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Socio-economic issues in the diagnostic approach and decision to treat of a child with familial cholestasis

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ABSTRACT

Objectives. The diagnostic approach in familial cholestasis cases involves using expensive investigations. The need for complex therapeutic resourses is predictable.

Material and Methods. We present the case of a 3 years 5 months old boy diagnosed with cholestasis and liver cirrhosis, admitted in the Pediatrics Department of "Grigore Alexandrescu" Children's Hospital for evaluation in order to check the criteria for liver transplantation.

Outcomes (case presentation). The patient is known to our clinic since he was 1 year 3 months; he was admitted at that time for green jaundice. He comes from a family with nine children, low socio-economic status and low education. The first four children have a different father, two of them were stillborn. The next five come from a consanguineous union (the father is maternal uncle of the mother): three (the patient included) presented with the same symptoms, two of them died before 3 years of age with liver cirrhosis. In time, infectious causes, autoimmune, neoplasic and metabolic disease were excluded. The liver biopsy describes cholestasis and fibrosis. Alagille syndrome and progressive familial intrahepatic cholestasis are still debated, but the genetic testing necessary for a positive diagnosis are not financialy available to the family. The patient presents with failure to thrive, developmental delay, intense jaundice and pruritus, hippocratic fingers, dyspnoea, enlarged abdomen with visible collateral circulation, significant hepatosplenomegaly. The lab tests show anemia, thrombocytopenia, liver cytolysis, normal gamma-glutamyltransferase, low prothrombin activity, normal renal function, no inflammatory syndrome, increased ammonia level, very high bile acids level. The upper endoscopy describes first degree esophageal varices and portal hypertensive gastropathy. A PELD (Pediatric End-Stage Liver Disease) score is calculated – 13.6 (76.3% one year survival rate on the transplant list, 90.9% one year survival rate after liver transplantation). The patient is enroled on the transplant waiting list provided we would expect suboptimal results considering the developmental delay and difficult post-transplant monitoring.

Conclusions. The low education level of the family correlated with a postponed positive diagnosis due to financial reasons and the lack of genetic advice already lead to the demise of four brothers. In this setting, the prognosis of the patient is very likely to be poor.

Keywords: familial cholestasis, liver transplantation, socio-economic issues

List of abreviations:

PELD – Pediatric End-Stage Liver Disease score
PFIC – progressive familial intrahepatic cholestasis
BSEP – bile salt export pump
ɣGT – gamma-glutamyltransferase.

INTRODUCTION

The diagnostic approach in familial cholestasis cases involves using expensive investigations. The need for complex therapeutic resourses is predictable throughout the lifetime of these patients. Little data exists in the pediatric literature regarding the best approach to introduce solid organ transplantation in general and liver transplantation in particu-

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lar as a treatment option. The transplant journey is a complicated and potentially unpredictable process thar requires a long-term view of patient and family needs. Many parents view the referal for transplantation as a new beggining, the end of a long series of attempts to improve the course of a chronic, progressive medical condition. It is important to clarify the family's expectations for transplant and correct any misconceptions they might have. The transplantation is not a cure, but merely the last treatment option to extend life. The most frequent unrealistic idea is that transplantation will put an end to persistent medical intervention and people are disappointed to learn that transplantation is a different chronic "disease" (1). A liver transplanted child is not a healthy child, but a patient for whom a fatal disease was substituted by a persistent, controlled medical condition, which has associated morbidities that might be stable or evolve despite a well preserved graft function (2). Also, in many cases, the transplanted organ is not expected to last throughout the remainder of the child's life. Emphasis should be placed on the fact that there are long term consequences, risks and potential complications beyond survival (infections due to the immunocompromised status, graft rejection, post-transplant malignancies) [1-3].

The impact in the child and family will vary based on multiple other factors than disease course: individual and family differences in social and psychological functioning, health literacy, adherence to medical care. Health literacy is defined as "the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions" [4].

MATERIAL AND METHODS

We present the case of a 3 years 5 months old boy diagnosed with cholestasis and liver cirrhosis, admitted in the Pediatrics Department of "Grigore Alexandrescu" Emergency Children's Hospital, Bucharest in July 2018 for evaluation in order to check the criteria for liver transplantation. We discuss the challenges we are facing in the diagnostic approach, looking from a socio-economic perspective. The decision to treat might also be influenced by the poor financial and educational status of the family.

