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Original contribution

Hepatocellular neoplasms arising in genetic metabolic disorders: steatosis is common in both the tumor and background liver☆

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Summary Hepatocellular neoplasms can develop in multiple genetic metabolic disorders. While there have been rare case reports, clinical and pathological characterizations have not been systematically performed. We conducted a retrospective study in 9 patients with these rare genetic metabolic disorders, including glycogen storage disease type 1, ornithine carbamyl transferase deficiency, hereditary tyrosinemia type 1, and Navajo neurohepatopathy, who developed hepatocellular neoplasms. Our results show that steatosis is a common finding in both tumor (6/9 cases, 67%) and background liver parenchyma (8/9 cases, 89%), underlying a possible role for steatosis in tumorigenesis in these genetic metabolic disorders. Our findings also raise a consideration of underlying genetic metabolic disorder when young patients with hepatocellular neoplasm show steatosis in both the tumor and background liver.

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1. Introduction

The liver is the center for the metabolism of carbohydrates, fat, and proteins. Hepatocytes are involved in multiple vital metabolic processes including glycogenesis, glycogenolysis, gluconeogenesis, fatty acid oxidation, lipid synthesis, urea cycle, and protein synthesis, among others. Hepatocellular adenoma (HCA) is a benign liver tumor which can be seen in patients with exposure to estrogen or anabolic androgen and, rarely, in patients with glycogen storage disease (GSD) [1] and ornithine carbamyl transferase deficiency (OCTD) [2]. The most common malignancy in the liver is hepatocellular carcinoma (HCC). The etiology of HCC is diverse. In adults, cirrhosis, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and nonalcoholic fatty liver disease are the common causes for HCC [3]. In pediatric patients, in addition to viral infections, multiple genetic metabolic disorders such as GSD, hereditary tyrosinemia (HT), and Navajo neurohepatopathy (NNH) can also lead to HCC [4,5]. We aimed to characterize the clinical and pathologic features of HCA and HCCs arising in GSD, OCTD, HT, and NNH to better understand these neoplasms arising in these conditions.

2. Material and methods

The study was approved by institutional review boards. The computerized surgical pathology archives from 2000 to 2017 at four academic centers (University of Washington, Yale University, Mayo Clinic at Rochester, and University of California at San Francisco) were retrospectively searched. Cases of hepatocellular neoplasms arising in genetic metabolic disorders were identified. All patients' medical records were reviewed. Demographic data and clinical history were collected. The surgical procedures were noted, and the pathology reports were reviewed. All available hematoxylin and eosin (H&E) and immunohistochemical study slides were rereviewed to confirm the diagnosis. The degree of steatosis was evaluated based on the methods of the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) [6]. Patients with viral hepatitis or excessive alcohol use were excluded. HCA was subclassified by immunohistochemistry as hepatocyte nuclear factor 1 alpha (HNF1A) inactivated (loss of staining on liver fatty acid binding protein [LFABP] stain), beta-catenin mutated (positive for beta-catenin nuclear stain or diffuse glutamine synthetase stain), inflammatory (positive for C-reactive protein [CRP] and/or serum amyloid A [SAA] stains), or unclassified (no loss of LFABP staining and negative for CRP, SAA, beta-catenin nuclear and diffuse glutamine synthetase stains). Beta-catenin nuclear and diffuse glutamine synthetase stains were used to look for activated mutation of the beta-catenin pathway, which increases risk for malignant transformation. HCC was diagnosed based on multiple histological features, including loss of normal reticulin staining in nonfatty regions, thickened hepatocyte plates, vascular or stromal invasion, or extensive pseudoglandular structures. When morphological changes are equivocal, positive immunoreactivities of at least 2 of 3 markers (Glypican 3, glutamine synthetase, and HSP70) are required for the diagnosis of HCC.

3. Results

The main clinical and pathological features are summarized in Table 1. A total of 9 cases of hepatocellular neoplasms arising in genetic metabolic disorders were identified. There is a moderate female predominance (6 patients, 67%). The age at presentation ranged from 5 months to 32 years.

