtubule formation[7].

It is however possible that vcp due to vincristine is likely to be under reported with only severe cases of patients with breathing difficulties, stridor of severe hoarseness being reported. Previous studies have described prevalence rates at 1.36% [8] and 1.9%[5]. This also generates the discussion as to whether any other chemotherapy agents are associated with vocal cord paralysis. Vinblastine, another vinca alkaloid is implicated in adult vcp[9] as well as cisplatin[10] .

There has been some work to see if anticholinesterase inhibitors such as pyridostigmine given prophylactically to prevent neurotoxicity in patientsgiven vincristine however these agents do not appear to be protective[5].

Clinical applicability of the study

To date this is the first UK based study and the largest case series reporting vocal cord paralysis secondary to vincristine chemotherapy. As cases that are referred to ENT are likely to be more severe cases in terms of symptoms at presentation, it is likely that there is under reporting, particularly of symptoms of unilateral paralysis. As symptoms resolve on cessation of vincristine, early detection of mild symptoms such as hoarseness via a prompt referral for diagnostic laryngoscopy is essential. This may prompt alteration of treatment and may possibly prevent the progress to more life threatening bilateral paralysis requiring tracheostomy.

Conclusion

Although rare, vcp is a known, potentially life threatening complication of vinca alkaloid chemotherapy agents such as Vincristine. Recovery is to be expected with cessation of therapy. Prompt diagnosis in terms of low threshold for requesting laryngeal examination by an ENT specialist can facilitate appropriate early treatment and recovery. An individualized approach to delivery of necessary chemotherapy can achieve both recovery of cord palsy allowing reversal of tracheostomy as well as maintaining long term remission from leukaemia.

Key points

1. We present the largest case series to date of seven patients sustaining vocal cord paralysis after receiving vincristine chemotherapy for acute lymphoblastic leukaemia.
2. Vocal cord paralysis was only seen in children under five years
3. Vocal cord paralysis appeared to be reversible following cessation of vincristine in our case series and in other cases reported in the literature
4. Prompt referral to an ENT specialist for bedside laryngeal examination is essential to promptly diagnose vocal cord palsy and guide management regarding the need to continue vincristine to achieve remission versus need for tracheostomy.

References

1. AnninoDJ, Macarthur CJ, FriedmanEM. (1992). Vincristine-induced recurrent laryngeal nerve paralysis. *The Laryngoscope* ,*102* (11), 1260–1262.
2. Vora A, Goulden N, Mitchell C, et al. Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial.*Lancet Oncol* 2014; published online June 10. http://dx.doi.org/10.1016/S1470-2045(14)70243-8.
3. United Kingdom National Randomised Trial For Children and Young Adults with Acute Lymphoblastic Leukaemia and Lymphoma 2011. Available at https://www.northerncanceralliance.nhs.uk/wp-content/uploads/2019/01/UKALL2011-Protocol-v3.0-01-Oct-2013.pdf . Accessed 21st January 2020.
4. ZavalaH, RobyBB, DayA, BostromB, Sidman,J, ChinnaduraiS. (2019). Vincristine-induced vocal cord paresis and paralysis in children.*International Journal of Pediatric Otorhinolaryngology* ,123:1-4
5. NazirHF, AlFutaisiA,Zacharia M, Elshinawy M, MevadaST, Alrawas A, WaliY. (2017). Vincristine-induced neuropathy in pediatric patients with acute lymphoblastic leukemia in Oman: Frequent autonomic and more severe cranial nerve involvement. *Pediatric Blood & Cancer* ,*64* (12), e26677.
6. Sathiapalan RK, El-SolhH. (2001). ENHANCED VINCRISTINE NEUROTOXICITY FROM DRUG INTERACTIONS: Case Report and Review of Literature.*Pediatric Hematology and Oncology* , *18* (8), 543–546.
7. Madsen M., Due H, Ejskjær N, Jensen P, Madsen J, Dybkær K. (2019). Aspects of vincristine-induced neuropathy in hematologic malignancies: a systematic review. *Cancer Chemotherapy and Pharmacology* ,*84* (3), 471–485.
8. Kuruvilla G, Perry S, Wilson B, El-Hakim H. (2009). The Natural History of Vincristine-Induced Laryngeal Paralysis in Children.*Archives of Otolaryngology–Head & Neck Surgery* ,*135* (1), 101–105.
9. Taha H, Irfan S, Krishnamurthy M. (1999). Cisplatin induced reversible bilateral vocal cord paralysis: An undescribed complication of cisplatin. Head Neck, 21: 78-79.
10. Cherif S, Danino S, YoganathanK. (2014). Autonomic neuropathy resulting in recurrent laryngeal nerve palsy in an HIV patient with Hodgkin lymphoma receiving vinblastine and antiretroviral therapy.*International Journal of STD & AIDS* , *26* (3), 206–208.

Figure legends

Table 1: Patient summary table

Figure 1: Proposed treatment algorithm for suspected vcp

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`Figure 1 flow diagram..pptx` available at https://authorea.com/users/324838/articles/452911-vocal-cord-paralysis-secondary-to-vincristine-treatment-in-children-a-case-series-of-seven-children-and-literature-review