OUTCOMES (CASE PRESENTATION)

History

The patient is known to our clinic since he was 1 year 3 months; he was admitted at that time for green jaundice.

He comes from a family with nine children (being the 8th offspring), low socio-economic status (leaving on welfare) and low education (primary school). The first four children have a different father, two of them were stillborn. The next five come from a consanguineous union (the father is maternal uncle of the mother): three (the patient included) presented with the same symptoms (severe jaundice, hepatosplenomegaly), two of them died before 3 years of age with liver cirrhosis. The pedigree of the family is represented in Figure 1.

At the time of first presentation in our clinic, the patient was admitted alongside with older brother with the same clinical picture. The latter was diagnosed with severe end-stage liver disease and died shortly after (Figure 2).

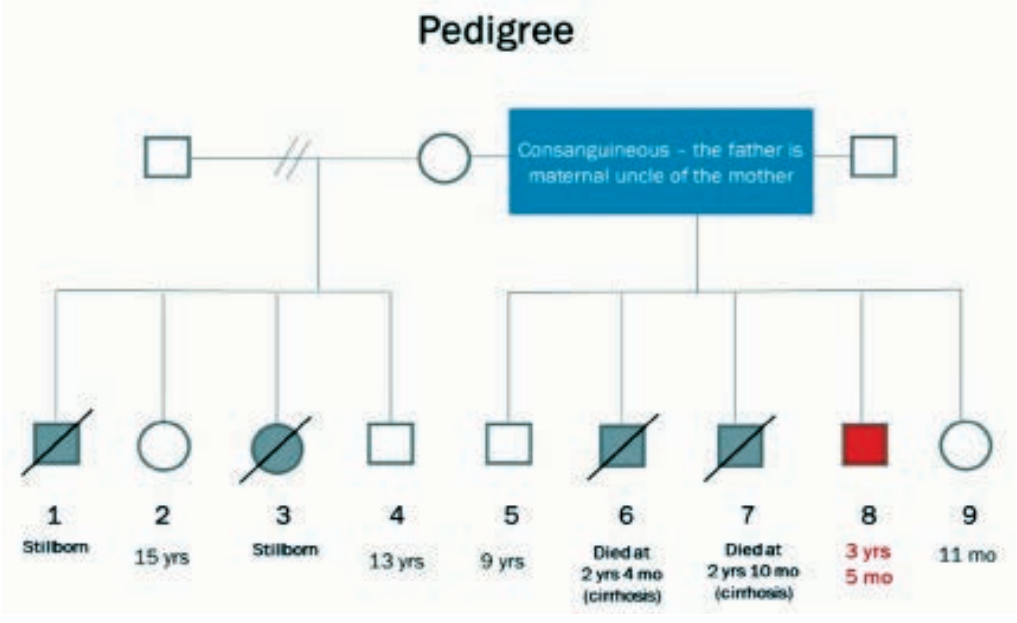

FIGURE 1. Pedigree of the patient's family depicting affected siblings and fatalities

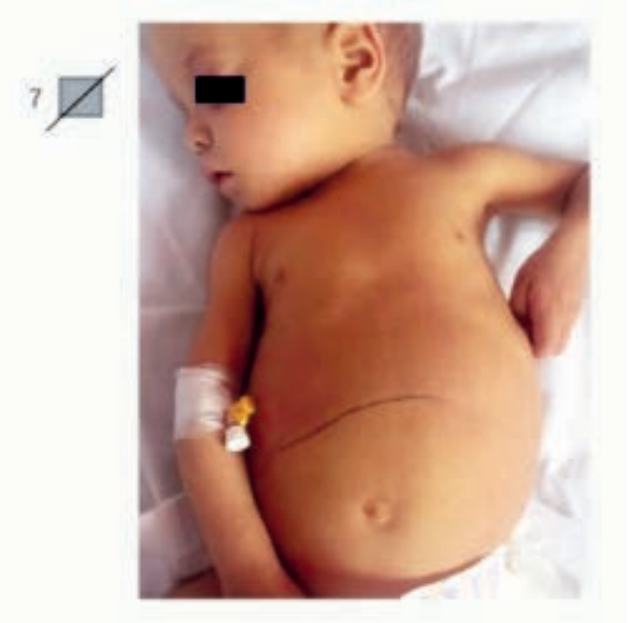

FIGURE 2. Brother of the patient (7th sibling) – died at 2 yrs 10 mo (liver cirrhosis)