Five patients had GSD type 1, with a male to female ratio of 1:4, and age ranged from 3 to 32 years. Among these five patients, three developed HCA, all multiple (3 to >15 tumor nodules). Two developed HCC, one was solitary and one was multiple (16 tumor nodules) (Table 2) (Figs. 1 and 2). Interestingly, the only male patient with GSD type 1 had multiple (>15) HCAs of the inflammatory subtype. The sizes of HCAs ranged from 0.2 to 4.5 cm and HCCs ranged from 0.7 to 9 cm. HCAs arising in the two patients with GSD were of the inflammatory subtype. The other was of the unclassified subtype of HCA. Both patients with GSD + HCC had well-differentiated HCCs.

One female patient had OCTD, who developed a 2-cm HCA, which was classified as the β-catenin−activated subtype [2].

None of the aforementioned six patients had cirrhosis, although three of the patients with GSD + HCA had bridging fibrosis.

Among the remaining three patients, two had HT (5 months old and 2 years old, respectively, both boys) and one had NNH (a 9-year-old girl). They all developed multiple well-differentiated HCCs (>5 in the patients with tyrosinemia and 2 in the patient with NNH) in a background of cirrhosis (Fig. 3).

Most patients (N = 6, 67%) had mild to severe steatosis in the tumors. In fact, steatohepatitic variant HCCs were observed in the patient with GSD + multiple HCCs. The background liver showed mild to severe steatosis in the majority of patients (N = 8, 89%). Most patients N = (8, 89%) received liver transplantation. All were alive without tumor recurrence at 3-year follow-up.

4. Discussion

Multiple genetic metabolic disorders can have liver tumors as one of the complications. We studied patients who developed HCA or HCC in a background of glycogen storage disease, Cheng et al. [6] ornithine transcarbamylase deficiency, tyrosinemia, or Navajo neurohepatopathy; and

Table 1 Compiled clinical and histological features of nine cases of hepatocellular tumors arising in genetic metabolic disorders.

Genetic abnormalities	Age (y)	Gender	Tumor			Tumor steatosis average score (NASH CRN)	Average background liver steatosis (NASH CRN)	Cirrhosis	Treatment
			Type	Number	Size (cm)				
GSD type 1 (n = 5)	3-32 (mean = 16.4)	M/F = 1/4 (n = 5)	2 well-differentiated HCCs; 3 HCAs (2 inflammatory subtype; 1 unclassified)	One to multiple (mean = 3.5)	0.2–9	2	1.8	N	All transplant except one resection
Tyrosinemia type 1 (n = 2)	5 m and 2	M (n = 2)	Well-differentiated HCCs	Multiple	Largest 1.4	1.5	2.5	Y	Transplant
Others (n = 2: Navajo neurohepatopathy and OCTD)	9 and 21	F (n = 2)	Well-differentiated HCCs and HCA (b-catenin–activated subtype)	One to 2 (mean = 1.7)	1.5–2	0.5	0.5	Y (Navajo neurohepatopathy) and N (OCTD)	Transplant

y,
year; m, month;
M, male; F, female; Y, yes; N, no; OCTD, ornithine carbamyl transferase deficiency; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; GSD, glycogen storage disease; NASH CRN, Nonalcoholic Fatty Liver Disease Clinical Research Network.

characterized the clinical features and pathology of liver tumors and background liver in these patients. Although these four genetic disorders affect different metabolic pathways in the liver, most of the patients showed macrovesicular steatosis in both the tumor tissue and the background liver parenchyma, suggesting a common finding for steatosis in these patients.

GSD is caused by abnormalities in glycogenesis or glycogenolysis. Depending on the affected enzymes, GSD can be divided into more than 10 types [7]. The most common form of GSD is type I, also known as von Gierke disease, which is an autosomal recessive disorder resulting from mutations in G6PC or SLC37A4 genes. Mutations of these two genes cause hypoglycemia and abnormal accumulation of glycogen in organs and eventually liver and kidney failure. Mutations also lead to hyperlipidemia due to excess glucose-6-phosphate shunting into alternative pathways [8]. HCA is a common complication in GSD type I, with prevalence between 22 and 75%, and 10% risk of malignant transformation into HCC [9].

