

# Liver Abnormalities in Turner's Syndrome – Effects of Estrogen Replacement Therapy

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## Short communication

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# Abstract

## Background

Turner's syndrome is one of the most frequently reported sex chromosomal abnormality, affecting approximately 40 in every 100,000 live female births. Due to insufficient estrogen production, induction of puberty and sexual development requires hormone replacement. The syndrome affects several organ systems with diverse clinical features (cardiovascular, reproductive, hepato-biliary). There is also an increased risk of developing immune-mediated inflammatory diseases (IMID). Hepatobiliary alterations embrace a broad spectrum of possible manifestations, from asymptomatic mild hypertransaminasemia to overt hepatitis and even cirrhosis. Although exogenous estrogen hormones might cause liver dysfunction, in Turner's syndrome hormone replacement can even alleviate the derangement of laboratory values and might prove beneficial in preventing the progression of hepatic architectural alterations.

## Findings

We report two patients, in whom cessation of estrogen replacement therapy lead to worsening of hepatic and cholestatic enzyme values. These changes were later alleviated by recommencing estrogen hormone administration. We aim to summarize the available literature on estrogen hormone replacement therapy in Turner's syndrome. We also provide a brief overview on the role of estrogen hormones in the pathology associated with the syndrome.

## Conclusions

Our findings are confirming, that estrogen replacement therapy has beneficial effects on hepatic enzymes and liver related laboratory studies in Turner's syndrome. Therefore it is recommended for physicians not to withdraw estrogen replacement, even with elevated concentrations of liver and cholestatic enzymes in Turner's syndrome patients.

## Introduction

Turner's syndrome is one of the most frequently reported chromosomal abnormalities, affecting 40 in every 100,000 live female births [1, 2]. The syndrome results from the total or partial loss of the X-chromosome, being the only monosomy compatible with life [3]. The karyotype is either X-monosomy (45, X) or mosaic-type, 45X, 46XX. Classic phenotypical findings are short stature, neck webbing, gonadal dysgenesis. Though seldom, patients might undergo spontaneous puberty, or even able to conceive. As the influence of female steroid hormones are widespread, it is not surprising, that multi-systemic involvement is typical in TS [4]. The syndrome can be accompanied by congenital cardiovascular, renal malformations, representing a major cause of morbidity and mortality. Growth hormone replacement therapy is also warranted, as it is shown to facilitate normal growth in affected girls. Patients are at increased risk for autoimmune and endocrine (mostly related to thyroid gland) disorders [2]. Though sex

steroid hormones are required for the development of the cerebral cortex, the intellectual capabilities of patients are generally normal [5, 6]. The syndrome is associated with decreased self-esteem and psychological consequences, both benefiting from ERT [7].

## Methods

Hereby we report the cases of two patients with Turner's syndrome, where, the cessation of estrogen replacement caused the deterioration of cholestatic liver enzymes in laboratory studies. The initial values improved greatly after re-commencement of estrogen replacement (For the laboratory studies on cholestatic enzymes and transaminases before and after re-commencing estrogen replacement, please refer to Tables 1 and 2). In both cases, other possible underlying causes of liver enzyme derangements (infections by hepatitis or herpesviruses, metabolic diseases, alpha-1 antitrypsin deficiency, Wilson's disease) were tested for and excluded.

Table 1

Laboratory values of transaminases,  $\gamma$ GT and alkalyne phosphatase of Patient #1. All of the values are displayed in units per liter (U/L)

	<b>normal range</b>	<b>06.11.2019.</b>	<b>22.01.2020.</b>	<b>Change</b>
AST	5–40	63	25	38 (-60%)
ALT	4–38	72	38	34 (-47%)
$\gamma$ GT	5–50	605	279	326 (-54%)
AP	100–300	354	110	244 (-70%)

Table 2

Laboratory values of transaminases,  $\gamma$ GT and alkalyne phosphatase of Patient #2. All of the values are displayed in units per liter (U/L)

