ECRONICON OPEN ACCESS

EC PAEDIATRICS
Research Article

Birth Defects among Patients with Cystic Fibrosis

N Rohovyk[1]*, N Kitsera[2], L Bober[3], H Makuh[2], O Marushchak[1] and M Rohovyk[4]

[1]*Danylo Halytsky Lviv National Medical University, Ukraine*

[2]*Institute of Hereditary Pathology of the National Academy of Medical Sciences of Ukraine, Lviv, Ukraine*

[3]*Western Ukrainian Specialized Children's Medical Centre, Lviv, Ukraine*

[4]*Helsingborgs hospital, Helsinborg, Sweden*

***Corresponding Author**: N Rohovyk, Danylo Halytsky National Medical University, Ukraine.

Received: June 10, 2020; **Published:** June 24, 2020

DOI: 10.31080/ecpe.2020.09.00738

Abstract

Introduction: Cystic fibrosis (CF) is an inherited disorder that characterized severe damage to the lungs, digestive system and other organs in the body. It is caused by mutations of the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The incidence of CF is one case per 2500 live births in Caucasians. The prevalence of CF in Ukraine is 1: 8400 and in the western part of it is 1:5917. Birth defect (BD) is structural or functional anomaly of the body that affects 1 in every 33 babies born. The frequency of BD in Ukraine is 3 - 5% of general amount newborns.

The Aim of the Research: to analyze and calculate the frequency of birth defects among patients with CF.

Methods: The study includes 181 CF patients from different regions of Ukraine, which monitored in Western Ukrainian Specialized Children's Medical Centre, Lviv Cystic Fibrosis Center. All of them had the identification of gene of cystic fibrosis transmembrane conductance regulator (CFTR) in the Institute of Hereditary Pathology of the Ukrainian Academy of Medical Sciences (Lviv). BD diagnose was made among CF patients according to international classification of diseases 10th edition (ICD-10) and chapter XVII code Q.

Results: BD were registered in CF patients more frequently (8,2%) than in general population (3 - 5%) in Ukraine. It was occurred more often in females than in males (11.62% vs 5.26%). The most frequent CFTR mutations among CF patients with BD were homozygous F508del and compound heterozygotes F508del/G542x. CF patients has the same prevalence of such BD as hepatobiliary and congenital heart defects that were registered in 4 (27%).

Conclusion: BD in CF patients are more common than in general population in Ukraine. It makes many problems because of combination in one child two severe disease that makes shortness of life and serious prognosis. To study deeper of prevalence and appearance mechanisms will help to find humanity options for prevention and prognosis.

Keywords: *Cystic Fibrosis (CF); Cystic Fibrosis Membrane Conductance Regulator (CFTR); Birth defects (BD); Mutation F508del*

Introduction

Cystic fibrosis (CF) is the most common autosomal recessive disorder among white populations with multiorgan pathology that characterized chronic airway infection, pancreatic insufficiency, gastrointestinal dysfunction, male infertility and others. It is caused by a mutation in the cystic fibrosis membrane conductance regulator (CFTR) protein [1-4].

The evaluation of long-term calculations shows that the incidence of CF is one case per 2500 live births in Caucasians. Due to newborn screening program and CF registry the estimation determines exactly distribution of CF in Europe: Ireland - 1:353, United Kingdom - 1:2381, Germany - 1:3300, Spain - 1:3750, Italy - 1:4238, Denmark - 1:4700, France - 1:4700, Netherlands - 1:4750, Portugal - 1:6000, Finland - 1:25000, The number of reported CF patients in West Asia is 1:4000 - 10,000, in East Asia is 1:100,000 - 350,000. The statistics in Japan is 1:350,000. The prevalence of CF in the US Whites is 1:2900. In Canada, the data are 1: 2500. In South America the data are depending on regions and countries of residence - 1:3500 - 8500. In Australia is 1:2021 because of the Britain immigrants [5-18]. The results of newborn screening program in Ukraine during 2013 - 2014 yy shows the prevalence of CF 1: 8400 generally in the country and in the western part of it is 1:5917 [19,23].

Birth defects (BD) are structural or functional anomaly as result of inborn errors of development that caused by genetic abnormalities and/or environmental exposures. There is registry European Concerted Action on Congenital Anomalies and Twins (EUROCAT) helps to estimate structural defects (congenital malformations, deformations, disruptions, dysplasia) and chromosomal abnormalities. It was calculated that the major birth defects are common and they occur in 1:33 births [20,21]. The frequency of BD in Ukraine is 3 - 5% of general amount newborns [22].

Aim of the Research

To analyze and calculate the frequency of birth defects among patients with CF.

Materials and Methods

There were 181 patients registered on the CF Lviv database (West part of Ukraine) during 2016 - 2019 years, of which 15 patients had birth defect according to international classification of diseases 10th edition (ICD-10) were grouped to chapter XVII and coded Q. Their age was from 3 months to 35 years old. Among them were 95 boys and 86 were girls, 109 patients were urban citizens and 72 patients were village citizens. All CF patients were analyzed and monitored in Western Ukrainian Specialized Children's Medical Centre, Lviv Cystic Fibrosis Center (Ukraine). The identification of gene CFTR was done in the Institute of Hereditary Pathology of the National Academy of Medical Sciences of Ukraine (Lviv).

Results

In our investigation BD were occurred more often in females than in males 10 vs 5 from the sample of 181 patients ($p < 0,05$). Among 95 males with CF only 5 (5.26%) had BD, among 86 females with the same diagnosis 10 (11.62%) had BD too.

During investigation, 13 patients were alive and 2 of them died. The reason of deaths in both cases was respiratory failure in the ages of 15 and 16 years old. These two patients were girls and the BD as bicuspid aortic valve disease and pulmonary valve stenosis.

In the study, the oldest patient had 35 years and the youngest had 3 months (average 14.4 years +- 7.46 SD). The median age when CF diagnosed was 2 years and 3 months and the median age among CF patients when BD diagnosed was 6 years and 4 months.

There were 15 patients with combination of CF and BD who had next mutations distribution of CFTR genes: 6 patients - F508del/F508del, 2 - F508del/G542x, 1 - F508del/2184insA, 1 - F508del/E92K, 1 - F508del/621+1G-T, 1 - F508del/R553X, 1 - F508del/N1303K, 2 - F508del/x (x - unknown mutation). Distribution of CFTR gene mutations among CF patients with BD depending of sex is demonstrated in table 1.

Male (number of patients)	Female (number of patients)
F508del/F508del - 2, F508del/2184insA - 1, F508del/G542x - 1, F508del/x - 1	F508del/F508del - 4, F508del/E92K- 1, F508del/G542x - 1, F508del/R553X - 1, F508del/621+1G-T - 1, F508del/N1303K - 1, F508del/x - 1.

Table 1: *Distribution of CFTR gene mutations among CF patients with BD depending of sex.*

It was found that the most frequent CFTR gene mutations in CF patients with BD were: homozygous F508del (c. 1521_1523delCTT) registered in 40% cases and compound heterozygotes with other mutations in 60% cases respectively. No one case of BD among CF patient without F508del was registered.

Hepatobiliary BD were registered in 4 (27%) CF patients with BD and it was coded as Q44 due to ICD-10. Among them, the hypoplasia of gallbladder were in three cases and liver cyst was in one case. The oldest of these patients has 23 years old and the youngest one is 9 years and 4 months and the sex distribution is 2 girls and 2 boys.

Congenital heart defects were diagnosed in 4 (27%) cases: pulmonary valve stenosis coded Q22.3, structural abnormality of mitral valve with mitral insufficiency - Q23.8, bicuspid aortic valve disease - Q23.1, sinus venosus defect - Q21.1. The oldest of these patients has 12 years old and the youngest one is 6 years and 2 patients died in the age of 15 and 16 years old. The sex distribution of this patient's group is 3 girls and 1 boy. In 2019 on February, the boy had operation because of sinus venosus defect in Italian CF Centre.

CF diagnosed firstly in 12 patients and then BD. The mean age when CF diagnosed was 2 years and 2 months, the earliest diagnosed child has 3 months and the oldest one has 10 years old. At one time CF and BD was diagnosed in 3 patients and there were such diagnosis as hypoplasia of gallbladder, pulmonary valve stenosis and bilateral partial ptosis.

The registered others BD as single cases were: bilateral cryptorchidism in 1 case, dolichosigma -1, grade 1 hydronephrosis - 1, bilateral congenital hip dysplasia -1, bilateral partial ptosis -1, multiple renal cysts and hydrocalycosis were in 1 patient.

Discussion

CF is the most common hereditary disease among European population. It is can be concomitant with other congenital abnormalities. There is a very little documentation in modern literature, but to know and to study this problem is very important because we can do the prognosis for perspective as for treatment, complications and life survivance.

In CF patients, such BD as microgallbladder is the specific unique imaging finding in patients with cystic fibrosis and it was reported on abdominal imaging in up to 45% of cases with CF [7]. In our study we saw less cases of this pathology 1,7% among all CF patients and 20% among all CF patients with BD.

Our work shows that the congenital heart defects occur with the same frequency as defects of hepatobiliary system among CF patients. However, the prognosis of these patients with heart defects are more serious and two CF children of our investigation died already.

