13 Pneumologie 3.2010:Pneumologie 2.2009 10/1/10 11:14 AM Page 170

Pneumologia vol. 59, nr. 3, 2010

PNEUMOLOGIE PEDIATRICĂ

Determination of mortality from cystic fibrosis

Nooshin Baghaie, Soheila Kalilzadeh, Maryam Hassanzad, Nazanin Parsanejad, AliAkbar Velayati

Pediatric Respiratory Diseases Research Center, NRITLD
Shahid Beheshti, University of medical sciences, Tehran, Iran

REZUMAT

Determinanții mortalității în fibroza chistică

***Context**: stabilirea prognosticului în fibroza chistică (CF) și evaluarea impactului indicatorilor de mortalitate sunt foarte importante în prezicerea speranței de viață a pacienților cu CF.*

***Obiective**: determinarea impactului a șapte variabile – sex, volumul expirator maxim pe secundă (FEV1), Body Mass Index (BMI), examenul bacteriologic, hemoglobina (Hb), presiunea în artera pulmonară (PAP) și numărul internărilor anterioare – asupra duratei de supraviețuire a 27 de pacienți internați în secția de Pediatrie a spitalului Masih Daneshvari în intervalul 2007-2009.*

***Metode**: în cadrul acestui studiu retrospectiv cros-secțional, au fost incluși 27 de pacienți cu CF. Datele referitoare la aceștia au fost colectate pe perioada a 2 ani de studiu. Datele pacienților care au decedat au fost comparate cu ale celor rămași în viață prin testele t și Chi-pătrat.*

***Rezultate**: au fost studiați 27 pacienți cu CF (11 fete, 10 băieți) cu vârste cuprinse între 5-19 ani și vârsta medie 13.11±4.69. Nu au existat diferențe semnificative statistic în ceea ce privește vârsta, sexul, FEV1, BMI, Hb, între grupul care a supraviețuit și cel al decedaților ($p> 0.05$).*

PAP medie pentru grupul decedaților, respectiv al supraviețuitorilor, a fost de 40 ±15.1 și respectiv 68 ± 11.5. Numărul internărilor în spital în timpul ultimelor 6 luni a fost mai mare în grupul celor care au decedat. 50 % dintre cei rămași în viață erau colonozați cu Pseudomonas, comparativ cu grupul decedaților – cu 100% colonizare cu Pseudomonas. A existat o corelație puternică între decese și numărul internărilor anterioare, PAP și infecția cu Pseudomonas ($p<0.05$).

***Concluzii**: infecția cu Pseudomonas, numărul internărilor anterioare și severitatea hipertensiunii pulmonare s-au dovedit a fi predictorii majori de mortalitate în studiul nostru.*

***Cuvinte cheie:** prognostic, predictori, speranța de viață, hipertensiune pulmonară, infecții pulmonare*

ABSTRACT

***Background**: Assessing the prognosis of cystic fibrosis (CF) and evaluating the effect of indicators of mortality is very important in predicting the life expectancy of the CF patients.*

***Objective**: Determining the effect of seven variables including sex, Forced Expiratory Volume in one second (FEV1), Body Mass Index (BMI), bacteriology, hemoglobin (Hb), pulmonary arterial pressure (PAP) and the number of previous admissions on the survival of 27 patients admitted in Pediatric Pulmonary Ward of Masih Daneshvari Hospital in 2007-2009.*

***Methods**: 27 CF patients were enrolled in a retrospective cross-sectional study. Patients data were collected during 2 years of study. Data of patients who died and those who remained alive were compared by independent samples t-tests and Chi-square.*

***Results**: Twenty seven CF patients (11 female, 10 male) with age range of 5-19 years and mean age of 13.11±4.69 were studied. There was no difference in age, sex, FEV1, BMI, Hb between the deceased and alive group ($p> 0.05$).*

Mean PAP for expired patients and alive patients was 40 ±15.1 and 68 ± 11.5 respectively. The number of admissions during last 6 months was dominant in those patients who died. 50 % of the alive patients were colonized with Pseudomonas. This is compared to deceased patients which 100 % were colonized with Pseudomonas .

There was a strong correlation between death and number of previous admissions, PAP and Pseudomonas infection ($p<0.05$).

