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Restriction of lung volumes but normal function of pulmonary tissue in mulibrey nanism

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Abstract

Background: Mulibrey nanism (MUL) is a rare growth restriction disorder with multiple organ manifestations caused by genetic defects affecting the TRIM37 protein. A perimyocardial heart disease is the most serious manifestation. Many MUL children appear to suffer from airway obstruction related to infection or exercise, prompting use of inhaled therapies. Asthma medication is continued up to adolescence or even to adulthood due to persisting of symptoms. The pulmonary pathophysiology has previously not been evaluated in any MUL cohort.

Methods: Thirty three finnish MUL patients (median age 20 years) were investigated with several lung function tests: spirometry with bronchodilatation test, single-breath diffusing capacity for carbon monoxide, single-breath lung volume measurements with helium dilution, and thoracic gas volume, airway resistance and specific conductance measurements with a body plethysmograph. As MUL typically affects body proportions, all variables were compared with reference values and with predicted values calculated from sitting height.

Results: Total lung capacity and forced vital capacity were markedly reduced (total lung capacity [TLC] and forced vital capacity [FVC], $P < .001$, 51%-63% of predicted) and also forced expiratory volume in the first second was reduced (FEV₁; $P < .001$, 47%-57%). No signs of airway obstruction was seen (normal FEV₁/FVC and specific airway conductance SGaw). Diffusing capacity (DLCO) was decreased ($P < .001$, 60%-67%) but when related to alveolar volume it was increased (DLCO/VA, $P < .001$, 130%-148%). Bronchodilatation suggesting active asthma (FEV₁ change $\geq 12\%$ and ≥ 200 mL) was found only in one patient.

Abbreviations: BNP, B-type natriuretic peptide; DLCO, diffusing capacity for carbon monoxide; DLCOc, hemoglobin corrected diffusion capacity; FEV₁, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; MEF₂₅, maximal expiratory flow at 25% of FVC; MEF₅₀, maximal expiratory flow at 50% of FVC; MUL, Mulibrey nanism; PEF, peak expiratory flow; Raw, airway resistance; RV, residual volume; RVEF, right ventricular ejection fraction; sGaw, specific airway conductance; TGV, thoracic gas volume; TLCb, total lung capacity in body plethysmography; TLCHe, total lung capacity with helium dilution technique; VA, alveolar volume; VC, vital capacity.

Johanna Sivunen and Päivi Piirilä contributed equally to this work.

Conclusion: MUL patients typically have volume restriction of the lungs, but function of the pulmonary tissue remains intact. Evidence of asthma in lung function testing at adult age is rare.

KEYWORDS

lung function, MUL, TRIM37

1 | INTRODUCTION

Mulibrey nanism (MUL) is a rare inherited disorder with multiorgan manifestations caused by mutations in TRIM37 gene encoding TRIM37 protein with unknown function. Growth restriction with prenatal onset is the most essential clinical feature. Patients are short (adult height less than 3 SD below population median) and gracile, with a small and bell-shaped thoracic cage, thin ribs, and slender extremities (Figures 1 and 2). The head growth is normal, and mild muscular hypotonia is the only neurological abnormality.¹

In children with MUL, respiratory tract infections together with feeding difficulties are the most common problems. In an earlier study from our group, 47% of the infants were diagnosed with pneumonia before the age of 2 years. Further, 25% of the infants had episodes of respiratory failure induced by an infection.¹ The reason for this susceptibility is not known and no immunological defects have been established. Our institution has since the 1970s administrated the clinical care and follow-up of Finnish MUL patients. According to our clinical experience, a substantial part of MUL patients appear to suffer from airway obstruction related to infection or exercise, prompting use of inhaled therapies during childhood. Continuation of asthma medication is due to persisting of symptoms up to adolescence or even to adulthood.

In thoracic X-rays the patients usually have normal pulmonary findings. The most severe manifestation of MUL is cardiopathy with

constriction of the pericardium and restriction of the myocardium, leading to diastolic dysfunction.^{2,3} However, respiratory symptoms are present also in patients with no clinical signs of heart disease. The aim of this study was to characterize the lung function disturbances of MUL patients in detail, an issue not systematically studied before.

2 | PATIENTS AND METHODS

We examined the lung function of 33 Finnish MUL patients, median age 20 years (15–49), who visited Helsinki15(naniTcois8.8(wa/F65(n007)-33.

(approval numbers 420/E7/2001 and HUS/1538/2016§38). Informed consent was obtained from all patients or their guardians.

2.1 | Spirometry

Spirometry was performed using a rolling seal spirometer (CPI 220; Cardio Pulmonary Instruments; Houston, TX) connected to a microcomputer system (Medikro 202; Medikro Oy; Kuopio, Finland) according to European recommendations of the time of the studies.⁵ The results from the envelope curve of at least three superimposed forced expiratory flow volume curves were recorded. Slow vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), peak expiratory flow (PEF) as well as maximal expiratory flow rate at 50% and 25% of the FVC (MEF₅₀ and MEF₂₅) were determined with the patient in the sitting position. Reference values for Finnish adults and adolescents were used.^{6,7} Bronchodilation tests with inhaled salbutamol aerosol (0.4 mg) (Ventoline, Glaxo, UK) were performed to 17 males and 15 females.