Over the last two years we excluded: infectious causes (chronic viral hepatitis B and C, cytomegalovirus, herpes and HIV infections), autoimmune hepatic disease (boy, young age, negative specific antibodies, no response to corticosteroids), neoplasia (normal findings on bone marrow biopsy, normal alpha-fetoprotein), Wilson disease (normal ceruloplasmin and cupruria), metabolic disease: normal activity of alpha-galactosidase excluded Fabry disease, normal activities of alpha-glucosidase at ph 3.8, with and without inhibition excluded Pompe disease, lysosomal enzymes activities (alpha-iduronidase, iduronate-2-sulphatase, arylsulphatase B, beta-galactosidase) were normal or slightly deviated from referance ranges, thus no indication of mucopolysaccharidosis (MPS) I, MPS II, MPS VI, as well as mucolipidoses II/III and multiple sulphatase deficiency. These tests were financed through a private company programme. No financial resources were available to test for Niemann-Pick disease.

The liver biopsy describes hepatocellular and canalicular cholestasis (Figure 3). In optical microscopy the sample reveals altered hepatic structure, cholestatic liver cell rosettes, giant multinucleated hepatocytes. Intracanalicular deposits of bile. Enlarged portal spaces with discrete inflammation and fibrosis extending in the parenchyma. Visible biliary ducts. Discrete centrilobular fibrosis. The electron microscopy sample shows hepatocytes filled with electrondense material (bile), multinucleated hepatocytes with giant mythocondria with crystalline inclusions, filled with glycogen. Frequent Kupffer cells filled with bile pigment. Disorganised biliary canaliculi. Portal inflammation with numerous polymorphonuclear cells and eosinophils.

Clinical Picture

At the time of admission (3 years 5 months) the patient presents with failure to thrive (11.5 kg), developmental delay (motor skills and cognitive behaviour of a 12 months old), intense jaundice (Figure 4) and severe, generalized pruritus with scratching lesions, hippocratic fingers and toes (Figure 5), dyspnoea with otherwise normal findings at respiratory system evaluation, cardiac murmur grade two, normal urine colour, pale stools, markedly enlarged abdomen with visible collateral circulation (Figure 6), significant hepatosplenomegaly (the lower margin of the liver and spleen at 12 and respectively 6 cm below the costal margin).

Lab Tests and Imaging

The lab tests show normochromic, normocytic anemia (hemoglobin level = 9.3 g/dl) and thrombo-

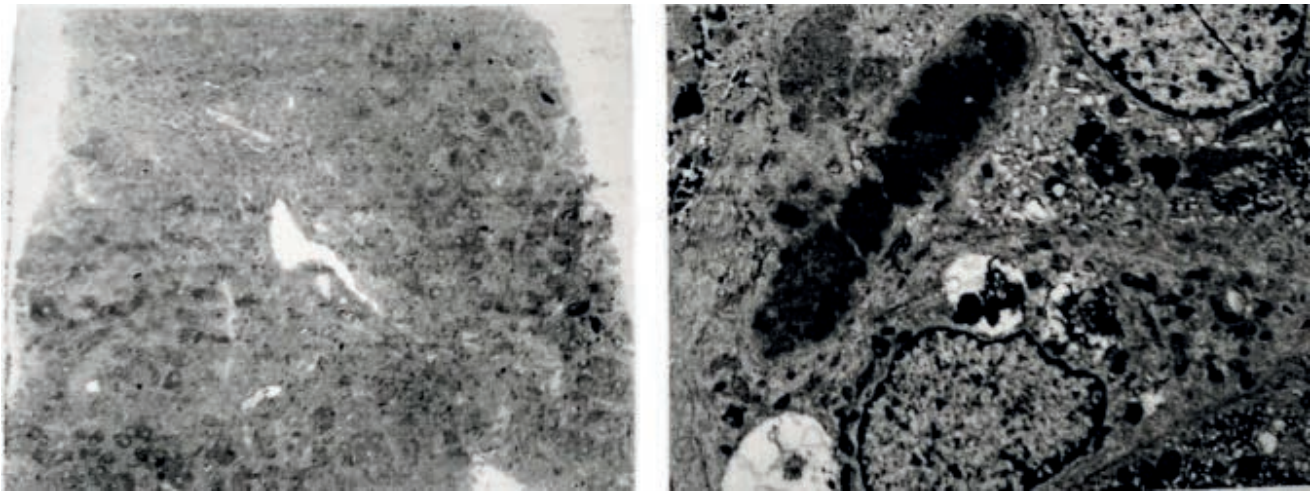

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FIGURE 3. Liver biopsy: optical (left) and electron (right) microscopy