***Conclusion**: Pseudomonas infection, number of previous admissions and the severity of pulmonary hypertension has shown to be the major predictors of mortality in our study.*

***Key words**: prognosis, predictors, life expectancy, pulmonary hypertension, pulmonary infections*

Contact: Dr. Soheila Khalilzadeh, Pediatric Ward,
Masih Daneshvari Hospital, Darabad, Shahid Bahonar,
Niavaran, Tehran, Iran
Fax: 0098-21-26109549, email: P_nritld@yahoo.com

13 Pneumologie 3.2010:Pneumologie 2.2009 10/1/10 11:14 AM Page 171

Introduction

Cystic fibrosis (CF) is a fatal autosomal recessive disorder[1]. The majority of patients die as a result of respiratory diseases. New and intensive treatments have improved the prognosis and life expectancy in these patients through last decades[2,3], but CF is still responsible for significant morbidity and early death[2,4].

Evaluation of prognosis of CF patients is of great value as it may influence the survival and postpone lung transplantation time[5]. There are many prognostic indicators and many studies have considered the effect of these indicators in cystic fibrosis survival[6,7,8]. FEV1, gender, age, nutritional status, genetic abnormalities, presence of *Pseudomonas* or *Burkholderia Cepacia* and other indicators have been defined as the variables associated with survival age. In most studies, FEV1 has been shown to be the most significant predictor of survival[6,7,9].

Upon our knowledge there was no study to identify the survival indicators in CF patients in Iran, therefore the aim of this study was to determine the effect some risk factors such as gender, FEV1, BMI, sputum culture, pulmonary artery hypertension, blood hemoglobin, pulmonary exacerbation during last six months on survival of our patients admitted in Pediatric Pulmonary Ward of Masih Daneshvari Hospital during 2007-2009.

Methods

27 CF patients were enrolled in a retrospective cross-sectional study in Masih Daneshvari Hospital during 2007-2009. All CF patients were diagnosed by 2 positive sweat test (Cl>60mg/l) and clinical manifestations compatible with CF[10]. Those who had suspicious sweat tests and no positive chromosomal analysis were excluded from the study. Patients data were collected from their files including sex, BMI, FEV1, PAP, Hb, Sputum culture, number of admissions due to pulmonary problems during last six months and the history of ICU admissions.

Data of patients who died and those who remained alive were compared by independent samples t-tests and Chi-square. A p value [0.05 was considered statistically significant. This study has been approved by the ethical committee of Masih Daneshvari Hospital.

Results

Twenty seven CF patients (11 female, 10 male) with age range of 5-19 y and mean age of 13.11± 4.69 were studied.

Patients' characteristics are summarized in table I.

The mean age of patients who died and those who remained alive was 15.14 ± 5.7 and 12.7 ± 4.54, respectively. There was no relation between age and death (p>0.05).

In the whole group there were 16 male patients and 11 female patients in comparison to the proportion of male to female in deceased patients which was 3 to 4. No correlation was found between sex and death (p>0.05).

FEV1 results were missing in 7 patients who were under 7 yrs and couldn't cooperate to perform the pulmonary function test. The mean FEV1 % predicted for deceased patients was 19.42 ± 6.75 and for alive patients was 33.46 ± 19.13. All the patients who died had a result of FEV1<70%. We couldn't find any correlation between FEV1 % predicted and death (p>0.05).

No significant difference was found between mean body mass index (BMI) of patients who died and those who survived (13.85 ± 1.75, 14.52 ± 1.71).

Table I.
Characteristics of the study group

Variables	Mean
No. of Patients:27	F: 11 M:16
Age	13.11 ± 4.69
FEV1	29.45 ±17.61
BMI	14.32 ± 1.7
PAP	33.2 ±13.9
Hb	12.14 ± 2.05
Admission number	1.9 ± 1.7

FEV1: Forced Expiratory Volume in 1 second
BMI: Body Mass Index
PAP: Pulmonary Arterial Pressure
Hb: Hemoglobin

Mean PAP for deceased patients and alive patients was 40 ±15.1 and 68 ± 11.5 respectively. 71.4% of deceased patients were distributed in the severe group (PAP>40mmHg) in comparison to those who remained alive, where only 16.7% of patients were distributed in the severe group and the majority of them (44.3%) had PAP result in the normal range. The result showed a correlation between death and pulmonary hypertension severity (p<0.05).

To compare the mean Hb results of deceased and alive patients no significant difference was found and no relationship was detected between Hb and death (p>0.05).

The number of admissions during last 6 months due to exacerbation of pulmonary problems was dominant in those patients who died. The proportion of mean admission days in deceased and alive patients was 3.5 ± 1.3 to 1.7 ± 1.4. There was a strong correlation between death and number of previous admissions (p<0.05). None of those patients who were alive had the history of ICU admission.

