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Effect of Altitude on Age of Loss of Ambulation in Boys with Duchene Muscular Dystrophy

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ABSTRACT

Introduction

Early loss-of-ambulation (LOA) and death at young age are inevitable in Duchene muscular dystrophy (DMD). Definite treatment of DMD is not available till date. Prolongation of ambulation and management of complications is the goal of treatment. In sports, high-altitude training is popular to improve athletic performance. We investigated the influence of altitude on DMD in relation to age at LOA.

Methods

It was a cross-sectional study done on 91 DMD patients, who have lost their ambulation, using the database of Muscular Dystrophy Foundation-Nepal. DMD boys living in different elevations of Nepal were divided into <200m (plain), 200-700m (intermediate), 700-1000m (middle), and >1000m (high) groups, and the age at LOA was recorded. Findings were tabulated and analyzed statistically using student's t-test and Log Rank test, with $p < 0.05$ considered significant.

Results

Out of 91 DMD cases registered, 36 (39.6%), 34 (37.4%) were from plain (Terai) area and high land area of Nepal respectively; accounting 77% of the total patients. The median age at LOA for each group increased with elevation, and the LOA age in the high-land group (median ± SD; 11.20 ± 2.78) was significantly higher than that in the low-land group (9.62 ± 2.02) by about 2 years ($p < 0.005$).

Conclusion

Our study indicated a longer period of independent walking for DMD patients living in high altitude areas. DMD boys might benefit by rehabilitation at higher altitude.

Keywords

Altitude; DMD; loss-of-ambulation; muscle wasting

INTRODUCTION

Duchenne muscular dystrophy is an X-linked recessive genetic disease due to mutation in the dystrophin gene leading to deficiency in dystrophin protein causing progressive muscular atrophy. This rare but fatal disease affects 16 to 20 per 100,000 live birth boys[1]. Usually, patients present at the age of 4 to 6 years with progressive muscle weakness leading to loss of independent ambulation (LOA) by the age of 12 years. Exon-skipping therapy using anti-sense nucleic acids that express dystrophin was proposed to treat DMD, however it has limited use[2,3]. Steroids are widely used because of their ability to preserve muscle strength by inhibiting the progression of DMD [4]. Use of antioxidants to increase reactive oxygen species (ROS) has also been tried[5,6]. There is no definitive treatment for this condition yet, thus more multifaceted treatment is being called for. In sports, high altitude training has been effective to improve athletes' athletic performance[7,8]. However, the correlation between DMD muscle performance and the high-altitude environment has not been studied yet.

Nepal has wide geographical range of elevations, from plain (<200 meters) to the Himalayan region at 8000 meters above sea level (capital Kathmandu located at 1400 meters). This has advantage on doing research on the effects of elevation differences on human health and disease in Nepal[9,10,11].

Effect of sitting culture has been correlated with less incidence of scoliosis among Nepalese DMD boys[12], and the age-related decline in average daily walking steps is somewhat slower in Nepalese DMD boys than in Japanese[13]. We studied the effects of elevation of residence on motor performance in DMD in terms of loss of ambulation (LOA) in Nepalese DMD patients.

METHODS

Duchene Muscular Dystrophy boys registered in Muscular Dystrophy Foundation (MDF)-Nepal, a non-profit making organization working for muscular dystrophy, were subjected in this study. Diagnosis was made by experienced clinicians with more than twenty years of experience in DMD management at MDF-Nepal, who evaluated DMD phenotypes such as typical gait abnormality, Gower's sign, pseudohypertrophy of calf muscle, positive family history, and markedly elevated serum creatinine kinase (CK) levels (>50 times normal). Genetic testing was performed only in 27 boys whose parents could afford the test, and was used as cross checking of clinical diagnosis, but was disregarded in this study. Registered DMD patients who were at least 10 years old and had clear records of residence, date of birth, age at LOA, and administration of steroids were included in this study. If information were unclear, they were excluded from the study.