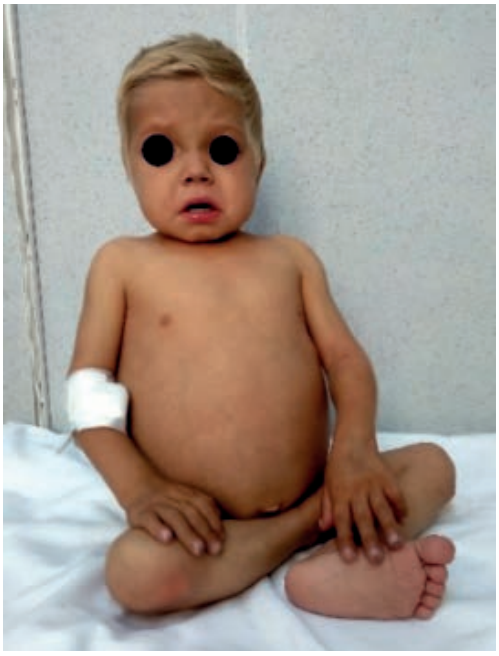

FIGURE 4. Intense, generalized jaundice

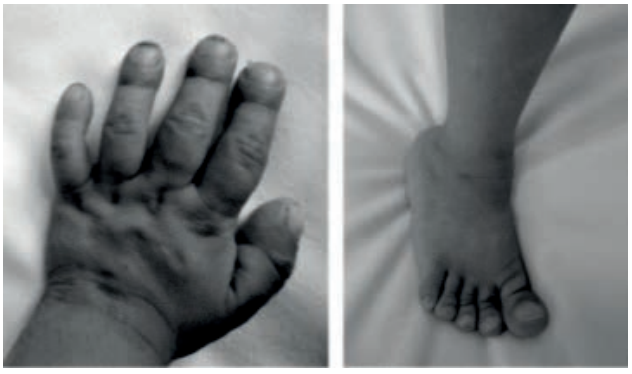

FIGURE 5. Hippocratic fingers and toes

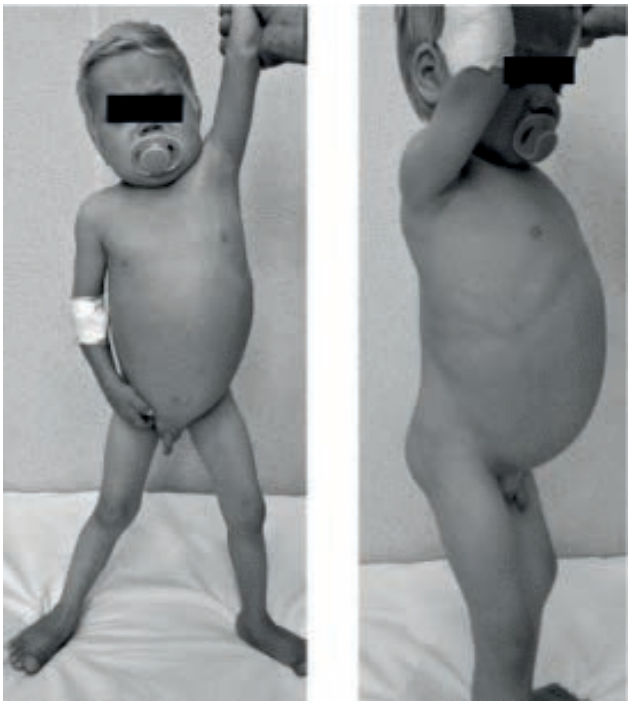

FIGURE 6. Failure to thrive, enlarged abdomen with collateral circulation

cytopenia (platelet count=103000/mm^3) due to hematologic hypersplenism, liver cytolysis (ALT=82 U/l, AST=170 U/l, three times the normal range), cholestasis (total bilirubin=4.5 mg/dl with conjugated bilirubin=2.5 mg/dl), normal gamma-glutamyltransferase (ɣGT=23 U/l) and cholesterol level (53 mg/dl), low prothrombin activity (52%), normal renal function, no inflammatory syndrome, slightly increased serum ammonia level (89 µmol/l), very high level of serum bile acids (570 µmol/l, 50 times the normal range), normal alpha-fetoprotein (4.05 UI/ml).

The abdominal ultrasound reveals hepatosplenomegaly, portal hypertension, normal diameter intrahepatic biliary ducts, multiple perigastric and peripancreatic portacaval collaterals.

The upper endoscopy describes first degree esophageal varices with no history of bleeding and portal hypertensive gastropathy.

Prognosis and Treatment

A PELD (Pediatric End-Stage Liver Disease) score is calculated – 13.6:76.3% one year survival rate on the transplant list, 90.9% one year survival rate after liver transplantation.

The patient is now on ursodeoxycholic acid and supportive treatment (hepatoprotective drugs, liposoluble vitamins). Spironolactone and propranolol are started. The liver transplantation is considered as the next step in therapy and the patient is referred to a Surgery Department in order to be placed on the transplant list.

DISCUSSIONS

Alagille syndrome and progressive familial intrahepatic cholestasis (PFIC) are still debated, but the expensive genetic testing necessary for a positive diagnosis are not financially available to the family. The JAG 1 and NOTCH mutations for Alagille syndrome are estimated at 2200 and 2800 euro respectively; ATP8B1 mutation for PFIC 1 and ABCB11 mutation for PFIC 2 cost around 2100-2300 euro each. As these tests are not available in the public hospital system in Romania, the positive diagnosis is delayed.

Clinical traits of Alagille syndrome in our patient are: some particular facial features – prominent forehead, blonde hair, deep-set eyes (the typical features with pointed chin giving a triangular appearance and straight nose are missing), heart murmur (the ecocardiography showed increased blood velocity through the pulmonary valve, with no other pathological findings). But there are no vertebral malformation or associated ocular signs, posterior embryotoxon. Visible bile ducts are described on liver biopsy [5].

The main clinical manifestations of PFIC include cholestasis, pruritus and jaundice. PFIC patients usually develop fibrosis and end-stage liver disease before adulthood. PFIC type 1 and 2 are caused by impaired bile salt excretion due to defects in ATP8B1 encoding FIC1 protein and in ABCB11 encoding bile salt export pump (BSEP) protein, respectively. Serum ɣGT and cholesterol levels are normal for these patients. The serum bile acid concentration is very high. In PFIC 1 patients liver histology is characterised by canalicular cholestasis and the absence of ductular proliferation. In PFIC 2 the liver architecture is more affected with more pronounced lobular and portal fibrosis, inflammation, hepatocellular necrosis and giant cell formation; the lesions are more likely to persist with time. Our patient's histology seems to best fit the PFIC 2 picture. Genotyping should be used to confirm the diagnosis of PFIC in affected children. Heterozygosity of parents for the genetic defects found in patients confirmes the recessive inheritance of the disease. Prenatal diagnosis is possible and would have saved this family of a great burden of morbidity and mortality [6-8].

Regardles the etiology of the cholestasis, the patient is enroled on the transplant waiting list provided we would expect suboptimal results considering the developmental delay and difficult post-transplant monitoring. The non-adherence rate in pediatric liver transplant recipients is about 30% and might contribute 15% to the graft loss [9]. Parental functioning is essential to children's development. Family strain is significantly correlated to psychosocial dysfunction in children post-liver transplantation. The risk of familial maladjustment to the post-transplant conditions has been demonstrated [10]. We have to emphasise the importance of psychosocial assessment of parents during transplant and follow-up to ensure the best achievable long-term outcome for the patient. Parental involvement and the understanding of the full extent of the situation is predictable low for this case. Issues such as the wider impact on the family at transplant referral (arrangements for siblings, practicalities related to travel and finances) also carry significant importance for a good outcome of the transplant [1]. Looking at our case, we are safe to assume that all of the above will take a toll on prognosis. Also the low health literacy of this family might contribute to misconceptions and inaccurate expectations regarding the transplant process. The main predictable danger is that they might consider the patient cured and disregard the crucial importance of post-transplant monitoring.

CONCLUSIONS

The low education level of the family correlated with a postponed positive diagnosis due to financial reasons and the lack of genetic advice already lead to the demise of four brothers. In this setting, the prognosis of the patient is very likely to be poor with or without liver transplantation.

Conflict of interest: none declared
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