50 % of the alive patients were colonized with *Pseudomonas* and 15 % were colonized with *Staphylococcus aureus*. This was compared to deceased patients which were 100 % colonized with *Pseudomonas* and 14.3 % were colonized with *Staphylococcus aureus*.

The results showed a significant correlation between *Pseudomonas* colonization and death (p<0.05).

Association of each variables with death is summarized in the table II.

Table II.
Association of variables with death

Variable	P_value
Sex	0.391
Age	0.244
FEV1	>0.05
BMI	0.393
Pseudomonas	**0.026**
Staph. aureus	>0.05
Hb	0.616
PAP	**0.004**
Number of admissions	**0.002**

13 Pneumologie 3.2010:Pneumologie 2.2009 10/1/10 11:14 AM Page 172

Discussions

Determining the indicator of mortality is a major challenge to evaluate the prognosis and changing the background of treatments.

We developed a study that evaluate the influence on survival of 7 variables in 27 patients admitted in Masih Daneshvari Hospital during 2007-2009 and compared the results between patients who died and those who remained alive.

Mean age of patients who died was higher in comparison to those who survived, but we couldn't find any association between age and death ($p>0.05$).

Female gender is an important predictor of mortality due to previous reports[3,5] although we couldn't demonstrate any relation between sex and death in our study ($p>0.05$). Limitation in the number of patients under the study could be a explanation of this results.

FEV1 is the basis of many survival models in CF[5,7,11,12]. In a previous study by J.M Courtney *et al*, lung function showed a lower result in patients who died in comparison to alive patients and that study suggested the FEV1 as a significant predictor of mortality[6].

Kerem *et al*, in a 12 year following up study suggested that patients with FEV1 less than 30% had the chance of dying within 2 year for 50%[5].

P. Aurora *et al*, through their study confirm that children with FEV1 of 30% predicted should be considered for lung transplantation although they suggest that regular assessment of FEV1 could be a better indicator than a single FEV1[11-13].

In our study we couldn't find any correlation between FEV1 % predicted and death ($p>0.05$) and we couldn't consider the lung function test as a prognostic indicator.

FEV1 result missing in 7 patients and the lack of regular measurement of FEV1 and judge on a single FEV1 is the cause of this contradiction between our study and other studies which majority of them indicate FEV1 as a significant indicator of mortality.

The lack of neonatal screening and absence of evaluation for genetic mutation in Iran have led to give the diagnosis only in the basis of clinical manifestations and sweat test resulting in higher age range of the patients compared to global statistics and this may lead to deterioration of lung function and other clinical manifestation in all of our patients in different ages.

BMI has shown to be an important predictor of survival in CF patients[14,15] but we couldn't demonstrate a correlation between BMI and death in our study ($p>0.05$) and the reason could be the impaired nutritional status in all of our patients.

Kerem *et al*[5] studied the survival of 673 patients from a pediatric hospital and found the influence of weight as an indicator of survival to be of small value particularly in younger patients.

J.M Courtney *et al*[6] recognized that BMI was not a significant predictor of survival in their population but BMI showed a correlation with lung function.

The results of our study found a correlation between *Pseudomonas* colonization and death ($p<0.05$). 50% of surviving patients and all patients who died were colonized with *Pseudomonas*. Many studies had shown that early infection with *Pseudomonas* is a great indicator of survival[6,16,17]; however some others considered the *Pseudomonas* infection as a cause or a consequence of pulmonary function test.

A study of Mary Corey and Vernon Farewell[18] demonstrated that *Ps. aeruginosa* largely reflected the effect of declining FEV1 in survival analysis and suggested a longer follow-up to determine the association between pulmonary obstruction and *Ps. aeruginosa* colonization.

Non of our patients had *Burkholderia Cepacia* infection. Theodor G Lious *et al*[8] suggested that infection with *Burkholderia Cepacia* had the most important effect on 5 year survival. The same result was found in previous reports[19,20].

Other bacterial infection in our patients include *Staph. aureus, Candida, Aspergillus* and Staph. coagulase negative.

We evaluated the pulmonary arterial hypertension in all patients. Our study results showed a correlation between death and severity of pulmonary hypertension ($p<0.05$) and PAP has shown to be one of the major predictors of mortality in our population.

Hemoglobin (Hb) as a marker of nutrition was also assessed in our study to determine the relation with death but no correlation was found ($p>0.05$). By the time all our patients had a poor nutritional condition, Hb as an indicator of nutritional status was expected to be impaired.

Haylar *et al*[21] considered Hb as a useful predictor at the time of initiation of their study but they didn't considered it in the final model.

