

# Charcot-Marie-Tooth Disease in a Child with Acute Lymphoblastic Leukaemia: A Case Report and Review of Literature

Type of Article: Case Report

Gracia .K. Eke, Nwadiuto .A. Akani

Department of Paediatrics and child health, College of Health Sciences, University of Port Harcourt Nigeria.

## ABSTRACT:

### Background

Charcot-Marie-Tooth disease (CMT) is a common inherited neurologic disorder with various modes of inheritance. Existing peripheral neuropathy is a generally accepted risk factor for increased susceptibility to neurotoxic agents and there is a general acceptance of the concept of medication-induced worsening of CMT. Several authors have reported vincristine neurotoxicity in CMT and vincristine treatment triggering the expression of asymptomatic CMT disease. We report the case of a 10 year old male patient who developed severe neuropathy following treatment with vincristine for his Acute Lymphoblastic Leukaemia.

**Methods:** The case records of the patient and a review of the relevant literature using available books, journals and online literature search was utilized.

**Results:** Facial nerve palsy, increasing lower extremities muscle weakness and abnormal gait were noticed 4 weeks into vincristine therapy in a ten year old male on treatment for acute lymphoblastic leukaemia (ALL). On a suspicion of vincristine neurotoxicity, vincristine was excluded from his chemotherapy regimen. Although remission of ALL was achieved within 6 weeks of treatment, the patient's neurological symptoms did not improve even with the withdrawal of vincristine. The patient was diagnosed with Charcot-Marie-Tooth disease resulting from vincristine toxicity.

### Conclusion:

Patients with Charcot-Marie-Tooth disease may show severe toxicities with vincristine. It is therefore recommended that an extensive neurologic examination should be conducted on any paediatric patient with a diagnosis of malignancy to identify any undiagnosed neurologic deficits and screen for suitability or otherwise of a vincristine containing cytotoxic therapy regimen. This case stresses the need for an urgent health sector response to provide adequate facilities for electrophysiological screening and genetic studies in resource limited centres like ours in order to identify possible cases of undiagnosed CMT and prevent the occurrence of exacerbation by vincristine administration.

**Correspondence:** Dr. Nwadiuto Akani

**E-Mail:** diutoph@yahoo.com

## INTRODUCTION

Charcot-Marie-Tooth disease (CMT) is the most common inherited neurologic disorder, affecting approximately 1 in 2,500 people in the United States<sup>1</sup>. It has various forms with various modes of inheritance. CMT1 is an autosomal dominant disease, while CMT4 is autosomal recessive and CMTX an X-linked dominant disease<sup>1</sup>. Existing peripheral neuropathy is a generally accepted risk factor for increased susceptibility to neurotoxic agents and there is a general acceptance of the concept of medication-induced worsening of CMT<sup>2</sup>. Several authors<sup>3-7</sup>, have reported vincristine neurotoxicity in CMT and vincristine treatment triggering the expression of asymptomatic CMT disease. The oldest report was from Weiden and Wright (1972)<sup>8</sup> followed by several individual reports in the mid to late 1980s. However, it was not until Graf et al reported 3 cases in 1996 that the issue gained widespread attention.<sup>2,9</sup>

Vincristine, a widely used vinca alkaloid, is a first-line chemotherapeutic agent for several malignancies. The drug is the only agent with multiple credible examples of inordinate toxicity in CMT patients, which can be severe and acute, in some instances after a lone exposure.<sup>2</sup> In the general population, a minimum total dose of 5-8mg is the described threshold for inducing sensory neuropathy in most cases. Motor involvement usually requires higher doses. In CMT patients, acute worsening or initiation of weakness, which may present sometimes as severe quadriparesis or a Guillain Barre-like pattern, is observed after administration of only 2-4mg or the equivalent paediatric dose of 1.5mg/m<sup>2</sup>/dose.<sup>2</sup>

There is paucity of reported cases in Nigeria. This may be because of under diagnosis rather than non occurrence. We report a case of vincristine induced neuropathy in a child with acute lymphoblastic leukaemia (ALL) and undiagnosed Charcot-Marie-Tooth disease.