In patients with GSD, hypoglycemia triggers oxidation of fatty acid in peripheral tissue to provide energy, which consequently increases the plasma free fatty acid (FFA) concentration. FFAs are then taken up by the liver and used for triglyceride synthesis, leading to increased fat deposition within hepatocytes and eventually steatosis [10]. One of the current hypotheses is that fat accumulation inhibits AMP-activated protein kinase (AMPK) pathway. AMPK can repress STAT3 and NFκB pathways. The STAT3 pathway is important for inflammatory responses, and the NFκB pathway is tumorigenic when overexpressing. Inhibition of AMPK may lead to overactivation of STAT3 and NFκB pathways; and eventually result in the formation of HCA or carcinoma. There are multiple studies supporting this hypothesis. For example, in a mouse model of GSD type 1a, when hypoglycemia was corrected by introducing G6Pase through adenovirus-associated vector, the mice showed increased activity of AMPK pathway and absence of hepatic tumors [11]. A different mouse model showed that liver-specific activation of AMPK pathway could decrease hepatic steatosis [12]. In addition, cell line studies showed that activating AMPK pathway by metformin could reduce the risk of hepatocarcinogenesis [13].

HNF1A–inactivated HCA (HCA-H) subtype usually shows steatosis. Other subtypes of HCA can show steatosis but are not as often. The HCA-H subtype has biallelic mutation in HNF1A gene with consequent loss of expression of LFABP [14]. In our study, the HCAs in patients with GSD did not show loss of LFABP. Instead, they showed either increase of inflammatory proteins (inflammatory subtype) or no specific changes (unclassified subtype). Hence, although the HCAs in patients with GSD in our study showed steatosis, the steatosis was likely caused by a different mechanism than loss of LFABP. The molecular feature of the inflammatory subtype of HCA is the activation of JAK/STAT pathway [14]. It is possible that the

Table 2 Pathological features of hepatocellular tumors arising in patients with glycogen storage disease type I.

Case #	Tumor			Tumor steatosis (NASH CRN)	Background liver steatosis (NASH CRN)	Cirrhosis
	Type	Number	Size (cm)			
1	Well-differentiated HCCs	16	0.7–9	2	3	N
2	Well-differentiated HCC	1	9	0	1	N
3	HCAs, inflammatory subtype	3	1, 3, 4	2	2	N
4	HCAs, inflammatory subtype	>15	0.2–2	2	1	N
5	HCAs, unclassified subtype	6	1.3–4.5	2	2	N

NASH CRN, Nonalcoholic Fatty Liver Disease Clinical Research Network; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma.

formation of the inflammatory subtype of HCA is due to the inhibition of AMPK. The other two of our patients with GSD had HCCs. It is not clear whether their HCCs are de novo or transformed from HCAs.

Ornithine transcarbamylase (OTC) is a mitochondrial enzyme that converts carbamoyl phosphate and ornithine into citrulline [15]. Mutations in OTC gene lead to OTCD, which is an X-linked recessive disorder of urea cycle. Patients with OTCD present with hyperammonemia and consequent multiple organ damages including liver. HCAs and HCCs are very rare in patients with OTCD [2,16]. Although there is no published study showing a direct relationship between OTCD and liver tumorigenesis, the enzyme downstream of OTC in urea cycle is argininosuccinate synthetase (ASS). ASS ligates citrulline to aspartate and hydrolyzes ATP into AMP, which increases the AMP/ATP ratio and consequently activates AMPK pathway [17]. When urea production is increased, the signals going through ASS are increased; hence, AMPK pathway is upregulated [17]. On the contrary, deficiency of ASS causes hyperammonemia, a similar condition to OTCD. The excess of ammonia decreases the activity of