	<b>normal range</b>	<b>24.08.2020</b>	<b>28.10.2020</b>	<b>Change</b>
AST	5–40	19	18	1 (-5%)
ALT	4–38	50	18	32 (-64%)
$\gamma$ GT	5–50	806	122	684 (-85%)
AP	100–300	342	91	251 (-73%)

Patient 1, born in 1973, was referred to our clinic with progressively worsening of gamma-glutamyl transferase ( $\gamma$ GT) and alkaline phosphatase (AP) laboratory results, with mildly elevated transaminases (aspartate aminotransferase – AST - and alanine aminotransferase - ALT). The patient was diagnosed with mosaic type Turner's syndrome at age of sixteen. Other notable diseases included thyroid-related

abnormalities (hypofunctioning). Psychiatric abnormalities, schizophrenia and bipolar affective disorder were present, requiring medication. The deterioration of cholestatic liver enzymes became worse after the cessation of ERT. Before estrogen withdrawal, the laboratory values were not as markedly elevated. Besides the elevation of  $\gamma$ GT and AP, abdominal ultrasound confirmed hepatic steatosis. Metabolic derangements (metabolic syndrome, diabetes, insulin resistance, adiposity) are common in TS.

After revising her medications, decreasing the dosage of valproate, and losing weight, the cholestatic enzyme levels improved significantly within 10 months. The laboratory values on subsequent follow-ups are listed in Table 1., two months apart. After recommencing ERT, elevations of  $\gamma$ GT and AP improved. Later studies also confirmed the beneficial effects of continuous ERT.

Patient 2, born in 1987, has been receiving ERT since the age of 16. Initial laboratory values were notable for  $\gamma$ GT and AP elevation, without marked increase in transaminases. Psychiatric and endocrine (thyroid) abnormalities were present, requiring medication. Despite her young age, she already shown to have fatty liver (and obesity) during the workup of her laboratory abnormalities. The levels of transaminases and cholestatic enzymes before re-commencing estrogen replacement, and on subsequent follow-up are listed in Table 2.

The psychiatric and behavioral problems started early, before the initiation of ERT. The first consultation of the subject with a clinical psychologist took place at the age of twelve, whereas the estrogen-replacement was initiated four years later. The earliest psychiatric alterations were acute psychotic events and anxiety. Estrogen replacement alleviated the deranged liver-enzyme laboratory values, but after abandoning ERT (non-compliance), the  $\gamma$ GT and AP levels worsened.

## Results

According to our findings, estrogen replacement therapy, contrary to some beliefs, can be beneficial for liver function and cholestatic enzyme derangements in patients with Turner's syndrome. The previous medical documentations and laboratory tests of the two patients were studied, and the findings related to hormone replacement, concomittant laboratory values were summarized briefly. Noteworthy, that, though the concentration of transaminases showed only mild impairment, even these improved upon estrogen replacement.

AST and ALT in our first patient showed a decrease from 63 and 72 UI/L to 38 and 34 UI/L respectively, thus a remarkable change of 60% and 47% was observed. The severely elevated levels of  $\gamma$ GT and AP also reacted well, the former showing 54% improvement (from 605 to 279 UI/L), whereas the latter decreased from 354 UI/L to 110 UI/L, therefore decreased by 70%.

The laboratory value changes in case of our second patient was similar, though her AST concentrations were well within normal range (19 U/L) even before recommencement of ERT. ALT showed a 64% decrease from the initial 50 U/L to 18 U/L, whereas the levels of cholestatic enzymes ( $\gamma$ GT and AP)

showed marked improvement from 806 U/L to 122 U/L and from 342 U/L to 91 U/L, respectively. Thus, the level of  $\gamma$ GT decreased by 85% and AP by 73%.

Our findings correspond to the previous literature reports, thereby they further reinforce, that in practice, ERT has numerous beneficial effects on the quality of life and health of patients with Turner's syndrome.

So, in both cases, the liver-related enzyme elevations reacted well to ERT. Before re-commencing estrogen replacement, the  $\gamma$ GT and AP concentrations were initially markedly impaired, whereas there was only mild derangement in transaminases. After re-introduction of hormone replacement therapy, these derangements attenuated. Following previous reports, thyroid-related comorbidities were encountered. Both our patients required thyroid-hormone replacement. Patients also had high body-mass indices, and excess adiposity with steatosis of the liver.

## Discussion

Hepatic manifestations are frequent in Turner's syndrome [8]. These are usually mild, though with a moderate propensity to progress with age. The liver pathology can present with elevated transaminases,  $\gamma$ GT, and AP in laboratory studies. The highest prevalence of abnormalities is seen in patients with advanced age, but not exclusively [9]. The reported prevalence of these alterations ranges from 20 to 80%, mostly correlated with age. A large cohort study of adults with Turner's syndrome found that 36% of patients at 33 years had liver test abnormalities, with an annual incidence increase of 3.4% in five years [10]. Liver enzyme changes can also present in children, even pre-dating the actual recognition of Turner's syndrome [10].

The exact cause of these findings is not elucidated. So far, a few possible explanations have been proposed. As TS patients generally have higher BMI (adiposity), it was proposed to be an underlying cause. Later studies were unable to confirm this suspicion. Patients with TS are often prescribed estrogen-replacement therapy (ERT), known to cause liver enzyme abnormalities [11]. Yet, in Turner's syndrome hormone replacement therapy can even improve the laboratory derangements [12]. There is no evidence for the role of either excess weight or ERT causing liver test alterations.

During the diagnostic workup of liver-related changes in TS, other possible causes should be excluded. These include hepatic viral infections, autoimmune and genetic diseases, hepatotoxic drugs, and chronic alcoholism. These do not seem to be increased in patients with TS.

Hepatic alterations in TS might range from mild elevation of liver-related laboratory parameters, with minimal to no change in liver histology, even to cirrhosis and nodular regenerative hyperplasia [9]. These require histological sampling to diagnose. So far no large cohort studies were evaluating the prevalence of more severe liver architectural changes in TS. An overview of hepatic pathology is depicted in Fig. 1.

Marked hepatic pathologies, like cirrhosis, nodular regenerative hyperplasia (NRH), and multiple focal nodular hyperplasia (FNH), were observed in TS. These might be caused by primary vascular involvement

[13]. NRH is typically characterized by multiple small parenchymal nodules, conserved portal tracts, without annular fibrosis [14]. NRH is thought to be an adaptation to microcirculatory disturbances, resulting in altered intrahepatic perfusion. Thus it is a combination of hepatocyte atrophy in areas of decreased perfusion, with compensatory hepatocyte hyperplasia in areas with preserved blood flow [14].

Focal Nodular Hyperplasia (FNH) is regarded as focal hepatocyte hyperplasia, resulting from uneven perfusion of the liver parenchyma. Areas affected by FNH are generally well perfused, unlike the rest of the organ. FNH characterized by large nodules, with, or without intranodular fibrosis, alternating with fibrotic areas, with abnormal vasculature and bile ductules [15, 16]. Abnormalities of the intrahepatic portal veins included thrombosis, intimal thickening, obstruction and replacement by fibrous tissue. These are frequently encountered in the presence of liver architectural alterations, and regarded as features of obliterative portal venopathy. Cirrhosis without known cause for chronic liver disease might represent the final stage of the vascular abnormalities seen in TS. Rarely patients might require transplantation [17].

Biliary involvement has been reported in TS. Alterations include sclerosing cholangitis, primary biliary cholangitis (PBC), biliary atresia, and paucity of the bile ducts. Concentric fibrosis of small intra-hepatic bile ducts, without inflammation, were reported. These lesions resemble primary sclerosing cholangitis (PSC). Also TS patients have elevated risk for developing inflammatory bowel diseases, which are associated with an increased prevalence of PSC [18, 19]. But, those cases of TS, where there is evidence of biliary pathology, are generally not accompanied by inflammatory bowel diseases. Also, PSC mostly involves extrahepatic bile ducts, whereas in Turner's syndrome, only intrahepatic bile ducts develop lesions. Therefore it is plausible, that the pathogenesis of biliary ductal fibrosis differs from that what is seen in the case of PSC. Bile duct fibrosis is frequently seen if there is arteriolar damage in the proximity of the biliary ducts. Therefore, it might represent a consequential manifestation of vascular compromise. It also raises the question, whether the presence of biliary ductal alterations without overt liver architectural changes might represent a milder degree of vascular involvement.

Estrogen induced liver toxicity has been initially regarded as a cause of deranged liver tests. This proposal was discarded. The hormone replacement in fact can facilitate the normalization of abnormal transaminase and  $\gamma$ GT levels in these patients. Alterations of liver tests in TS are observed, regardless of whether patients are on ERT or not [20]. These laboratory findings do not normalize with the discontinuation of hormone therapy. On the contrary, they might even worsen without adequate estrogen replacement. Now it is accepted, that the cessation of estrogen replacement is not warranted in Turner's syndrome, and could even have detrimental effects.

Intrahepatic biliary duct atresia was described in pediatric TS patients. A possible explanation that abnormal angiogenesis might underlie the abnormal development of bile ducts. Cholangitis and ductopenia are frequently seen in patients with PBC, as well as in Turner's syndrome. Though the prevalence of PBC in TS is unknown, the picture of biliary involvement share commonalities. The X-chromosome contains genes involved in immune tolerance. The loss of an X-chromosome predispose

patients to the breakdown of self-tolerance and the development of autoimmune diseases. Thus, there were reports of PBC in Turner's syndrome. PBC patients also display increased risk for developing other autoimmune disorders. The partial or total loss of an X chromosome characterizes TS, and a study reported X-monosomy in women with PBC to be more common [21].

Short stature is common phenotypical finding in Turner's syndrome, seen in up to 95% of patients. Girls affected by TS usually require growth hormone replacement therapy, shown to be effective in alleviating their hindered growth [22].

In addition to alleviating liver enzyme abnormalities, estrogen replacement (with higher than usual doses) can also reduce the markers of cardiovascular risk in TS [23, 24]. Higher than normal doses of estrogen replacement were also shown to be beneficial on hepatic involvement by some authors. Furthermore, it should be kept in mind, that sex steroid hormones are implicated in the development and differentiation of the cerebral structures as well [25]. Thereby TS patients left untreated display deranged cerebral maturation. Thus, the ERT should be initiated according to the accepted guidelines, not only to induce puberty but also to enhance the physiologic female pattern development of the cerebral structures.

So far, detailed information on the longterm follow-up of TS patients with hepatic involvement is lacking. A smaller cohort study with an average follow-up time of 9 years found mostly favorable outcomes. Mild liver involvement did not deteriorate into an overt disease in most cases. More serious complications were observed in three patients, all of them displaying hepatic architectural changes. One patient died due to uncontrolled refractory ascites, pleural effusion, and heart failure. Another patient required liver transplantation six years after the diagnosis of hepatic involvement. The patient suffered from bleeding from esophageal varices and intractable cholestasis [13]. Therefore, serious complications seldom occur in Turner's syndrome, and only observed in those, with hepatic architectural alterations.

Cardiovascular pathologies represent a major cause of disease-related mortality in Turner's syndrome [8]. Extrahepatic vascular alterations are represented by coarctation of the aorta, bicuspid aortic valve, cerebral aneurysms, and gastrointestinal telangiectasias. These are not uncommon in TS. The abnormalities of thoracic vessels are seen in up to half of the patients with TS [8]. The abnormalities of the aorta are more frequently encountered in patients with overt architectural changes in the liver parenchyma.

More complex cardiovascular phenotypes were described, even in otherwise asymptomatic patients. With the combination of echocardiography and magnetic resonance imaging, it was found, that nearly 75% of adult TS patients have dilated ascending aorta, that might be associated with increased diameter of other major arteries (brachial and carotid arteries) [26].