## CASE REPORT

We report the case of a 10 year old male who presented to the Paediatric oncology unit of the University of Port Harcourt, teaching hospital with a 5 month history of generalised body pains, joint pains, recurrent fever, weight loss and weakness. There was no history of trauma or previous blood transfusion. Systemic review revealed poor appetite, vomiting, gum bleeding and bone pains. The patient was an average primary 4 pupil; who had not attended school since the onset of illness because the mother had to carry him about as he was too weak to walk. He was last of 3 children. His elder sibling died of sickle cell anaemia. There was no family history of neuropathy. His mother was a 38 year old petty trader while his father, was a 50 year old store keeper in a health institution.

At presentation, the patient appeared chronically ill and wasted, with marked pallor. He was febrile (temperature of 38.6°C) with generalised non tender lymphadenopathy. His weight was 22kg (67%) of expected. Abdominal examination revealed an enlarged liver which was 4cm below the sub costal margin. Neurologically, the extremities were not wasted but muscle power was grade 3 in the right and 2 in the left lower limbs.

Laboratory data revealed anaemia (packed cell volume of 18%), leukocytosis of  $16.3 \times 10^9/L$  (with 14% neutrophils, 70% lymphocytes, 9% blasts) and thrombocytopenia of  $65 \times 10^9/L$ . Haemoglobin genotype was AA and retroviral screening was negative for HIV I and II. Bone marrow aspiration confirmed acute lymphoblastic leukaemia type L<sub>1</sub> (40% blasts). Serum electrolytes, urea and creatinine were unremarkable; however the uric acid level was elevated.

He was commenced on supportive therapy, including allopurinol, blood transfusions and antibiotics. Induction of remission was commenced four weeks after admission with intravenous (iv) cyclophosphamide, iv vincristine, and oral prednisolone. He also received intrathecal methotrexate and hydrocortisone. In the 4<sup>th</sup> week of therapy, he complained of heaviness of the lower limbs, and was then noticed to fall easily with difficulty in standing from a squatting position. He also had an abnormal gait. Vincristine neurotoxicity was suspected and, the drug was withdrawn from his anti-cancer regimen and vitamin B complex was added to his prescriptions.

Remission was achieved after 6 weeks of cytotoxic therapy and patient was discharged home to continue treatment consolidation phase on outpatient basis.

He was seen on follow up a week after discharge and noticed to have left facial nerve palsy. He was unable to walk unsupported, but could stand with support. His lower limbs were jittery and easily gave way at the knee joint. He had a high stamping gait, with feet in the plantar flexed position and grade 2 muscle power in both lower limbs. Sensation was intact.

He was given a one week outpatient appointment to be reviewed a week later, but the patient defaulted from follow up only to be rushed to the children's emergency Ward 4 weeks later, with a 7 day history of fever, gum bleeding, weakness and leg swelling. He had marked pallor, bilateral peri-orbital and pedal oedema, altered blood in the mouth and nostrils, hepatomegaly and splenomegaly of 12cm and 5cm respectively. He was lethargic, had diffused tenderness over lower limbs and spine, and had an urgent packed cell volume of 17%. His primary illness ALL had worsened and child died before blood could be made available for transfusion.

## DISCUSSION

Charcot-Marie-Tooth (CMT) Disease, also known as Peroneal Muscular Atrophy or Hereditary Motor-Sensory Neuropathy (HMSN) is the most common genetically determined neuropathy<sup>10</sup> and the commonest cause of chronic, progressive polyneuropathy seen in children<sup>11</sup>. The

disease is named after the three physicians who first identified it in 1886. Jean-Martin Charcot and Pierre Marie in Paris, and Howard Henry Tooth in Cambridge<sup>1</sup>. It comprises a group of disorders that affect peripheral nerves and presents with non-inflammatory degeneration of the nerve cell body and peripheral axon or Schwann cells (myelin)<sup>12</sup>. Affected nerves may be hypertrophic due to demyelination followed by attempts at re-myelination<sup>13</sup>. Onset is usually in the first decade. The child presents with clumsiness and easily falls or trips over his/her own foot. Muscular atrophy is distal, accompanied by progressive weakness of dorsi-flexion of the ankle and eventual foot drop<sup>10</sup>, loss of sensation and absent reflexes<sup>11</sup>. Peroneal and tibial nerves are the earliest and most severely affected nerves. The process is bilateral but may be slightly asymmetric<sup>10</sup>. Later in the disease, weakness and muscle atrophy may occur in the hands, resulting in difficulty with fine motor skills<sup>1</sup>. The axial muscles are usually not involved and pain can range from mild to severe. Those affected have normal intelligence, normal life expectancy and rarely lose the ability to walk.

Several authors<sup>3,4</sup> have reported cases of children with leukaemia who developed acute polyneuropathy after treatment with vincristine. Bay et al<sup>3</sup> reported the development of bilateral ptosis and complete ophthalmoplegia with normal papillary and corneal reflexes in a 5-year old with pre B cell ALL five days after the 4<sup>th</sup> dose of vincristine. The bilateral ptosis resolved completely after 2 weeks of treatment with pyridoxine and pyridostigmine.

Our patient's symptoms worsened after the 4<sup>th</sup> dose of vincristine which he received weekly, following the standard regimen for the treatment of ALL. Similarly, his neurological deterioration also involved the cranial nerves, as the patient developed left facial nerve palsy.

Nearly all reports described eventual improvement with vincristine withdrawal or dose reduction but frequently not to baseline levels and most with previously unsuspected and undiagnosed CMT<sup>2,7,9</sup>. Unfortunately, our patient did not live long enough for us to make that observation. Although he was commenced on Vitamin B complex which contains pyridoxine and vincristine withdrawn, there was no improvement of the polyneuropathy, but rather a marked deterioration of both neuropathy and ALL. The fact that patient defaulted from his treatment probably led to a relapse of his leukaemia with severe anaemia causing further muscle weakness, infiltration of the marrow causing bone pains which made even more difficult for patient to stand or walk and eventual death less than 2 hours into his second admission through the emergency.

Many cases of undiagnosed CMT prior to vincristine treatment had, in retrospect, overt clinical signs or a close relative with known CMT. The index case, in retrospect, presented with typical features of CMT which include weakness of lower limb muscles. However, the severe anaemia at presentation may have beclouded the suspicion of the likelihood of a neurologic problem thus allowing for the commencement of a vincristine-containing regimen where it probably should have been excluded. Medication-induced exacerbation of CMT had been reported with several drugs,

e.g. quinidine, nifedipine, cyclosporine A, metronidazole, Nitrofurantoin and Nitrous oxide<sup>2</sup>. However, vincristine appears to be in a separate high risk category for patients with demyelinating forms of CMT and the possibility of acute worsening after only a single dose makes cautious administration problematic.

The diagnosis of CMT begins with a standard patient history, family history, and neurologic examination. If suspected, nerve conduction studies, electromyography, and genetic testing (which is also available for some types of CMT) should be done and the diagnosis confirmed with nerve biopsy. In CMT, nerve conduction and electromyography studies are abnormal, and nerve biopsy confirms the diagnosis with “onion bulb” formation.<sup>1</sup>

Unfortunately, none of the above investigations could be done for our case since the facilities were not immediately available within the hospital and his default from follow up compounded the issue of Logistics.

There is no cure for CMT, but physical therapy, occupational therapy, braces and other orthopaedic devices, and even orthopaedic surgery can help patients cope with the disabling symptoms of the disease. Stabilization of the ankle, which is usually the primary concern, can be achieved with stiff boots in early stages and external short leg braces in advance cases. Surgical fusion of the ankle may be considered. No medical treatment is available to arrest or slow the disease progression. The severity of symptoms is quite variable in different patients and even among family members with the disease. It is difficult to establish if this “patient's severity variation” contributed to the early demise of the patient since he already had a terminal illness.

## CONCLUSION

The diagnosis of CMT requires a high index of suspicion. This has become even very pertinent in the face of increasing prevalence of acute lymphoblastic leukaemia in children in our environment which implies an increasing need for vincristine as a first line drug in its treatment.

It is therefore recommended that an extensive neurologic examination should be conducted on any paediatric patient with a diagnosis of malignancy to identify any undiagnosed or unidentified neurologic deficits and screen for suitability or otherwise of a vincristine containing cytotoxic therapy regimen; and vincristine withheld from patients with an existing or a family history of neuropathy.

This case stresses the need for an urgent health sector response to provide adequate facilities for electrophysiological screening and genetic studies in resource limited centres like ours in order to identify possible cases of undiagnosed CMT and prevent the occurrence of exacerbation by vincristine administration. A high index of suspicion, increasing awareness and reporting of documented cases are highly valuable.

## REFERENCES

1. Institute's Brain Resources and Information Network (BRAIN). Charcot-Marie-Tooth Disease. [Http://www.ninds.nih.gov](http://www.ninds.nih.gov)
2. Weimer LH, Podwall D. Medication-induced exacerbation of neuropathy in Charcot-Marie-Tooth Disease. *Journal of the Neurological Sciences* 2006; 242: 47-54.
3. Bay A, Yilmaz N, Oner AF. Vincristine induced cranial polyneuropathy. *Indian J Pediatr* 2006; 73: 531-533.
4. Olek MJ, Bordeaux B, Leshner RT. Charcot-Marie-Tooth disease type 1 diagnosed in a 5-year-old boy after vincristine neurotoxicity, resulting in maternal diagnosis. *J Am Osteopath assoc* 1999; 99(3): 165-167
5. Neumann Y, Toren A, Rechavi G, Seifried B, Shoham NG, Mandel M, et al. Vincristine treatment triggering the expression of asymptomatic Charcot-Marie-Tooth disease. *Med Pediatr Oncol* 1996; 26: 280-283
6. Nishikawa T, Kawakami K, Kumamoto T, Tonooka S, Abe A, Hayasaka K, Okamoto Y, Kuwano Y. Severe neurotoxicities in a case of Charcot-Marie-Tooth disease type 2 caused by Vincristine for acute lymphoblastic leukaemia. *Journal of Paediatric Haematology/Oncology* 2008;30(7) 519-521
7. Chauvenet AR, Shashi V, Selsky C, Morgan E, Kurtzberg J, Bell B. Vincristine induced neuropathy as the initial Presentation of Charcot-Marie-Tooth disease in acute lymphoblastic leukaemia: A Paediatric Oncology Group Study. *J Pediatr Haematol Oncol* 2003; 25:316-320.
8. Welden PL, Wright SE. Vincristine Neurotoxicity *N Engl J Med.* 1972; 286: 1369-1370.
9. Graf WD, Chance PF, Lensch MW, Eng LJ, Lipe HP, Bird TD. Severe Vincristine neuropathy in Charcot-Marie-Tooth disease type 1A. *Cancer* 1996; 77: 1356-1362
10. Stanton BF Charot-marie tooth disease In: Behrman RE, Kliegman RM, Jenson HB(eds). *Nelson textbook of Paediatrics.* 15th Edition, Philadelphia, Pa, Saunders, 2004; 2559-2560
11. Levene MI. Disorders of the Nervous System: Muscular Dystrophy, In: *Jolly's Diseases of Children.* 6<sup>th</sup> edition. Blackwell Scientific Publications 1990; 298-301
12. Keller KR, Nordli DR, Bingham P, Clancy RR. Neurology: Neuromuscular Disorders. In: Polin RA, Ditmar MF(eds). *Paediatric Secrets.* 3<sup>rd</sup> edition Philadelphia. Hanley & Belfus 2001; 548 557
13. Lissauer T, Clayden G. Neurological disorders: Neuromuscular disorders. *Illustrated Textbook of Paediatrics* 2<sup>nd</sup> edition. Mosby 2002; 378-381