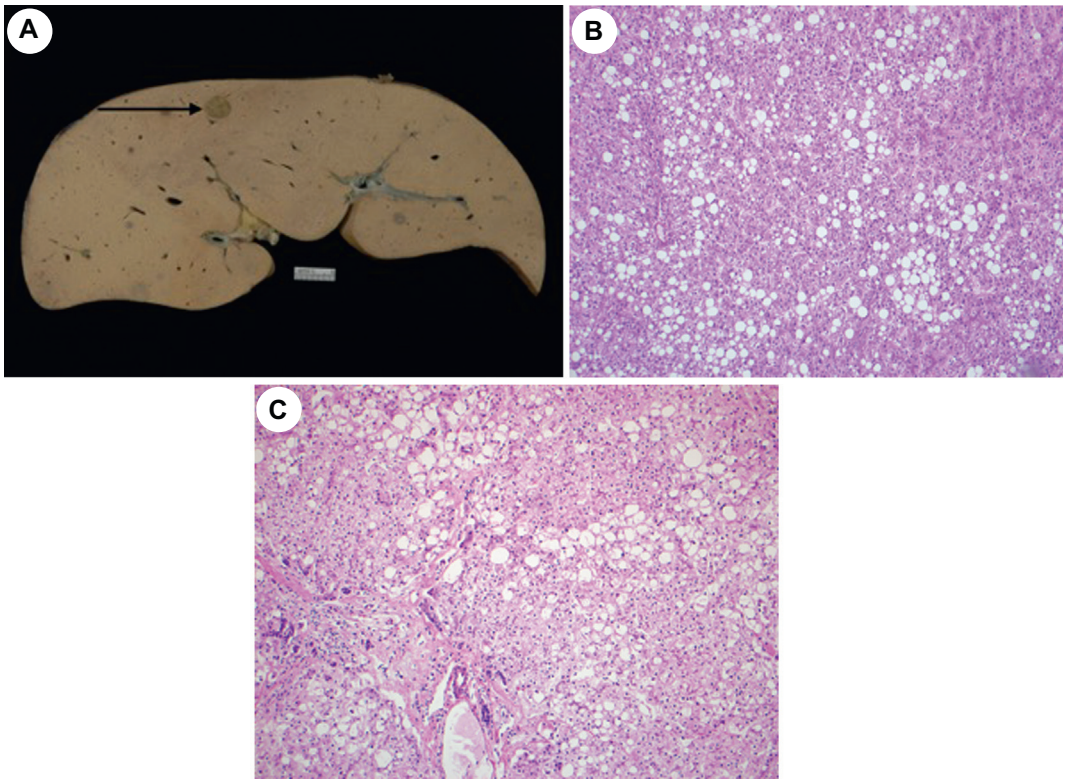

Fig. 1 Explanted liver from a patient with glycogen storage disease type 1 contains multiple hepatocellular adenomas. A, One slice of the liver shows a 1.3 cm hepatocellular adenoma (arrow). B, Micrograph of the hepatocellular adenoma shows bland architecture, unpaired arteries, and absence of portal tracts. Marked intratumoral steatosis are seen (H&E stained, ×100). C, Background liver shows moderate steatosis (H&E stained, ×100).