Conclusion

1. BD were registered in CF patients more frequently than in general population. According to our investigation, the frequency of BD among CF patients was 8.2% at the time the frequency of BD in Ukraine is 3 - 5% of general amount newborns.

2. BD were occurred more often in females than in males 11.62% vs 5.26% among patients with CF.

3. The most frequent CFTR gene mutations in CF patients with BD were: homozygous F508del registered in 40% cases and compound heterozygotes with other mutations in 60% cases respectively. All CF patients with BD had always one or two F508del mutation.

4. Congenital heart defects such as bicuspid aortic valve disease and pulmonary valve stenosis is worsening seriously prognosis of life among CF patients.

Bibliography

1. JA Copel., *et al.* "Obstetric Imaging: Fetal Diagnosis and Care: Second Edition. Elsevier Inc". Elsevier Inc (2018): 776.

2. Bell SC., *et al.* "New pharmacological approaches for cystic fibrosis: promises, progress, pitfalls". *Pharmacology and Therapeutics* 145 (2015): 19-34.

3. Boyle MP and K De Boeck. "A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect". *The Lancet Respiratory Medicine* 1.2 (2013): 158-163.

4. LK Tuchman., *et al.* "Cystic Fibrosis and Transition to Adult Medical Care". *Pediatrics* 125.3 (2010): 566-573.

5. S Mirtajani., *et al.* "Geographical distribution of cystic fibrosis; The past 70 years of data analysis". *Biomedical and Biotechnology Research Journal* 1 (2017): 105-112.

6. M Schwartz., *et al.* "Genetic analysis of cystic fibrosis in Denmark. Implications for genetic counselling, carrier diagnosis and prenatal diagnosis". *Acta Pædiatrica* 81 (1992): 522-526.

7. Farrell PM. "The prevalence of cystic fibrosis in the European Union". *Journal of Cystic Fibrosis* 7.5 (2008): 450-453.

8. T Klaassen., *et al.* "Neonatal screening for the cystic fibrosis main mutation ΔF508 in Estonia". *Journal of Medical Screening* 5.1 (1998): 16-19.

9. Nichols E. K. "Human gene therapy". E. K. Harvard University Press (1988): 251.

10. D Salvatore., *et al.* "An overview of international literature from cystic fibrosis registries. Part 3. Disease incidence, genotype/phenotype correlation, microbiology, pregnancy, clinical complications, lung transplantation, and miscellanea". *Journal of Cystic Fibrosis* 10.2 (2011): 71-85.

11. S Schulz., *et al.* "Increased frequency of cystic fibrosis transmembrane conductance regulator gene mutations in infertile males". *Fertility and Sterility* 85.1 (2006): 135-138.

12. A Bossi., *et al.* "What Is the Incidence of Cystic Fibrosis in Italy? Data from the National Registry". *Human Biology* 76.3 (2004): 455-467.

13. Kate LPT. "Cystic fibrosis in the Netherlands". *International Journal of Epidemiology* 6.1 (1977): 23-34.

14. V Santos., *et al*. "Cystic fibrosis - comparison between patients in paediatric and adult age". *Revista Portuguesa de Pneumologia (English Edition)* 23.1 (2017): 17-21.

15. IJM Doull., *et al.* "Newborn screening for cystic fibrosis in Wales over 20 years. Changes in incidence dependent on screening protocol". *European Respiratory Journal* 52.62 (2018): 4628.

16. Y Yamashiro., *et al*. "The Estimated incidence of cystic fibrosis in Japan". *Journal of Pediatric Gastroenterology and Nutrition* 24.5 (1997): 544-547.

17. Fernández A. "Nutrition in cystic fibrosis". *International Journal of Gastroenterology Hepatology, Transplant and Nutrition* 1 (2016): 40-46.

18. Allan JL and PD Phelan. "Incidence of Cystic Fibrosis in Ethnic Italians and Greeks and in Australians of Predominantly British Origin". *Acta Pædiatrica* 74 (1985): 286-289.

19. Approval and implementation of medical-technological documents on the standardization of medical care for cystic fibrosis: Order of the Ministry of Health of Ukraine (2016): 723.

20. ML Feldkamp., *et al.* "Etiology and clinical presentation of birth defects: population based study". *British Medical Journal* 357 (2017): 2249.

21. FD Tucker., *et al.* "EUROCAT: an update on its functions and activities". *The Journal of Community Genetics* 9.4 (2018): 40-46.

22. Toryanik VN and NV Pokutny. "Prevalence of congenital defects among infants of Lebedinsky District Sumy region". *Prirodničì Nauki* 15 (2018): 37-42.

23. H Makukh., *et al.* "The results of four year IRT/IRT CF-NBS screening program in four districts of Ukraine". *Journal of Cystic Fibrosis* 16.1 (2017): S28.

Volume 9 Issue 7 July 2020