# SOCIO-DEMOGRAPHIC CHARACTERISTICS AND REPORTED PSYCHO-MEDICAL SYMPTOMS FOR CHILDREN WITH RARE DISEASES. A COMPARATIVE STUDY BETWEEN PATIENTS WITH PHENYLKETONURIA, CYSTIC FIBROSIS AND HYPOTHYROIDISM

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SOCIO-DEMOGRAPHIC CHARACTERISTICS AND REPORTED PSYCHO-MEDICAL SYMPTOMS FOR CHILDREN WITH RARE DISEASES. A COMPARATIVE STUDY BETWEEN PATIENTS WITH PHENYLKETONURIA, CYSTIC FIBROSIS AND HYPOTHYROIDISM (Abstract). Rare diseases have great impact on both patients and family members' life. **The aim** of the study was to identify socio-demographic characteristics and factors related to psychological and medical condition for pediatric patients diagnosed with phenylketonuria, cystic fibrosis and hypothyroidism. **Material and methods**: 37 children (24 boys and 13 girls) aged M = 7.61 ± 6.37 (1-22-years-old) were included in the research. A total of 44.7% are diagnosed with cystic fibrosis, 31.6% with phenylketonuria and 23.7% with hypothyroidism. Socio-demographic characteristics and psychological and medical data reported by mothers were registered to point the presence of some characteristics related to the diseases and to identify differences between the three categories of patients. Data have been processed using *SPSS Statistics v23.0.0* for MAC.OSX. **Results**: Almost 1/5 of children diagnosed with hypothyroidism and phenylketonuria were found to have depression symptoms and 1/3 of patients with hypothyroidism are having cognitive impairment associated in 40% of cases with language difficulties, and 20% of them present difficulties to adapt to social environment. A total of 18.3% of children with cystic fibrosis presented enuresis and 20% of them has bruxism. **Conclusions**: children with rare disease present several psychological symptoms and social difficulties, psychotherapeutically and educational support for both patients and families are needed. **Keywords**: CHILD, CYSTIC FIBROSIS, HYPOTHYROIDISM, PHENYL-KETONURIA.

A disease is considered rare when it affects one person out of 2,000 or less. They are between 5,000 and 8,000 rare diseases, most of them genetic. A rare disease is, according to the definition of World Health Organization (1), a life-threatening or chronically debilitating condition from which not more than 5% of citizens in the European Community suffer. It is estimated that 30 million Europeans and 25 million Americans are suffering from a rare disease that coincide with 6-8% of the total popula-

tion (2).

As WHO guidelines, there is a strong recommendation to sustain and develop research in this area to help knowledge about rare diseases and to improve quality of life of patients suffering from orphan diseases. Social support should not be neglected also, *EURORDIS Care Survey Program* conducted in 23 countries between 2004-2004 included 12,000 patients with rare diseases (3). The survey concluded that "social security systems are usually designed around common diseases are not flexible enough to take into consideration unprecedented health need" as is an orphan disease.

Some diseases are more frequent and programs are already implemented in many countries.

*Phenylketonuria (PKU)* is a rare metabolic disease that has consequences on cognitive development. The cognitive impairment appears if the patient is not treated with a strict protein-restricted diet. Even with early diagnosis and treatment of PKU children, these patients present some deficiencies intellectually compared to normal children (4). Following the medical recommendation regarding diet are extremely important for medical development of the disease and for the quality of life of patient. In many cases, diet and its restrictions are the most stressful factor for parents having a child diagnosed with this disease and perceived social support and diagnosis resolutions seems to improve coping strategies and quality of life for caregivers (5, 6). Some studies assessing the occurrence of psychiatric disorders identified in patients with early treatment for PKU a high rate of anxiety disorder and the tendency of withdrawal were mentioned being the most frequent self-reported symptoms. A study of Manti *et al*. (7) showed that patients with good metabolic control in the first eleven years of life proved higher frequency of psychiatric diagnosis comparing to those having more years from diagnosis, meaning that respecting diet represents a distressful situation and children or adolescents are feeling more frustrating. Psychological and psychiatric evaluation is recommended for all children under medical treatment.

