Title

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CASE REPORT

Severe vincristine-induced polyneuropathy in a teenager with anaplastic medulloblastoma and undiagnosed Charcot-Marie-Tooth disease

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SUMMARY

Severe neuropathy is a known adverse effect of vincristine in patients with Charcot-Marie-Tooth disease (CMT). We present the case of a 16-year-old girl with anaplastic medulloblastoma treated with gross total resection and high-dose craniospinal radiation with adjuvant vincristine chemotherapy who developed acute-onset severe quadriplegia and vocal cord paralysis. Vincristine and radiation therapy were discontinued. Although her neuropathy slowly improved over several weeks, she developed metastatic extraneural medulloblastoma and died 5 months after diagnosis. Subsequent genetic testing revealed previously asymptomatic and undiagnosed CMT1A. Our case highlights the importance of early recognition of acute vincristine neurotoxicity that should raise suspicion of an underlying hereditary neuropathy.

BACKGROUND

Charcot-Marie-Tooth disease (CMT) is a common hereditary motor and sensory neuropathy affecting up to 1 in 2500 individuals in the USA.[1] Symptoms may arise in childhood or adolescence, and include slowly progressive motor neuropathy of the arms and legs, distal limb-muscle wasting, sensory loss and reduced deep-tendon reflexes. Patients may also have pes cavus, hammer toes, gait difficulties, foot drop, twisting of the ankle and muscle cramps.[2] Although family history or physical examination may raise suspicion for CMT, some patients are asymptomatic and undiagnosed until later in life. Vincristine is known to cause a severe neuropathy and is not recommended in patients with a history of neuropathy. We present a case of a 16-year-old previously healthy teenager with anaplastic medulloblastoma treated with gross total resection, vincristine and craniospinal radiation therapy who subacutely developed quadriplegia and vocal cord paralysis. Vincristine and radiation therapy were stopped and genetic testing revealed a peripheral myelin protein 22 (PMP22) Exon 1–5 duplication consistent with CMT1 disease (CMT1A). Given the significant morbidity associated with vincristine toxicity, it is essential to recognise the signs and symptoms of vincristine neurotoxicity that may raise the suspicion of an underlying hereditary neuropathy.

CASE PRESENTATION

A previously healthy 16-year-old girl presented with a 2-week history of episodes of loss of consciousness with tonic clonic movements. Neurological examination was significant for upgaze nystagmus, bilateral sixth nerve palsies, bilateral appendicular dysmetria, vibratory loss and ataxic gait. CT of the head revealed a posterior fossa neoplasm filling the fourth ventricle and causing obstructive hydrocephalus. MRI of the brain and spine showed an enhancing mass arising from the roof of the fourth ventricle with restricted diffusion and foci of internal haemorrhage and leptomeningeal metastatic disease. The patient then underwent gross total resection followed by ventriculoperitoneal shunt placement for persistent hydrocephalus. Pathology revealed anaplastic medulloblastoma with cerebrospinal fluid dissemination. Her postoperative course was complicated by encephalopathy, decreased spontaneous speech, eye movement abnormalities and dysmetria consistent with cerebellar mutism syndrome. She was started on weekly vincristine and daily craniospinal radiation therapy. She subacutely developed progressive upper and lower extremity weakness following her first dose, which was subsequently reduced by 30%. After her second dose of vincristine, she developed dysphagia, and hypophonia with vocal cord paralysis and paraparesis. The patient was transferred to the intensive care unit for airway management, and vincristine and radiation therapy were discontinued. Electrodiagnostic studies revealed reduced compound muscle action potential amplitudes, delayed distal motor latencies and absent sensory studies consistent with a demyelinating and axonal polyneuropathy. The patient slowly made improvements in strength and vocalisation over the span of 2 months, and was transferred to rehabilitation.

Genetic testing revealed a PMP22 Exon 1–5 duplication consistent with CMT1A. Family history was negative for neuropathy. A repeat MRI 2 months after diagnosis showed no evidence of recurrent intracranial disease; however, it did redemonstrate leptomeningeal spread along the cord. Approximately 4 weeks later, she was readmitted with acute renal failure with associated anaemia, thrombocytopaenia and encephalopathy. Bone marrow biopsy at that time contained 60% neoplastic cells. MRI of the brain and spine showed marked mediastinal and retroperitoneal lymphadenopathy with intra-abdominal masses and diffuse abnormal marrow signal consistent with metastatic extraneural medulloblastoma. The patient was

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transitioned to end-of-life care and unfortunately died 5 months after her initial diagnosis.

DISCUSSION

CMT is a genetically and phenotypically heterogeneous condition affecting motor and sensory peripheral nerves.[1 2] It is the most prevalent hereditary neuromuscular disease affecting 1 in 2500 individuals.[1] CMT is commonly inherited as an autosomal-dominant trait; however, it may be transmitted as X linked or autosomal recessive as well.[2] There are many subtypes of CMT; the two main groups are a demyelinating form (CMT1) and an axonal form (CMT2). CMT1A is a result of a duplication on chromosome 17p11.2-p12 involving the PMP22 gene,[2] as was discovered in this patient. The typical phenotype involves painless, symmetric, slowly progressive motor neuropathy of the arms and legs, distal limb-muscle wasting, sensory loss and reduced deep-tendon reflexes. Patients may also have pes cavus, hammer toes, gait difficulties, foot drop, twisting of the ankle and muscle cramps.[2] Symptom onset is usually in childhood or adolescence.[2] Of note, some patients are asymptomatic or have only mild manifestations of the condition. Vincristine, a microtubule inhibitor and peripheral neurotoxin, has been known to exacerbate the severity of CMT.[3] A total dose of 5–8 mg may induce sensory neuropathy in the general population; CMT patients experience adverse effects at much lower doses.[2] Acute worsening quadriparesis and even quadriplegia, vocal cord paralysis, dysphagia, and dysphonia may be observed in a patient with vincristine toxicity. Most patients improve or return to baseline within months after cessation of the drug. Any severe vincristine toxicity should prompt genetic testing for CMT. In addition, use of vincristine is not recommended in any patient with the demyelinating form of CMT (CMT1).[3] There is one successful report of vindesine treatment for acute lymphoblastic leukaemia in a patient following vincristine-induced neurotoxicity.[4] The mechanisms of vindesine and vincristine are similar; further studies are necessary to evaluate the safety of vindesine in patients with CMT. The use of vincristine has not been well studied in the other subtypes of CMT; one study found Vincristine toxicity in an asymptomatic patient discovered to have an EGR2 gene mutation.[5] Further studies are warranted to characterise vincristine toxicity in the many subtypes of CMT.

Our case highlights the importance of early recognition of severe vincristine neurotoxicity that should raise awareness of the possibility of an undiagnosed hereditary neuropathy such as CMT.

Learning points

- Charcot-Marie-Tooth disease (CMT) is a common hereditary motor and sensory neuropathy that may be undiagnosed in asymptomatic patients.
- The use of vincristine is not recommended in any patient with known CMT due to the risk of severe neurotoxicity (acute progressive quadriparesis, quadriplegia, vocal cord paralysis and dysphagia).
- A thorough family history and physical examination should be conducted prior to initiating vincristine therapy to evaluate for signs of an underlying neuropathy that may predispose the patient to neurotoxicity.
- Patients with severe acute vincristine neurotoxicity should raise suspicion of an underlying hereditary neuropathy.

Contributors JRC and JMY were involved in the diagnosis and treatment of the patient. YA and JRC did the literature search and wrote the manuscript. All authors have reviewed the case report and agree to its content prior to submission.

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