Subjects were divided into four groups according to the altitude of their residence: plains (Terai <200m), midlands (inner-terai 200 to 700 meters), mid-altitudes (Mahabharat range 700 to 1000 meters), and high uplands (above 1000 meters). Data collected were tabulated and statistical analysis was performed by Student's t-test and Log Rank test, with $p < 0.05$ considered significant. The study was reviewed and approved by Institutional Review Committee of the Institute of Medicine, Tribhuvan University, Nepal.

RESULTS

A total of 91 boys were included in this study. Among the four groups, the plain group was the largest, with 36 patients (39.6%), followed by the highland group with 34 patients (37.4%), and these two groups accounted for 77% of the total patients (Table 1). The remaining 15 patients were in the midland and 6 were in the mid-altitude group, indicating that the distribution of residence corresponded to the distribution of the population in Nepal.

The prevalence rates were 0.22 and 0.25 per 100,000 populations in the plain and highland groups, respectively. The rate of steroid prescriptions in four groups differed from 66.7% to 80.5%, but there were no significant differences between the groups.

The median (95% confidence interval) age at LOA

Table 1. Postoperative Outcomes of patients with and without sepsis

Altitude Group	Zone	Altitude	Population		Patients		Steroid (%)
			(million)	(%)	No.	(%)	
Plain	Terai	<200	15,66	53.7	36	39.6	80.5
Mid-low	Inner Terai	200-700	-	-	15	16.5	75.0
Mid-altitude	Mahabharat	700- 1000	-	-	6	6.6	66.7
Upland	Higher	> 1000	13,52	46.3	34	37.4	79.4

was lowest in the plain group (9.00 years (8.17-9.83 years), followed by the midland and mid-altitude groups, increasing with elevation, and the highest in the highland group (11.00 years (10.14-11.86 years) (Figure 1). There was a 2-year difference in median age at LOA between the highlands and plains group indicating that DMD patients living in highland areas (>1000 meters) were able to walk independently 2 years longer than those living in plains (<200 meters). The mean (95% confidence interval) estimate of age at LOA also showed a difference of about 1.8 years for the highland group (11.38 (10.39~12.38) than for the plain group (9.63 (8.96~10.29).

Kaplan-Myer curves for age at LOA were generated for the upland and plain groups and compared (Figure 2). The mean age of LOA was 11.38 (10.39~12.38) years and 9.63 (8.96~10.29) years for the highlands and plains groups, respectively. The curves showed a clear and statistically significant difference between the two groups (p <0.004). These results suggest that the upland environment inhibits DMD progression.

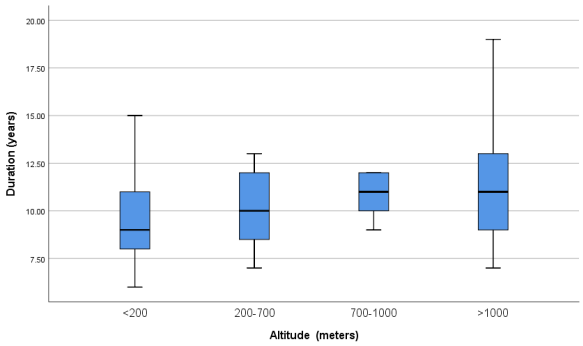

Figure 1. Comparison of median age at LOA for the four altitude groups.

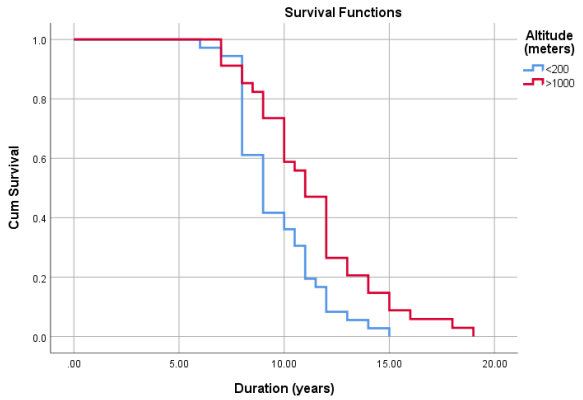

Figure 2. Kaplan-Meier curves for age at LOA. Age at LOA was plotted for the flatland group (blue line) and the highland group (red line). The mean age of LOA was 11.38 (10.39~12.38) years and 9.63 (8.96~10.29) years for the highlands and plains groups, respectively.

