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Identification of low gamma-glutamyl transferase familial intrahepatic cholestasis – benign recurrent intrahepatic cholestasis in a 22-year-old woman: a case report and literature review

Łagodna nawracająca cholestaza wewnątrzwątrobowa z małą aktywnością gamma-glutamylotranspeptydazy (GGTP) – opis przypadku 22-letniej pacjentki oraz przegląd literatury tematu

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Abstract: *Introduction:* Benign recurrent intrahepatic cholestasis (BRIC) is a rare genetic disorder characterized by recurrent episodes of cholestatic jaundice that may last days to months. It can start at any age, but often in a first decade of life. The syndrome does not lead to progressive liver dysfunction and cirrhosis. Between cholestatic episodes patients have no symptoms and laboratory levels are within the norms. The exact mechanism of cholestasis in BRIC and many other cholestatic conditions is poorly understood. Syndrome the first time was described in 1959r., in 2004 was proposed the following diagnostic criteria. The report presents a 22-year-old woman with the diagnosis of jaundice with an accompanying severe pruritus (first episode of BRIC). *The aim:* This article describes clinical presentation, laboratory abnormalities, and proposed etiologic factors responsible for BRIC. We intend to report this case due to rarity of this disease in Poland. *Clinical case:* Described as a clinical case course features of the BRIC. Knowledge of this entity is important issue as an early recognition that might prevent performance of expensive diagnostic algorithm. The laboratory tests and the whole clinical picture had conclusive results. Moreover, despite negative genetic test, the authors were sure that it is BRIC. *Conclusions:* BRIC is a disease not leading to progressive liver dysfunction and cirrhosis. It should be remembered the characteristic symptoms of BRIC, a very low level of GGT accompanied by jaundice and itching. It has a great diagnostic importance (by shortening the procedure algorithm), allowing for a quick diagnosis. BRIC is associated with good prognosis in most cases. However, some patients presented with intermittent cholestasis may progress to PFIC and develop permanent cholestasis and porto-portal fibrosis and progressive liver damage. Therefore, patients diagnosed with BRIC require hepatological care.
Key words: cholestasis, BRIC (benign recurrent intrahepatic cholestasis), PFIC(progressive familial intrahepatic cholestasis), low GGT, jaundice.

Abstrakt: *Wprowadzenie:* Łagodna nawracająca cholestaza wewnątrzwątrobowa (BRIC) to rzadko występująca , genetycznie uwarunkowana, dziedziczona autosomalnie recesywnie choroba, która charakteryzuje się nawracajacymi epizodami cholestazy z towarzyszącym świądem skóry. Wyróżnia się dwa typy BRIC, odpowiednio BRIC-1 i BRIC-2. Choroba należy do grupy rodzinnych cholesaz wewnatrzwątrobowych. Objawy żółtaczki mogą pojawić się w każdym wieku, zwykle jednak występują przed drugą dekadą życia i mogą utrzymywać się przez kilka tygodni do kilku miesięcy. Jak wskazują wyniki badań molekularnych mutacje genetyczne leżą u podłoża etiopatogenetycznego choroby–rozwoju zaburzeń funkcjonowania mechanizmów przezblonowego transportu kwasów żółciowych. *Cel badania:* W naszej publikacji prezentujemy przypadek 22-letniej pacjentki z rozpoznaniem pierwszego epizodu BRIC. W pracy analizujemy przebieg kliniczny, algortytm diagnostyczny oraz leczenie w świetle przeglądu piśmiennictwa tematu. Podsumowując, w oparciu o obraz kliniczny korelujący z odchyleniami w badaniach biochemicznych, po wykluczeniu innych przyczyn cholestazy oraz pomino negatywnych wyników badań molekularnych w kierunku typowej mutacji, należy postawić rozpoznanie BRIC. *Konkluzja:* Prezentowany kliniczny przypadek BRIC naszej pacjentki wskazuje na trudności diagnostyczne zwłaszcza w trakcie pierwszego epizodu choroby. Charakterystyczny obraz kliniczny wraz z profilem odchyleń w badaniach laboratoryjnych, w tym małą aktywnością GGTP, stanowi cenną wskazówkę diagnostyczną ułatwiającą rozpoznanie. U większości pacjentów z rozpoznaniem BRIC rokowanie jest dobre. Jednak z uwagi na możliwość klinicznej progresji do PFIC z następowym uszkodzeniem wątroby ta grupa pacjentów wymaga dalszej obserwacji w hepatologicznej.
Słowa kluczowe: cholestaza, łagodna nawracająca cholestaza wewnątrzwątrobowa (BRIC), postępująca rodzinna wewnątrzwątrobowa cholestaza (PFIC), małe stężenie, GGTP, żółtaczka