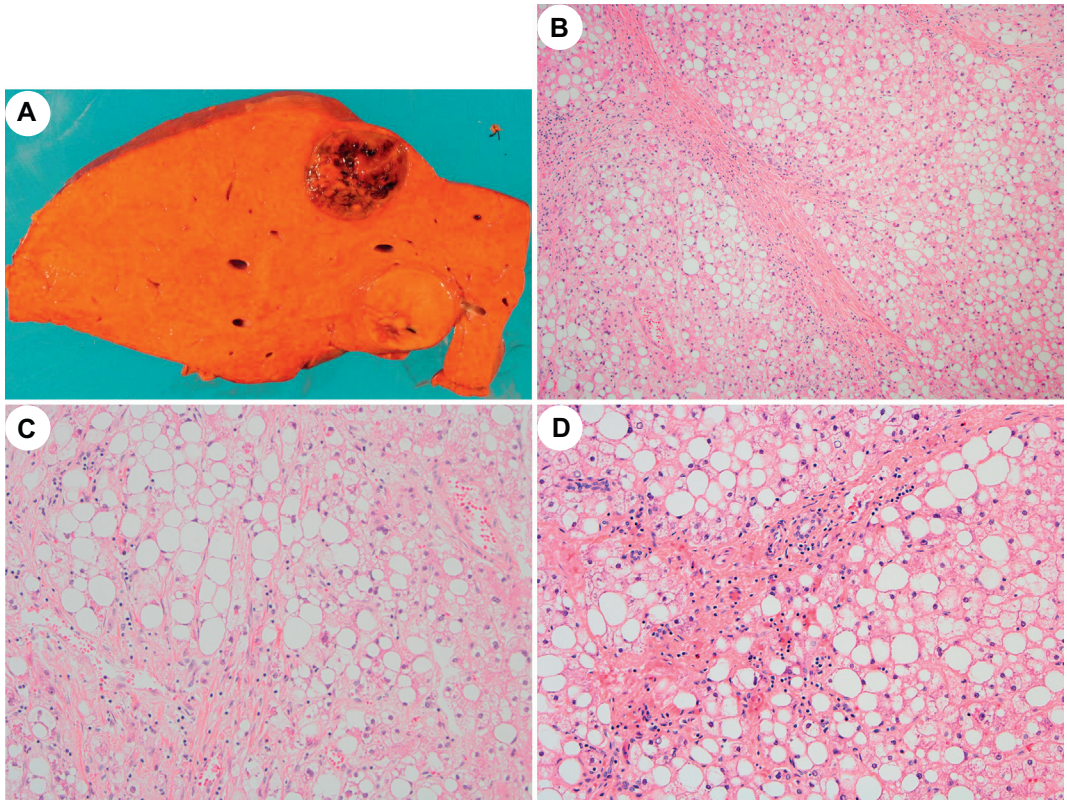

Fig. 2 Explanted liver from a patient with glycogen storage disease type 1 contains multiple hepatocellular carcinomas. A, One slice of the liver shows two hepatocellular carcinomas. B, Micrograph of the hepatocellular carcinoma shows altered architecture, marked intratumoral steatosis, unpaired arteries, inflammation, thick collagen fibers, and lack of portal tracts (H&E stained, ×100). C, Higher magnification shows features of steatohepatitic variant of hepatocellular carcinoma, including intratumoral steatosis, inflammation, and many ballooned cells, most containing Mallory-Denk bodies (H&E stained, ×200). D, Background liver shows marked steatosis (H&E stained, ×200).

AMPK and fatty acid oxidation and leads to accumulation of fat within hepatocytes [18]. It may be plausible that OTCD leads to steatosis by decreasing the signals going through ASS, which subsequently inhibits the AMPK pathway. The downstream targets such as STAT3 and NFκB pathways lose the negative control from AMPK, which may result in tumorigenesis. Further studies are warranted to fully understand the mechanisms.

HT is the abnormal accumulation of tyrosine and its metabolic products in blood, caused by impairment of enzymes involved in the tyrosine breakdown. It can be divided into three types, and all three types are autosomal recessive disorders. HT type 1 is the most severe form, caused by fumarylacetoacetate hydrolase (FAH) gene mutations. Deficiency of FAH leads to accumulation of toxic intermediate products. Patients present with symptoms mainly involving the liver and kidney. Hepatomegaly, liver cirrhosis, and HCC can be seen in infancy. The current treatment for HT type 1 is use of nitisinone (NTBC) to prevent tyrosine breakdown and diet restricted in tyrosine and phenylalanine intake [19]. All patients with HT type 1 have increased risk of developing HCC. Treatment with NTBC has markedly decreased the incidence of HCC in those patients. The reported HCC frequency was 18% before NTBC treatment was widely adopted, and <1% if NTBC treatment started before 1 year old [20].

The two patients with HT in our study are both type 1, and both presented with multiple well-differentiated HCCs in early childhood. It has been reported that upregulation of p21 and mTOR pathways in tyrosinemia type 1 mouse model contributed to the hepatic tumorigenesis [21]. Interestingly, activating of AMPK pathway can inhibit mTOR pathway and delay tumor development [22]. AMPK pathway not only inhibits mTOR pathway but also activates UNC51-like kinase 1 complex and stimulates the autophagy (self-eating), which serves as the quality control process in the liver [23]. Therefore, inhibition of the AMPK pathway seems to be a potential explanation of the tumorigenesis in HT.