Carotid intima-media thickness (CIMT) and arterial diameters are increased in TS, compared to healthy subjects [23, 26, 27]. One proposed explanation for these findings was estrogen-deficiency. Supporting this, estrogen replacement therapy seems to attenuate these alterations, thus reducing CIMT in young

women with TS. Additionally, ERT had beneficial effects on several metabolic parameters (HDL, triglycerides, and glucose levels, HbA1c) [24].

TS subjects display increased cardiovascular mortality, mostly due to aortic dissection, regarded as the leading cause of early mortality in Turner's syndrome patients with cardiovascular alterations. The risk of aortic dissection reported being twelve-times higher in TS, than in healthy individuals [28]. In addition to structural abnormalities, there is an increased prevalence of ischemic heart disease [27].

Highly sensitive 3D cardiovascular MRI techniques were used to evaluate aortopathy in adults with Turner's syndrome. Findings indicated accelerated ascending aortopathy, with marked growth of aortic diameter during the 2.4 years of follow-up [26]. Whether changes in other vascular areas might also develop is not yet known. As mentioned, with increasing age, patients have more tendency to develop liver architectural and circulatory changes. Thereby, possibly these findings share a common etiological origin.

Not only arteries are affected in TS. Malformations of the venous system, like agenesis or hypoplasia of the portal system, might be seen in women with Turner's syndrome [29]. Druveilhier-Baumgarten disease corresponds to presinusoidal portal hypertension due to congenital hypoplasia of the intrahepatic portal system [30]. Examination revealed no cirrhosis, but parenchymal atrophy, causing liver dysfunction.

Thromboembolic events are more common in TS patients [31]. There is also evidence for increased levels of von Willebrand-factor, factor VIII, fibrinogen, and C-reactive protein. The factor V Leiden mutation is frequent as well [32]. The aforementioned disorders could favor the development of obliterative portal venopathy, observed in some patients with Turner's syndrome [33]. The risk for DVT and portal vein thrombosis is also enhanced in Turner's syndrome [34].

## Conclusions

Our findings reflected that was expected. Previously, liver abnormalities (higher levels of  $\gamma$ -glutamyltransferase, mild hypertransaminasaemia with steatohepatosis) were reported in TS. The exact etiology of these is not yet elucidated, one can almost rule out of exogenous estrogen replacement agents as an underlying cause. More studies reported improvement in liver related laboratory values in TS, after the initiation of ERT. We were able to confirm this. Thus it should be emphasized, that hormone replacement should be initiated in TS patients, and regular follow-ups of laboratory studies is recommended [22].

## Abbreviations

ALT – alanine aminotransferase, AP – alkaline phosphatase, AST – aspartate aminotransferase, BMI – body mass index, CIMT – carotid intima-media thickness, DVT – deep venous thrombosis, ERT – estrogen replacement therapy, FNH – focal nodular hyperplasia,  $\gamma$ GT – gamma-glutamyltransferase, HDL

– high density lipoprotein, MRI – magnetic resonance imaging, NRH – nodular regenerative hyperplasia, PBC – primary biliary cholangitis, PSC – primary sclerosing cholangitis, TS – Turner’s syndrome

## Declarations

### **Ethics approval and consent to participate:**

This study was approved by the the local Ethics Committee of University of Debrecen Clinical Center. Written informed consent was provided by all patients at inception.

### **Consent for publication:**

Both patients consented for publishing their individual data in de-identified form.

### **Availability of data and materials:**

All data generated or analyzed during this study are included in this published article and are available from the corresponding author on reasonable request.

### **Conflicts of interest:**

The authors declare no competing interests.

### **Fundings:**

This study was not funded.

### **Author’s contributions:**

IF was responsible for writing the main text, summarizing literature findings. EV and ZB provided invaluable assistance in the correction of the manuscript. All authors reviewed the manuscript.