Comparison of the number of admissions during last 6 months in the group of deceased patients and those who remained alive, revealed a significant higher mean in the deceased group. The results showed a strong correlation between previous admissions and death ($p<0.05$).

Theodore *et al*[8] in a 5 year study confirmed that each acute pulmonary exacerbation have a negative impact on the 5 year survival.

Beside the number of previous admissions, which was significantly higher in the deceased patients, all of these patients had a history of ICU admissions, when compared to alive patients.

In conclusion, the number of previous admissions as a marker for exacerbations was shown to be the strongest predictor in our patients. *Pseudomonas* infection and the severity of PAP were the other predictors of mortality in our study.

Our study had its own limitations including the small sample size and its retrospective pattern. Following up the patients and monitoring the lung function and nutritional status and their rates of decline in patients is very important in assessing the effect of these variables on survival, on the response to therapy and for finding the best time for transplantation.

References

1. Tizzano Ef, Buchwald M. Cystic fibrosis: beyond the gene to therapy, *J pediatr* 1992;12:337-49.

2. Dode JA, Morison S, Lewis PA, Coles FC, Geddes D, Russet G. Incidence ,population and survival of cystic fibrosis in UK,1968.UK cystic fibrosis survey management committee, *Ach dis child* 1997;77:493-496.

3. Elborn JS, Shale DJ, Britton JR. Cystic fibrosis : current survival and population stimation to the year 2000. *Thorax* 1991;46:881-85.

4. Sharma R, Florea VG, Bolger AP, et al.Wasting as an independent predictor of mortality in patients with CF. *Thorax* 2001; 56: 746-750.

5. Kerem E, Reisman J, Corey M, Canny G. Prediction of mortality in patients with cystic fibrosis, *NEng J Med* 1992;32:1187-1191.

6. JM Courtney, JBradly. J Mccaughan, TM Oconnor, C short. Predictors of mortality in adults with cystic fibrosis. *Pediatric Pulmonology* 2007;42:525-532.

7. Corey M, Edward L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. *J pediatr* 1997;131:809-814.

8. Theodore G Liov, Frederick R Adler, Stace C Fitzsimmons, Barbara C CGhill. Predictive 5 year survivalship model of cystic fibrosis. *AmJ Epidemiol* 2001;153(4):345-352.

13 Pneumologie 3.2010:Pneumologie 2.2009 10/1/10 11:14 AM Page 173

9. Rosenfeild M, Davis R, Fitzsimmons,et al. Gender gap in cystic fibrosis mortality 1997 ; 145 :794-803.

10. Klieman, Behrman, Jenson, Stanton. Nelson Textbook of Pediatrics, 2007,18 th ed . vol 2. p. 1806-08.

11. P. Aurora, A. Wade, P. Whitemore, B. Whitehead. A model for predicting life expectancy of children with Cystic fibrosis. *Eur Respir J* 2000;16:1056-1060.

12. Mila CE, Warwick WJ, Risk of death in Cystic fibrosis patients with severely compromised lung function. *Chest* 1998;113:1230-1234.

13. Haung NN, Schidlow DV, Szatrowski Th, Palmary J. Clinical features, survival rate and prognostic factor in young adults with CF. *AM J Med* 1987; 82 :871-879.

14. Elborn Js, Bell Sc. Nutrition and survival in cystic fibrosis. Thorax 1996; 51:971-972.

15. Durie PR, Pencharz PB. Cystic fibrosis nutrition. *Br Med Bull* 1992; 48 :823-846.

16. Henry Rl, Mellis CM.Petrovic L. Pseudomonas aeroginosa is a marker of poor survival in patients with Cystic fibrosis. *Pediatr Pulmonol* 1992; 12 :158-161.

17.Gibsa Rl. Pseudomonas aeroginosas and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol* 2002 ; 34: 91-100.

18. Mary Corey , Vernon Farewell.Determinants of mortality from cystic fibrosis. 1970-1989. *Am J Epidemiol* 1996, 143: 1007-17.

19. Aris RM, Gilligan PM, Neuringer IP, et al. The effects of panresistant bacteria in cystic fibrosis patients on lung transplant outcome. *Am J Respire Crit Care Med* 1997; 155:1699-704.

20. Snell GI, Hoyos A, K rajden M, et al. Pseaudomonas, cepacia in lung transplant recipients with cystic fibrosis. *Chest* 1993 ; 103 :466-71.

21. KM Hayllar, SG Williams, AE Wise et al. A prognostic model for the prediction of survival in cystic fibrosis. *Thorax* 1997;52:313-317.