Both our patients with HT had cirrhotic background liver, which is also a risk factor for developing HCC. It is proposed that the inflammatory pathways including NF-κB, STAT3, and c-Jun N-terminal kinase are the missing links between cirrhosis and HCC [24]. Because AMPK is upstream of these inflammatory pathways, it

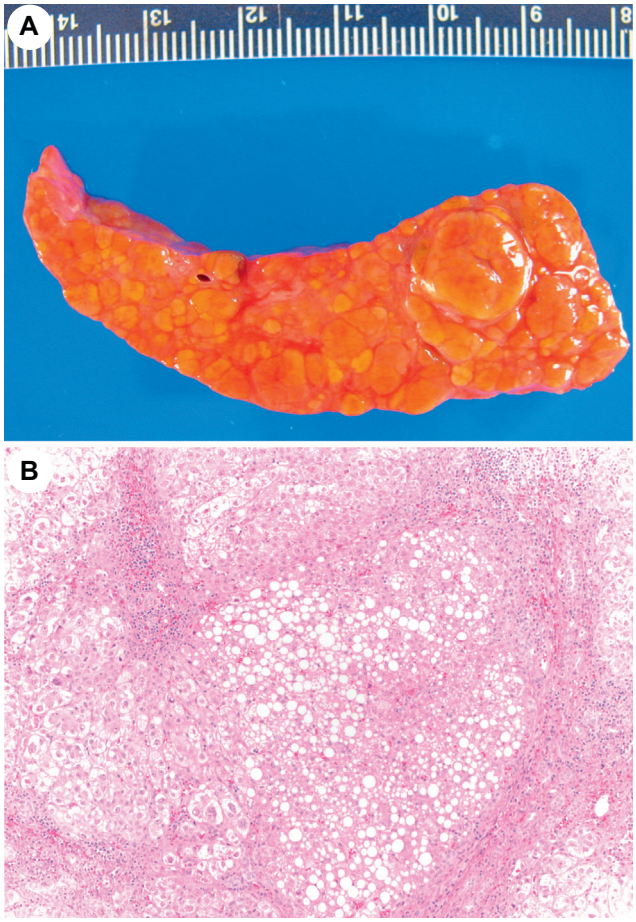

Fig. 3 Explanted liver from a patient with hereditary tyrosinemia type 1 contains multiple well-differentiated hepatocellular carcinoma and dysplastic nodules. A, One slice of the liver shows a 1.4 cm hepatocellular carcinoma (arrow). B, Nontumor liver shows cirrhosis and steatosis (H&E stained, ×100).

is possible that AMPK also plays a role in the development of HCC in cirrhotic livers of other etiologies.

NNH is a rare autosomal recessive genetic disorder. It is seen in the Navajo Indian population in the United States. Depending on the clinical features, NNH can be divided into 3 types [25]: Infantile NNH presents with jaundice and failure to thrive shortly after birth and develops liver failure and death within first 2 years of life. Childhood NNH has a sudden onset of liver damage between 1 and 5 years of age and shows rapid progression to liver failure within months. Classic NNH presents mainly with progressive neurological disorders, in addition to the gradually deteriorated liver function. Rare cases of HCC developed in patients with NNH have been reported [5,26]. The patient in our study has classic NNH. Mutations of *MPV17* gene have been identified in patients with NNH, which cause a hepatocerebral form of mitochondrial DNA depletion [5]. MPV17 protein locates in the inner membrane of mitochondria and functions as a nonselective channel that modulates membrane potential [27]. When mutated, mitochondria homeostasis is disrupted and results in mitochondrial DNA depletion. It is conceivable that depletion of mitochondrial DNA can cause dysregulation of metabolism in the liver and eventually liver tumors. One of the treatment strategies for mitochondrial diseases is to increase mitochondriogenesis by activating AMPK pathway. Use of the AMPK agonist AICAR in mitochondrial disease mouse model has shown increased respiratory chain activities and improvement of motor endurance. Whether AICAR can delay or reverse the steatosis and tumorigenesis in NNH remains to be investigated [28].