DISCUSSION

The current study showed that DMD patients living in the highlands of Nepal were significantly older at the time of LOA and walked independently for two years longer than those living in the plains. Steroid administration has been reported to increase the duration of independent walking[14]. However, the rate of steroid prescriptions was not particularly high in the upland group, making it unlikely that steroid prescriptions were involved in prolonging the duration of independent walking. Socio-economic factors may play a role in the treatment of diseases. Some of the patients in the highland group live in Kathmandu, the capital of Nepal, and it is assumed that they live in an area with a superior economic or residential environment, but many of them live in remote hilly areas of Nepal where developmental infrastructures are not developed. However, this point could not be adequately examined at this time, and future studies are needed. Difference in oxygen concentration due to the difference in elevation may have an effect on muscle performance. In sports, high-altitude training is recommended to be performed at 2000 m above sea level[7]. Therefore, DMD patients in the high-altitude group living around 1400 meters above sea level are likely to be in an environment close to high altitude training on a daily basis.

In DMD muscle cell undergo fatty degeneration due to dystrophin deficiency. Type II fast muscle fibers, which have high glycolytic enzyme activity and exert instantaneous force, undergo fatty degeneration earlier, while type I slow muscle fibers, which are mitochondria-rich and exert endurance force, and are predominate[15]. The fact that these slow muscle fibers are more resistant to dystrophin deficiency suggests that promoting the conversion of fast muscle fibers to slow muscle fibers in DMD may result in increased residual muscle mass. The conversion of fast to slow muscle fibers not only occurs in pathological hypoxia, but also in high altitude environments where oxygen levels are lower[16]. At high altitude, hypoxia increases the expression of hypoxia inducible factor, leading to the expression of Peroxisome proliferator-activated receptor (PPAR) γ coactivator 1α (PGC1α), and an increase in mitochondria[17]. There are number of signaling pathways and regulatory factors that promote transition of fast skeletal muscle fiber to a slower more oxidative, utrophin rich muscle fibers that are resistant to dystrophin deficiency.[18]

It is assumed that these molecular changes lead to an increase in slow muscle fibers in DMD patients in the upland group, resulting in the higher LOA age

in this study. Future analysis on conversion of fast to slower muscle fibers by doing muscle biopsy of DMD boys will put light on it. Also, increased mitochondria may repair mitochondrial damage in DMD[19]. Besides difference in oxygen concentration between highland and plain, difference in temperature and other living conditions may have role in progression of DMD[20], that needs further study.

Serial CT scans or muscle biopsy to objectively assess the progression of muscle atrophy would make the study more scientific. However, exposure hazard and invasive procedures are of ethical concerns. The clinical course of DMD differs depending on the type of genetic abnormality of the dystrophin gene[21]. However, genetic testing was expensive, and genetic diagnosis was performed in only a limited number of cases, making it impossible to study genetic abnormalities and age at LOA.

The results of this study indicate that providing DMD patients with an elevated environment may extend the duration of ambulation. Just as resistance training under hypoxia is now being considered as a new treatment for sarcopenia[22], it is hoped that new strategies to control the progression of DMD will be established based on these results.

CONCLUSION

Duchene Muscular Dystrophin boys living in higher altitude might walk independently with longer LOA thus rehabilitation for DMD boys might be preferred in higher altitude for prolonged ambulation. Living at a higher altitude might be one of the factors for longer independent walking among DMD boys, thus rehabilitation programs at high-altitude might be helpful for longer age of LOA.

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CONFLICT OF INTEREST

The author(s) declare that they do not have any conflicts of interest with respect to the research, authorship, and/or publication of this article.

AUTHOR CONTRIBUTIONS

All authors contributed to conceptualize, collect and analyze data and prepare the manuscript.

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