*Cystic fibrosis* (CF) is a genetic disease of the exocrine glands that affects all races but primarily whites. For this reason, since 2001, the American College of Obstetricians and Gynecologists recommends that white women be tested for the gene if they are pregnant or considering pregnancy (8) and three years later, in 2004, the Centers for Disease Control and Prevention (CDC) published their pivotal recommendation that regions "begin newborn screening for CF" (9, 10). A patient with CF and members of the family may have tremendous physical, psychosocial, and educational needs. As the patient get older, some new problems may arise or existing problems may worsen requiring comprehensive, multidisciplinary lifelong care (11). Sometimes patients with CF could be misdiagnosed earlier in life as having asthma or chronic bronchitis.

*Hypothyroidism* can manifest with different signs and symptoms. In the pediatric population, the prevalence of this thyroid disorder is estimated to be less than 10% (12). This disorder has a wide range of presentation from subclinical hypothyroidism to overt form. Hearing loss is more common in hypothyroid patients than normal population so diagnosing earlier the deafness will help children to be cognitively stimulated. Dental problems and cardiac

manifestations need also to be identified to improve quality of life for these patients.

Living with these rare diseases demand a lot of effort of family members, multidisciplinary team and a strong determination to empower the patient (if possible) to care about own medical and psychological problems. Early diagnosis, adherence to treatment, family, medical and social support are important for a high level of quality of life. The care for the patients must be doubled by the care for the family members to improve life standards for all persons touched by the diseases.

In the majority of cases, mothers are the carrier of children with a rare disease. One of the most common behavior identified in mothers having a child with a rare disease is the hyper-protection, attitude with a negative impact over the years, causing a lot of reactiveness in children during their pre/adolescence period. That is why mothers or caregivers must be well trained to help, supervise, interfere and treat their children.

The aim of this study is to identify psychological and medical symptoms of pediatric patients suffering from these three rare diseases (cystic fibrosis, hypothyroidism and phenylketonuria) as that are declared by their mothers.

## MATERIAL AND METHODS

A number of 37 patients aged 1-22 years old were included in the study (M = 7.61 ± 6.37). In Romania, patients older than 18 are continuing to be hospitalized in pediatric clinics till the age of 25 if they are registered in the educational system. The children were diagnosed and under medical supervision in "Saint Mary" Emergency University Hospital for Children in Iasi, Romania with one of the following three rare disease: cystic fibrosis, hypothyroidism and phenylketonuria.

The study has been approved by the Ethical Committee of "Sf. Maria" Emergency Clinical Hospital for Children and questioned mothers and children were informed about the confidentiality and use of data and results and mothers signed an informed consent before filling in the items.

Socio-demographic and family member's information (age for patient and both parents, sex, religion, department, environment and level of education for both parents) were registered. The mothers of the patients had to indicate psychological, social and physical symptoms that they have been identified to their children.

Statistical analysis was performed using *SPSS Statistics version 23.0.0* for MAC. OSX.

## RESULTS AND DISCUSSION

### Descriptive statistics – general results

The socio-demographic and self-reported data were gathered during their hospitalizations from 2016. For 24 boys and 13 girls hospitalized in 2016, mothers reported psychological and medical symptoms for their children and appreciated their social interactions with peers. More than half of the patients (69.4%) are aged between 2 and 6 years old, 27.8% are aged between 6 and 12 years old, and the rest (2.8%) are older than 12 years old.

The patients are coming from 6 districts of North-eastern part of the country (Bacau, Botosani, Iasi, Neamt, Suceava, Vaslui), 17 of patients (45.95%) living in urban area and 20 (54.05%) living in countryside. The distribution of patients considering their gender and disease is presented in Table I.

TABLE I.

**Data referring to the distribution of patients accordingly to disease, gender and age at diagnostics**

| Disease | Male | Female | Age at diagnostic (M ± SDV) |
|---|---|---|---|
| **Phenylketonuria** | 10 (41.7%) | 1 (7.7%) | M = 1.12 ± 1.24 months |
| **Hypothyroidism** | 3 (12.5%) | 6 (46.2%) | M = 1.66 ± 0.70 months |
| **Cystic fibrosis** | 11 (45.8%) | 6 (46.2%) | M = 20.58 ± 34.71 months |

*Family data*

Mothers were asked about their marital situation at the time of diagnosis and 25 of them (67.57%) declared that they were married. Eleven of them (32.35%) are having one child, 18 (52.94%) are having 2 children, 3 (8.82%) are having 3 children and 2 (5.88%) are having 4 children (the number of births/mother is M = 2 ± 0.76).

Data about the religion of the family members revealed that the majority patients are Orthodox-Christian (92.1%), and a small number is Pentecostal (5.3%) and Adventist (2.6%).

The minimum age of mothers is 18 and the maximum is 55 years old (M = 33.05 ± 8.52). For the fathers, the minimum age is 21 and the maximum is 56 years old (M = 37.87 ± 7.79).

Data regarding the educational level of parents was also registered. A total of 6.1% of the mothers have primary education background, 21.2% gymnasium level, 57.6% have reached high school level, and 15.2% graduated college. In what concern the level of education of fathers, 5.7% have primary education background, 22.9% gymnasium level, 68.6% have reached high school level, and 2.9% graduated college.

TABLE II.

**The distribution of patients accordingly to their age**

| Age | 1 | 2 | 3 | 4 | 5 | 7 | 8 | 11 | 12 | 13 | 16 | 19 | 20 | 21 | 22 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **N** | 2 | 5 | 6 | 4 | 4 | 1 | 3 | 1 | 3 | 1 | 1 | 2 | 1 | 1 | 1 |
| **%** | 5.6 | 13.5 | 16.2 | 10.8 | 10.8 | 2.7 | 8.1 | 2.7 | 8.1 | 2.7 | 2.7 | 5.4 | 2.7 | 2.7 | 2.7 |

*Patients with phenylketonuria*

The minimum registered age at diagnosis for this category of pediatric patients is 0 months (3 weeks) and the maximum is 4 months, with a mean of 1.12 ± 1.24 months. In the case of *phenylketonuria* none of the patients (with M =3.36 ± 3.29, minimum age of 1 year old and maximum age of 13 years old) displayed loss of appetite, bowel movement problems, muscular dystrophy, intellectual disability, bradypsychia, language difficulties, memory difficulties, unhealthy behaviors, bruxism, night terrors, bed wetting, behavioral problems, isolation (by others or themselves), panic attacks, or a high caloric diet. 40% of the patients presented nutritional problems and 40% of the patients presented sleep-related problems. Most them (80%) complied with their treatment.

Considering anger outbursts, 25% of the patients had them, and more than half of the patients (60%) were advised on a nutrition diet. 20% of the children had depression, and more than half of the patients (66.7%) followed nutritional recommendation.

*Patients with hypothyroidism*

The minimum registered age at diagnosis for this category of disease is at birth (more frequent is the third week of life) and the maximum is 3 months, with a mean of 1.66 ± 0.70 months. The age at the time of the study is M =3.62 ± 1.68, with a minimum age of 1 and a maximum age of 7. In the case of *hypothyroidism*, patients did not display bowel movement problems, muscular dystrophy, bradypsychia, and memory difficulties, nutrition problems, bruxism, night terrors, bed wetting, behavioral problems, panic attacks or a high caloric diet. In case of 16.7% we identified a loss of appetite, and 33.3% presented intellectual disability. Almost 40% of the patients had language problems and 20% of the patients displayed unhealthy behaviors. In case of 16.7% of the patients, mothers reported sleep problems.

In case of 20% of the patients, mothers were reported having depressive symptoms. More than half of the patients (60%) complied with their treatment and 83.3% were taking medication. 20% of the patients experienced isolation (by others or themselves) and 20% of the patients displayed anger outbursts. Half of the patients were advised on a diet. Many of the patients (80%) followed their nutritional recommendations.

Our findings are congruent to the scientific data from the literature. Findings published by Rovet and Ehrlich (13) indicated cognitive problems for children with hypothyroidism that persist into adolescence (memory, attention, or visual and spatial processing areas). For these problems, the educational support is extremely important, to supervise medical condition, intellectual achievement and behavior.

In our study, mothers identified in case of 20% that children suffering from hypothyroidism are having depression symptoms, angriness and unhealthy behaviors and isolation. Their physical aspect, the cognitive impairment, language problems and motor skills (14, 15) are factors that influence their social interaction and family members and teachers must be informed about these aspects to diminish the child's distress. Social and educational difficulties should not be underestimated, as the scientific results are proving that physical condition is usually more supervised and cared compared to psychological and social well-being (16, 17). Despite the results presented by many researches referring to the negative cognitive development in case of under-treatment, few studies have been focused on the effects of overtreatment of patients with this disease. A study of Bongers-Schokking (18) shows that overtreatment during the first two years determines lower cognitive outcomes (the study being lead on patients aged 11). The authors suggest also that fast TSH normalization at initial treatment leads to above-normal development scores at a young age but does not affect the quotient of intelligence at the age of 11 years.

*Patients with cystic fibrosis (CF)*

The minimum registered age at diagnosis for this category of disease is at birth (first month) and the maximum is 132 months, with a mean of 20.58 ± 34.71 months. The age at the time of the study is M =12.23±6.13; the minimum registered age is 5 years old the maximum is 22 years old.

The patients diagnosed with CF have no record of bradylalia, memory difficulties, unhealthy behaviors, night terrors, behavioral problems or panic attacks. 23.1% had

a loss of appetite, 66.7% had bowel movements problems, 30.8% had muscular dystrophy and 9.1% presented intellectual disability and bradypsychia.

Most patients suffering from CF present nutritional problems (25%), 10% had sleep problems, 20% present bruxism and 18.2% were diagnosed with enuresis. A small number of pediatric patients (9.1%) presented symptoms of depression.

Almost half of the patients (45.5%) complied with their treatment and large majority of patients (91.7%) took medication.

In case of 7.7% of patients' mothers declared that children experienced isolation and 8.3% of the patients displayed anger outbursts. A percentage of 41.7% from the patients were on a high caloric diet. More than half of the patients (69.2%) were advised on a nutrition diet, and all the patients followed their nutritional recommendations.

Early medical intervention is essential for these patients so neonatal screening is demanded. Understanding the ethical issues in CF is an important factor for providing optimal care of newborn with CF (19). Our results prove that children with CF have an older age at the moment of their diagnostic comparing to the pediatric patients suffering from the other two diseases.

**Comparative statistics**

Comparative results for the three diseases are presented in Table III. The higher number of symptoms identified by mother are those having children diagnosed with cystic fibrosis.

TABLE III.

**Comparative results for variables in phenylketonuria, hypothyroidism and cystic fibrosis**

| Variables | | Phenylketonuria | Hypothyroidism | Cystic fibrosis |
|---|---|---|---|---|
| **Loss of appetite** | Yes | 0% | **16.7%** | **23.1%** |
| | No | 100% | 83.3% | 76.9% |
| **Bowel movement problems** | Yes | 0% | 0% | **66.7%** |
| | No | 100% | 100% | 33.3% |
| **Muscular dystrophy** | Yes | 0% | 0% | **30.8%** |
| | No | 100% | 100% | 69.2% |
| **Intellectual disability** | Yes | 0% | **33.3%** | **9.1%** |
| | No | 100% | 66.7% | 90.9% |
| **Bradipsychia** | Yes | 0% | 0% | **9.1%** |
| | No | 100% | 100% | 90.9% |
| **Bradylalia** | Yes | 0% | **40%** | **0%** |
| | No | 100% | 60% | 100% |
| **Memory difficulties** | Yes | 0% | 0% | 0% |
| | No | 100% | 100% | 100% |
| **Fertility problems** | Yes | 0%% | 0% | **28.6%** |
| | No | 100% | 100% | 71.4% |
| **Unhealthy behaviors** | Yes | 0% | **20%** | 0% |
| | No | 100% | 80% | 100% |
| **Nutrition problems** | Yes | **40%** | 0% | **25%** |
| | No | 60% | 100% | 75% |

| Variables | | Phenylketonuria | Hypothyroidism | Cystic fibrosis |
|---|---|---|---|---|
| **Sleep problems** | Yes | **40%** | **16.7%** | **10%** |
| | No | 60% | 83.3% | 90% |
| **Bruxism** | Yes | 0% | 0% | **20%** |
| | No | 100% | 100% | 80% |
| **Night terrors** | Yes | 0% | 0% | 0% |
| | No | 100% | 100% | 100% |
| **Bed wetting** | Yes | 0% | 0% | **18.2%** |
| | No | 100% | 100% | 81.8% |
| **Behavioral problems** | Yes | 0% | 0% | 0% |
| | No | 100% | 100% | 100% |
| **Depression** | Yes | **20%** | **20%** | **9.1%** |
| | No | 80% | 80% | 90.1% |
| **Compliance with treatment** | Yes | **80%** | **60%** | **45.5%** |
| | No | 20% | 40% | 54.5% |
| **Medication** | Yes | 0% | **83.3%** | **91.7%** |
| | No | 100% | 16.7% | 8.3% |
| **Isolation** | Yes | 0% | **20%** | **7.7%** |
| | No | 100% | 80% | 92.3% |
| **Panic attacks** | Yes | 0% | 0% | 0% |
| | No | 100% | 100% | 100% |
| **Anger outbursts** | Yes | **25%** | **20** | **8.3** |
| | No | 75% | 80% | 91.7% |
| **High caloric diet** | Yes | 0% | 0% | **41.7%** |
| | No | 100% | 100% | 58.3% |
| **Diet** | Yes | **60%** | **50%** | **69.2%** |
| | No | 40% | 50% | 30.8% |
| **Following nutritional recommendations** | Yes | **66.7%** | **80%** | **100%** |
| | No | 33.3% | 20% | 0% |