2.2 | Diffusing capacity

A single breath diffusing capacity test (Master Lab; Erich Jaeger, Würzburg, Germany) was used for measurement of diffusing capacity of the lungs for carbon monoxide (DLCO) and total lung capacity with single breath helium dilution method (TLCH_e). The reference values for adult Finns and European adolescents were used, obeying the guidelines of the European Respiratory Society.⁸⁻¹⁰ DLCO was corrected for the patient's actual hemoglobin concentration (DLCO_c). The mean value of two successive measurements was recorded for the analysis and compared with the predicted values.

2.3 | Body plethysmography

Thoracic gas volume (TGV), airway resistance (Raw), and specific airway conductance (sGaw) were measured using a constant volume body plethysmograph (Bodyscreen II; Erich Jaeger; Würzburg, Germany) during tidal breathing timed with a metronome (30/min).¹¹ The mean value of three to five determinations was recorded for analysis. VC, TLC measured using body plethysmograph (TLC_b), residual volume (RV), and functional residual capacity were calculated based on slow spirometric measurements and TGV measurement. Reference values of adult Finns and European adolescents were used.^{9,11} The nonventilated lung compartment was calculated as the difference between TLC_b and TLC_{He}.

2.4 | B type natriuretic peptide (BNP)

Plasma BNP was determined from fasting venous blood samples taken from an antecubital vein after the patient had rested for 15 minutes in the sitting position using a standard method. The upper limit of the normal range was 18.7 ng/L.³

2.5 | Statistics

The statistical analysis was performed using IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY). Measured values of lung function variables were compared with two sets of reference values; those based on actual height and those conducted from sitting height. Comparisons were made with paired T test for normally distributed parameters and otherwise with the Wilcoxon signed rank test.

Different patient groups were compared with Student T test for normally distributed parameters and otherwise with the Mann-Whitney U test. P values below 0.05 were considered statistically significant.

3 | RESULTS

The lung function of 33 Finnish MUL patients was investigated with various lung function tests (Table 2).

3.1 | Spirometry and body plethysmography

All measured lung volumes (VC, FVC, TLC_{He}, and TLC_b) were significantly lower ($P < .05$, mostly $< .001$) than the reference values based either on actual or estimated height. Lung volumes were about 50% of predicted, based on estimated height (range 45.1–53.6%). Most values were significantly higher as percent of predicted values compared with those measured as percent of estimated reference values. No significant difference of percentage values was found between men and women by any lung volume variable (Figure 3A).

Also the parameters FEV₁ and MEF₅₀ were significantly reduced ($P < .001$, men and women), as well as PEF_R $< .01$ in women, $P < .001$ in men, range 33.0

estimated height predicted values). Raw was higher than estimated height predicted ($P < .001$ in women and $P < .01$ in men), but sGaw did not differ from the predicted values, except for one patient. RV/TLC was not elevated in any comparisons. In Figure 3B and 3C individual values of FEV₁/FVC, RV/TLC, SGaw and Raw are shown.

3.2 | Diffusing capacity

DLCO corrected with actual hemoglobin (DLCOc) was significantly reduced both in women and men ($P < .001$, around 60–67% of estimated height predicted values), but when related to effective alveolar volume (DLCOc/VA) it was significantly higher than predicted values ($P < .001$, range 130–148% of estimated height predicted values). Individual data are presented in Figure 3D. Nonventilated lung compartment was on average normal (0.21–0.23l).

3.3 | Bronchodilatation test

In the bronchodilatation test (Table 3) the mean increase of FVC was 3% in men and 1% in women and in every subject less than 47 ml. The mean increase of FEV₁ was 98 ml in men and 71 ml in women (both 5%). Four of 15 women and 1 of 17 men showed an increase of FEV₁ at least by 12%. Among those, the absolute FEV₁ change varied from 160 to 230 ml. Only one patient showed an increase of FEV₁ at least by 12% and 200 ml, suggesting asthma.¹²

The female patients on steroid medication showed significantly lower values of FEV₁/FVC and MEF50 in absolute values and as % predicted, as well as FEV₁/FVC as % estimated height predicted, than those with no medication. Likewise, Raw values were higher in patients on medication.

3.4 | Cardiac parameters

Pericardiectomy had earlier been performed to nine male (53%) and four female (25%) patients. The heart function and structure of all patients was studied earlier with pulsed Doppler echocardiography.³ Significant diastolic dysfunction of the left ventricle¹³ was diagnosed in seven males (41%) and four females (25%). The BNP level in blood was slightly elevated (over 18.7 ng/L) in 6 of 17 males (35%) and 11 of 16 females (69%). The lung function variables showed no significant differences, when patients with diastolic dysfunction were compared with patients with normal heart function. Right ventricular ejection fraction (RVEF) did not correlate significantly with the lung function variables. For further information on cardiac parameters please see Table 1.

4 | DISCUSSION

The results show marked volume restriction of the lungs in MUL patients; VC and TLC were around 50% of the predicted values. The ventilatory capacity in terms of FEV₁ was also markedly limited

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