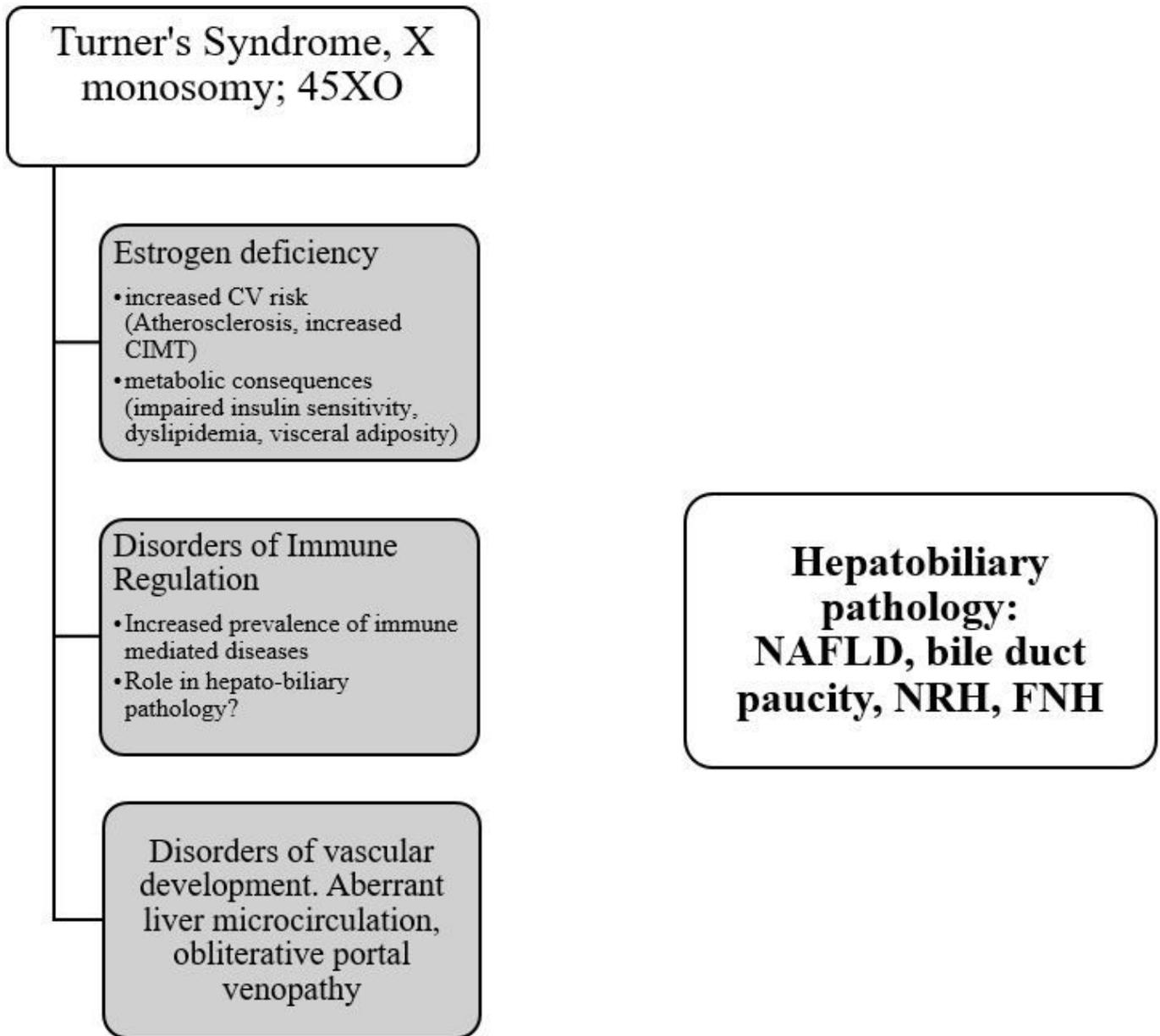
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## Figures



**Figure 1**

Contributing factors behind Turner's hepatobiliary abnormalities CV: cardiovascular, CIMT: carotid intima-media thickness, NAFLD: non-alcoholic fatty liver disease, NRH: nodular regenerative hyperplasia, FNH: focal nodular hyperplasia