Introduction

Benign recurrent intrahepatic cholestasis (BRIC) is a rare autosomal recessive condition characterized by intermittent episodes of severe pruritis and jaundice that may last from few days to months. BRIC was described by Summerskill and Walshe in 1959 (Summerskill, Walshe, 1959). Although the syndrome does not lead to progressive liver dysfunction and cirrhosis, symptoms occurring with each attack may be associated with significant morbidity. The diagnostic criteria proposed by Tygstrup are in use today and include a history of several episodes of jaundice separated by symptom-free interval of at least 6 months in the absence of an inciting drug or toxin (Tygstrup, Jensen, 1969). Laboratory values consistent with intrahepatic cholestasis, severe pruritus secondary to cholestasis, liver histology demonstrating centrilobular cholestasis, normal intrahepatic and extrahepatic bile ducts confirmed by cholangiography.

Low gamma-glutamyl transferase (GGT) familial intrahepatic cholestasis presents with recurrent episodes of cholestasis without progressive liver disease. This is a genetic autosomal recessive disease. It can start at any age, but often in a first decade of life with appearing attacks lasting from several weeks to months. A characteristic phenomenon in this disease is low or normal serum levels of GGT enzyme. There are 2 forms of the disease – mild and severe. The milder forms are known as BRIC1 and BRIC2 and severe forms are known as progressive familial intrahepatic cholestasis–PFIC1 and PFIC2. The different forms are caused by mutations. PFIC1 and BRIC1 have a mutation in a gene ATP8B1, which encodes FIC1 protein (familial intrahepatic cholestasis 1). PFIC2 and BRIC2 have mutations in a gene named ABCB11, which encodes a BSEP protein (bile salt export pump)[1] (Sohn, Woo, Seong et al., 2019; van Ooteghem, Klomp, van Berge Henegouwen et al, 2002). Sometimes the patients do not have mutations in either of these genes. This situation suggests that there are other gene forms and mutations which are yet to be discovered. Low GGT familial intrahepatic cholestasis occurs in equal percentage within males and females. Generally, this disease is very rare (Sohn, Woo, Seong et al., 2019).

It is unclear what is the stimulus for the BRIC attacks. Important is that BRIC1 and BRIC2 are self-limiting and are not causing progressive, chronic liver damage. The first symptoms before attacks are not specific. It could be fatigue, weakness and loss of appetite. Next time patients have or could have following symptoms which are: intense itchiness, yellowing of the skin, mucous membranes, whites of the eye may follow, liver may be enlarged, weight loss because absorption of nutrients and vitamins is impaired[2] (Ermis, Oncu, Ozel et al., 2010). Between cholestatic episodes patients have no symptoms and laboratory levels are within the norms. Liver biopsies are characterized histologically by intrahepatic cholestasis with preservation of normal liver architecture (van Ooteghem, Klomp, van Berge Henegouwen et al, 2002). BRIC is associated with good prognosis in most cases and does not usually lead to liver fibrosis. However, progression from BRIC to PFIC has been reported in the literature (van Ooteghem, Klomp, van Berge Henegouwen et al, 2002). We should remember that pruritus may be a devastating symptom causing a significant reduction of life quality (Ołdakowska-Jedynak, Jankowska, Hartleb et al., 2014).

1. The Aim

The BRIC clinical case report aims to highlight the importance of making a correct diagnosis. It has great importance for the treatment algorithm (quick diagnosis), but also significantly affects the patient's well-being–the patient can be informed regarding benign nature of this disease.

1 https://rarediseases.org/rare-diseases/low-gamma-gt-familial-intrahepatic-cholestasis
2 ibidem

2. Clinical case

A 22-year-old woman was admitted to the Clinic on May 13th, 2019 with the diagnosis of jaundice with an accompanying severe pruritus. Patient did not have any other symptoms, any other concomitant diseases and did not take any medicine permanently (sometimes metamizole). In the past, patient had two operations: left inguinal hernia surgery and skin plastic post-burn surgery years ago. At the beginning of 2018 when the patient was pregnant itching has appeared however cholestasis was at the normal level.

During clinical examination, patient had deep icterus, there was yellow discoloration of the skin and scleral icterus. A few scratch marks were noticed over patient's body. No evidence of hepatomegaly, ascites or encephalopathy. General condition was good, normal body weight. The patient did not feel any stomach pain and ultrasound of the abdomen did not present any pathologies.

Before the patient was admitted to the Clinic, on April 18th, 2019 the first symptoms appeared: epigastric pain, chest pain, back pain. Patient was admitted to emergency room in another hospital. Liver function tests were deranged. Showed elevated liver and cholestatic enzymes, bilirubin within the norm. Other biochemical parameters including renal function tests and serum electrolytes were normal. The ultrasound of the abdomen showed the features of microcholelithiasis, biliary colic was diagnosed.

On May 1st, 2019 another episode of abdominal pain appeared presenting jaundice accompanied by pruritus. Results of laboratory test were the following: alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were decreased. Virology (hepatitis C, B CMV, EBV and HIV) and immunological serology (ANA, AMA, SMA) were all negative. The patient denied any alcohol or drug abuse. No liver diseases were known in the family history. Ultrasound examination revealed normal liver morphology without signs of obstructive cholestasis. Magnetic resonance cholangiopancreatography (MRCP) showed normal intra and extra hepatic biliary tree and pancreatic ductal system. MRCP did not show choledocholithiasis. Due to the lack of therapeutic options, the patient was transferred to our Clinic on May 13th, 2019.

Table 1. The main parameters during the first hospitalization (13.05.2019 and 16.05.2019) and the following month (28.06.2019)

	13.05.2019	16.05.2019	28.06.2019
ALT [5 – 41U/l]	133	81	11
AST [5 – 37U/l]	115	51	14
ALP [40 – 129U/l]	185	171	86
GGT [< 60U/l]	7	5	9
Bilirubin [0.30 – 1.20mg/dl]	38	35	2
Albumin [3.50 – 5.20g/dl]	4.52		
PT [9.4 1– 2.5sec.]	10.2	10.6	12.4
PLT [150–400k/ul]	419	317	267

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; ALP, alkaline phosphatase; PT, prothrombin time; PLT, blood platelet

After admission to our Clinic conducted laboratory tests of ALP and bilirubin levels were elevated with the low level of GGT. The prothrombin time, albumin, CRP, amylase, lipase and lipid profile were within the range. Liver biopsy was not performed because in control laboratory tests we saw idiopathic low level of all parameters. Interestingly, GGT activity was always relatively low (table 1).

For the treatment we used hydroxyzine, rifampicin and ursodeoxycholic acid (UDCA). After 1,5 months the parameters were still idiopathically low, liver function improved dramatically, patient was visibly less icteric, and the pruritus had stopped. We recommended genetic testing ABCB11 and ATP8B1, but it was negative. Based on the whole clinical picture we were convinced that it was BRIC.

3. Discussion

BRIC is a rare genetic disorder characterized by intermittent episodes of jaundice and pruritus. The exact mechanism of cholestasis in BRIC and many other cholestatic conditions is poorly understood. We report a patient with characteristic

features of BRIC, occurring frequently with insistent symptoms. In 2004 Luketic and Shiffman proposed the following diagnostic criteria of BRIC: 1. at least two episodes of jaundice separated by a symptom-free interval lasting several months to years, 2. consistent laboratory data with intrahepatic cholestasis, 3. normal or minimally elevated GGT level, 4. severe pruritus secondary to cholestasis, 5. centrilobular cholestasis evident on a liver biopsy, 6. normal intra- and extrahepatic bile ducts shown on cholangiography 7. absence of factors known to be associated with cholestasis (Luketic, Shiffman, 2004). This case report does not meet all mentioned assumptions. Diagnosis was made by classical clinical presentation. The very important laboratory symptom, which we should stress is low level GGT. In this case we see it clearly. The patient had first episodes of jaundice and didn't have the biopsy. Also, the genetic test appeared negative.

The treatment of BRIC is symptomatic and medication therapy involves relieving symptoms, such as pruritus. Therapeutically, in moderate cases, conservative treatment with cholestyramine, 5-adenosylmethionine, steroids, phenobarbital, UDCA or rifampicin may be applied (Ołdakowska-Jedynak, Jankowska, Hartleb et al., 2014). In this case we used hydroxyzine, rifampicin and UDCA.

As a result of the treatment, itching has stopped. Our patient made an uneventful recovery within six and half weeks. The patient has been in remission for about a half of year. Also, there is no specific treatment available to prevent attacks or limit their duration. Opinion on UDCA treatment is divided. Some authors say that patients respond poorly to the above treatment, while others just the opposite (Gupta, Kumar, Bhatia, 2005). There are few reports that early pharmacological treatment may reduce the duration of the cholestatic episodes, most observations showed that use of UDCA or bile salt sequestrants were ineffective for both therapy and prevention of forthcoming episodes. Data concerning rifampicin treatment are equivocal. The long-term rifampicin treatment should be used with caution because of its potential hepatotoxic effect. In addition, there are few reports about treating cholestatic pruritus using Molecular Adsorbent Recirculation System (MARS) or Fractioned Plasma Separation and Adsorption System (Prometheus). Prometheus is probably more effective than MARS. Patients who were treated using Prometheus check into higher reduction clearance rates of protein-bound and water-soluble substances. Bile salts removal was the same in both systems. So, Prometheus may be more efficient in removing low molecular pruritogens and non-pruritogenic toxins other than bile salts, which are responsible for development of cholestatic attacks (Ołdakowska-Jedynak, Jankowska, Hartleb et al., 2014). Fortunately, our patient did respond to commenced treatment and Prometheus was not needed. Our patient was treated with conservative medication with complete recovery.

Conclusions

In conclusion, BRIC is a rare syndrome and does not lead to progressive liver dysfunction and cirrhosis. However, some patients presented with intermittent cholestasis, typical BRIC, may progress to PFIC and develop permanent cholestasis and porto-portal fibrosis and progressive liver damage. Therefore, patients diagnosed with BRIC require hepatological care.

BRIC should be considered in the differential diagnosis of cholestasis. Knowledge of this entity is important issue as an early recognition can prevent performance of expensive diagnostic algorithm and patient can be counseled regarding benign nature of this disease.

Bibliography

Ermis, F., Oncu, K., Ozel, M., et al. (2010). Benign recurrent intrahepatic cholestasis: late initial diagnosis in adulthood, *Annals of Hepatology, 9*, 207-210.

Gupta, V., Kumar, M., Bhatia, B.D. (2005). Benign recurrent intrahepatic cholestasis, *Indian Journal of Pediatrics, 72,* 793-794. https://rarediseases.org/rare-diseases/low-gamma-gt-familial-intrahepatic-cholestasis

Luketic, V,A., Shiffman, M,L. (2004). Benign recurrent intrahepatic cholestasis, *Clinical Liver Disease*, 133-149.

Ołdakowska-Jedynak, U., Jankowska, I., Hartleb, M., et al. (2014). Treatment of pruritus with Prometheus dialysis and absorption system in a patient with benign recurrent intrahepatic cholestasis, *Hepatology Research, 44*, E304-308.

Sohn, M.J., Woo, M.H., Seong, M.W., et al. (2019). Benign Recurrent Intrahepatic Cholestasis Type 2 in Siblings with Novel ABCB11 Mutations, *Pediatric Gastroenterology, Hepatology and Nutrition, 22*, 201–206. https://doi.org/10.5223/pghn.2019.22.2.201

Summerskill, W.H., Walshe, J,M. (1959). Benign recurrent intrahepatic 'obstructive' jaundice, *Lancet, 2*, 686–690.

Tygstrup, N., Jensen, B. (1969). Intermittent intrahepatic cholestasis of unknown etiology in five young males from the Faroe Islands, *Acta Medica Scandinavica, 185*, 523–530.

van Ooteghem, N.A., Klomp, L.W., van Berge Henegouwen, G.P., et al. (2002). Benign recurrent intrahepatic cholestasis progressing to progressive familial intrahepatic cholestasis: low GGT cholestasis is a clinical continuum, *Journal of Hepatology, 36*, 439-443.