In conclusion, our study shows hepatocellular neoplasms can arise in multiple congenital metabolic disorders. Close clinical follow-up and surveillance in these patients may be necessary. Steatosis in the tumor and background liver in these patients is common, raising a consideration of underlying genetic metabolic disorders in young patients with hepatocellular neoplasms when steatosis in both the tumor and background liver is seen. Dysregulation of fatty acid oxidation and increased oxidative stress in hepatocytes may lead to steatosis and subsequent tumorigenesis, with AMPK pathway as one of the potential candidate connections and targets in the cross-talk between metabolic processes and cell proliferation regulations. Further studies are warranted in patients with these genetic metabolic disorders for early prevention and treatment of the liver neoplasms arising in these patients.

References

[1] Franchi-Abella S, Branchereau S. Benign hepatocellular tumors in children: focal nodular hyperplasia and hepatocellular adenoma. Int J Hepatol 2013;2013:215064. https://doi.org/10.1155/2013/215064. Epub 2013 Mar 11. PubMed PMID: 23555058.

[2] Cheng L, Liu Y, Wang W, et al. Hepatocellular adenoma in a patient with ornithine transcarbamylase deficiency. Case Reports Hepatol 2019 Oct 2;2019:2313791. https://doi.org/10.1155/2019/2313791. eCollection 2019. PubMed PMID: 31662921.

[3] Choo SP, Tan WL, Goh BKP, et al. Comparison of hepatocellular carcinoma in Eastern versus Western populations. Cancer 2016 Nov 15;122:3430–46. https://doi.org/10.1002/cncr.30237. Epub 2016 Sep 13. Review. PubMed PMID: 27622302.

[4] Khanna R, Verma SK. Pediatric hepatocellular carcinoma. World J Gastroenterol 2018 Sep 21;24:3980–99. https://doi.org/10.3748/wjg.v24.i35.3980. Review. PubMed PMID: 30254403.

[5] Karadimas CL, Vu TH, Holve SA, et al. Navajo neurohepatopathy is caused by a mutation in the MPV17 gene. Am J Hum Genet 2006 Sep;79:544–8. Epub 2006 Jun 28. PubMed PMID: 16909392.

[6] Kleiner DE, Brunt EM, Van Natta M, et al. Nonalcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005 Jun;41:1313–21. PubMed PMID: 15915461.

[7] Marion RW, Paljevic E. The glycogen storage disorders. Pediatr Rev 2020 Jan;41:41–4. https://doi.org/10.1542/pir.2018-0146. Erratum in: Pediatr Rev. 2020 Feb;41(2):99. PubMed PMID: 31894075.

[8] Wang DQ, Fiske LM, Carreras CT, et al. Natural history of hepatocellular adenoma formation in glycogen storage disease type I. J Pediatr 2011 Sep;159:442–6. https://doi.org/10.1016/j.jpeds.2011.02.031. Epub 2011 Apr 9. PubMed PMID: 21481415.

[9] Liau SS, Qureshi MS, Praseedom R, et al. Molecular pathogenesis of hepatic adenomas and its implications for surgical management. J Gastrointest Surg 2013 Oct;17:1869–82. https://doi.org/10.1007/s11605-013-2274-6. Epub 2013 Jul 9. Review. PubMed PMID: 23835731.

[10] Jensen-Urstad AP, Semenkovich CF. Fatty acid synthase and liver triglyceride metabolism: housekeeper or messenger? Biochim Biophys Acta 2012 May;1821:747–53. https://doi.org/10.1016/j.bbalip.2011.09.017. Epub 2011 Oct 8. Review. PubMed PMID: 22009142.

[11] Kim GY, Kwon JH, Cho JH, et al. Downregulation of pathways implicated in liver inflammation and tumorigenesis of glycogen storage disease type Ia mice receiving gene therapy. Hum Mol Genet 2017 May 15;26:1890–9. https://doi.org/10.1093/hmg/ddx097. PubMed PMID: 28334808.

[12] Woods A, Williams JR, Muckett PJ, et al. Liver-specific activation of AMPK prevents steatosis on a high-fructose diet. Cell Rep 2017 Mar 28;18:3043–51. https://doi.org/10.1016/j.celrep.2017.03.011. PubMed PMID: 28355557.

[13] Chen HP, Shieh JJ, Chang CC, et al. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. Gut 2013 Apr;62:606–15. https://doi.org/10.1136/gutjnl-2011-301708. Epub 2012 Jul 7. PubMed PMID: 22773548.

[14] Zucman-Rossi J, Jeannot E, Nhieu JT, et al. Genotype-phenotype correlation in hepatocellular adenoma: new classification and relationship with HCC. Hepatology 2006 Mar;43:515–24. PubMed PMID: 16496320.

[15] Ah Mew N, Simpson KL, Gropman AL, et al. Urea cycle disorders overview [updated 2017 Jun 22]. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle. 1993-2020; 2003 Apr 29. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1217/. PubMed PMID: 20301396.

[16] Wilson JM, Shchelochkov OA, Gallagher RC, et al. Hepatocellular carcinoma in a research subject with ornithine transcarbamylase deficiency. Mol Genet Metabol 2012 Feb;105:263–5. https://doi.org/10.1016/j.ymgme.2011.10.016. Epub 2011 Nov 7. PubMed PMID: 22129577.

[17] Madiraju AK, Alves T, Zhao X, et al. Argininosuccinate synthetase regulates hepatic AMPK linking protein catabolism and ureagenesis to hepatic lipid metabolism. Proc Natl Acad Sci U S A 2016 Jun 14;113:E3423–30. https://doi.org/10.1073/pnas.1606022113. Epub 2016 May 31. PubMed PMID: 27247419.

[18] Leung TM, Lu Y, Yan W, et al. Argininosuccinate synthase conditions the response to acute and chronic ethanol-induced liver injury in mice. Hepatology 2012 May;55:1596–609. https://doi.org/10.1002/hep.25543. PubMed PMID: 22213272.

[19] US Food and drug administration website. ORFADIN (nitisinone) Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206356Orig1_toc.cfm. [Accessed 8 July 2020].

[20] Chinsky JM, Singh R, Ficicioglu C, et al. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. Genet Med 2017 Dec;19. https://doi.org/10.1038/gim.2017.101. Epub 2017 Aug 3. Review. PubMed PMID: 28771246.

[21] Tanguay RM, Angileri F, Vogel A. Molecular pathogenesis of liver injury in hereditary tyrosinemia 1. Adv Exp Med Biol 2017;959:49–64. https://doi.org/10.1007/978-3-319-55780-9_4. Review. PubMed PMID: 28755183.

[22] Robert M. Tanguay. Hereditary tyrosinemia: pathogenesis, screening and management. Springer; 2017.

[23] Kim J, Kundu M, Viollet B, et al. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol 2011 Feb;13:132–41. https://doi.org/10.1038/ncb2152. Epub 2011 Jan 23. PubMed PMID: 21258367.

[24] Ramakrishna G, Rastogi A, Trehanpati N, et al. From cirrhosis to hepatocellular carcinoma: new molecular insights on inflammation and cellular senescence. Liver Cancer 2013 Aug;2:367–83. https://doi.org/10.1159/000343852. Review. PubMed PMID: 24400224.

[25] Holve S, Hu D, Shub M, et al. Liver disease in Navajo neuropathy. J Pediatr 1999 Oct;135:482–93. PubMed PMID: 10518083.

[26] El-Hattab AW, Li FY, Schmitt E, et al. MPV17-associated hepatocerebral mitochondrial DNA depletion syndrome: new patients and novel mutations. Mol Genet Metabol 2010 Mar;99:300–8. https://doi.org/10.1016/j.ymgme.2009.10.003. Epub 2009 Oct 13. PubMed PMID: 20074988.

[27] Antonenkov VD, Isomursu A, Mennerich D, et al. The human mitochondrial DNA depletion syndrome gene MPV17 encodes a non-selective channel that modulates membrane potential. J Biol Chem 2015 May 29;290:13840–61. https://doi.org/10.1074/jbc.M114.608083. Epub 2015 Apr 10. PubMed PMID: 25861990.

[28] