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Original Article

Peripheral neuropathy in cystic fibrosis: A prevalence study

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Abstract

Background: Information on peripheral neuropathy in children with cystic fibrosis is scanty. The etiology can be multifactorial (micronutrient deficiency, chronic hypoxia, impaired glucose tolerance, immunological, vasculopathic, critical illness).
Methods: Forty five cystic fibrosis children aged 1–18 years on vitamin E supplementation for at least 6 months underwent detailed neurological examination, serum vitamin E, vitamin B12, folate, copper levels and detailed nerve conduction studies.
Results: The mean age of the study population was 8.35 years (±4.9 years) with 62.2% being males. Overall 22 out of 45 (48.88%,CI: 33.7–64.2) had electrophysiological evidence of peripheral neuropathy which was predominantly axonal (86.4%), sensory (50%), and polyneuropathy (95.45%). There was no significant association between status of serum micronutrients and electrophysiological evidence of peripheral neuropathy.
Conclusion: Patients with cystic fibrosis have electrophysiological evidence of peripheral neuropathy (predominantly axonal, sensory and polyneuropathy). There is significant association of higher chronological age with occurrence of peripheral neuropathy.

Keywords: Axonal; Cystic fibrosis; Micronutrients; Polyneuropathy; Sensory

1. Introduction

Cystic fibrosis is an autosomal recessive genetic disease occurring in 1/3200 Caucasian births [1]. Mutations in CFTR (Cystic Fibrosis Transmembrane Regulator) result in channelopathy with impaired sodium and chloride conductance causing mucosal obstruction of exocrine glands. It is a multisystem disorder involving pulmonary, gastrointestinal, endocrine, musculoskeletal, male genitourinary system, joints and sinuses.

With improvement in quality of care, cystic fibrosis has evolved into a disease of adults. In the last 45 years dramatic advances in medical management of this disease have resulted in remarkable improvement in the median age of survival. In 1959 infants with cystic fibrosis lived only for about 6 months, whereas by 2003 it was around 30 years. Currently the predicted median survival of patients with cystic fibrosis is greater than 50 years [2].

More than 85% of cystic fibrosis patients show evidence of malabsorption from exocrine pancreatic insufficiency [3]. This causes fat malabsorption which leads to multiple nutritional deficiencies in children with cystic fibrosis. This includes various fat soluble vitamins. Studies in children with cystic fibrosis have shown biochemical vitamin E deficiencies in 90–95% of cases [4–6]. Vitamin E deficiency causes various neurological complications including peripheral neuropathy [7].

Although there have been attempts over the last 3 decades to evaluate peripheral nerve dysfunction in patients with cystic

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fibrosis, none of the studies have come up with a definite and conclusive evidence. Most of them have less sample size [8–10]. Very few have tried to study the relation of serum vitamin E levels with peripheral neuropathy [8]. Vitamin E deficiency peripheral neuropathy is completely reversible with vitamin E supplementation.

There are various other nutrients other than vitamin E whose deficiencies cause peripheral neuropathy viz., thiamine (vitamin B1), riboflavin (vitamin B2), pyridoxine (vitamin B6), vitamin B12, folic acid and copper [11]. In this study we reported the frequency and nature of peripheral neuropathy in cystic fibrosis patients and relation of this morbidity with serum levels of micronutrients.

2. Methods

The study was conducted in the Department of Pediatrics, All India Institute of Medical Sciences and Centre for Promotion of Nutrition Research & Training with special focus on North-East, Tribal and Inaccessible population (Indian Council of Medical Research), New Delhi from January to December 2011. Patients with confirmed diagnosis of cystic fibrosis, aged 1–18 years, on vitamin E therapy for at least 6 months were enrolled in the study. Children with cardiorespiratory instability, known neuromuscular disease, family history of inherited muscle/nerve disease, other systemic illness and on any drugs known to cause peripheral neuropathy were excluded. Diagnosis of cystic fibrosis was based on clinical phenotype with two abnormal sweat chloride values of greater than 60 mEq/L.

With an anticipated prevalence of 50% [10], precision of 15%, 95% confidence, sample size calculated was 45. The study was approved by the Institutional Ethics Committee.

All patients underwent detailed age appropriate neurological examination including higher mental functions, speech, cranial nerves, motor functions, sensory functions (pain, touch, temperature, vibration and proprioception in age appropriate manner) and cerebellar system.

Serum vitamin E, vitamin B12, folate and copper levels of the cases were determined at Centre for Promotion of Nutrition Research & Training with special focus on North-East, Tribal and Inaccessible population (Indian Council of Medical Research), New Delhi. Serum vitamin E was measured using HPLC (high performance liquid chromatography), serum vitamin B12 and folate were measured using chemiluminescence whereas serum copper was measured using coupled plasma mass spectrometer.

All enrolled subjects underwent detailed nerve conduction studies following standard protocol. Motor nerves evaluated included median, ulnar, tibial and common peroneal nerves, and sensory nerves evaluated included median, ulnar and sural nerves. Detailed nerve conduction studies of both sides were planned. The parameters evaluated were amplitude of compound muscle action potential of motor nerves, amplitude of sensory nerve action potential of sensory nerves, conduction velocity of motor and sensory nerves, distal latency and F waves for motor nerves and latency for sensory nerves [12,13]. Distal limb temperature was maintained above 33 °C throughout the study [14]. During summer the ambient temperature was high enough to keep the limbs warm, whereas in winter room heaters were used for the same.

After completion of nerve conduction studies, the values of the parameters were matched with normal reference values for age [15]. Abnormal nerve conduction values were classified either as axonal or demyelinating or unclassified neuropathy. Axonal neuropathy was defined as reduced (<80% of lower limit of normal, lower limit of normal being −2.5 standard deviation)/absent CMAP (Compound Muscle Action Potential)/SNAP (Sensory Nerve Action Potential) amplitude with or without low conduction velocity (but not <75% of lower limit of normal) and prolonged distal latencies (but not >130% of upper limit of normal). Demyelinating neuropathy was defined as conduction velocity <75% of lower limit normal, distal latencies >130% of upper limit of normal, with or without conduction block (at least 50% drop in CMAP amplitude between proximal and distal stimulation sites), with or without absent or delayed F wave responses and normal CMAP and SNAP values. If the results were not fulfilling any of these 2 criteria but were abnormal, the neuropathy was labeled as unclassified [16,17].

Patients less than 5 years of age were sedated with oral syrup preparation of Triclophos (20 mg/kg) for electrophysiological study. Cystic fibrosis being a systemic disease, it is expected that if neuropathy is present, it would be a generalized disease. The current recommendation for electrophysiological evaluation of polyneuropathy is evaluation of at least 1 upper and lower limb [17,18]. Of the 45 patients, 35 cooperated for complete evaluation of all 4 limbs, remaining 10 were less than 5 years of age and so they cooperated for evaluation of 1 upper and lower limb. Only 14 patients cooperated for F wave response evaluation as it requires repetitive trains of 10 successive electrical stimulations.

2.1. Statistical analysis

Prevalence of electrophysiologically defined peripheral neuropathy in cystic fibrosis children aged 1–18 years on vitamin E therapy for at least 6 months has been expressed as percentage with confidence interval.

For comparison of the serum level of micronutrients and baseline clinicodemographic variables in patients with and without peripheral neuropathy bivariate analysis was done using Wilcoxon rank sum test, *t*-test or Fisher exact test wherever applicable.

3. Results

3.1. Baseline clinicodemographic profile

Forty five patients attending the Pediatric Chest Clinic, fulfilling the inclusion criteria and with consenting guardians were included in the study. Of the 45 cases, 28 (62.2%) were boys and 17 were girls (37.8%). The mean age at enrolment was 8.35 years (±4.95, range: 1.1–17 years) and the mean age at diagnosis was 37.2 months (±42.7 months, range: 0.25–156 months). The mean FEV_1, percentage predicted FEV_1 (both wherever feasible) and severity of disease score [19] of all