It is important to notice that, regarding the way the patients follow the nutritional recommendations, the rate of affirmative responses is very high, for all three of diseases. This result proves that families understand very well importance of the nutritional diet and respect the medical recommendation to negative effects on child's development. For example, prevention or early treatment of iron deficiency may improve cognitive development and behavior of children with PKU (20). It is important to register from the beginning of the diagnostic family rules for food and nutrition and to identify restriction imposed, for example, by the religious believes. Multidisciplinary counsel is imposed for these medical cases.

Our results reveal psychological symptoms and important factors related to patients suffering from the considered diseases. We found that important rate of pediatric patients questioned are presenting nutritional problems and sleep disturbance (higher rate in phenylketonuria), cognitive impairment (higher rate for hypothyroidism), and enuresis and bowel syndrome (higher rate for cystic fibrosis). Almost 1/5 of children diagnosed with hypothyroidism and phenylketonuria were found to have

depression symptoms, as their mothers declared. The physical and psychological problems seem to be frequent and care for these patients must be done in a multidisciplinary team, as soon as possible after the diagnostic. Personalized educational support plan is required for children having cognitive delay such those with congenital hypothyroidism and hearing tests, memory deficit, speech and visual development must be targeted from the beginning (21).

*Study limits*. This study has some limitations. The first one is due to the small number of children and comparative study must be treated with precautiousness. The second one is referring to children's age. Some items targeting data, like fertility problems are not available for newborn baby or before the age of puberty. So, comparative results could not be generalized.

## CONCLUSIONS

Children with a rare disease present several psychological symptoms and social difficulties that can been identified by the family members, especially mothers who are the most frequent the responsible and dependable caregiver.

The educational support of pediatric patient and psychotherapy intervention for both patients and families are needed as soon as possible after the medical diagnostic. Psychological support must not be neglected or not prioritized due to the medical outcomes.

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**NEWS**

## NANOMEDICINES IN CANCER THERAPY – MICELLAR CYTOCHROME P450 INHIBITORS

Nanomedicines are mainly used as drug delivery systems. Recently was evaluated a new therapeutic possibility of inhibiting a drug's metabolism thereby enhancing its effective dose. Most of the phase I drug metabolism is carried out by the hepatic cytochrome P450 (CYP450) enzymes, which due to genetic polymorphisms leads to high inter-individual variability. Micelles containing the natural furanocoumarin 6′,7′-dihydroxybergamottin (DHB), a known CYP450 inhibitor, were developed and studied for the influence on metabolism and bioavailability of the oncology drug docetaxel. It was observed that the administration of DHB-micelles in mice at 24 h prior to the drug enhanced antitumor efficacy in the tumor xenograft models HT-29 and MDA-MB-231, when compared to the drug alone. The researchers encapsulated in nanocarrier natural compounds, known for their metabolism-blocking capacity and absence of reported toxicity, with intravenous administration for the inhibition of the hepatic metabolism of drugs to enhance the useful dose and/or reduce the ineffective proportion of the dose often responsible for the toxicity of the injected drug. These findings are encouraging in terms of increased efficacy and prolonged overall survival in xenografted murine models with good tolerance to treatment. The preclinical benefit–risk ratio of introducing such a metabolism-blocking agent in association with drugs with a narrow therapeutic window or relying too much on the CYP450 status of patients is under studies. Despite not being optimized in terms of targeting hepatocytes, DHB-micelles represent the first injectable example of nanosized metabolism-blocking agents and open the way for further work on such nanomedicines in man (Paolini M, Poul L, Darmona A, Germain M, Pottier A, Levy L, Vibert E. A new opportunity for nanomedicines: Micellar cytochrome P450 inhibitors to improve drug efficacy in a cancer therapy model. *Nanomedicine: Nanotechnology, Biology, and Medicine* 2017; 13: 1715-1723).

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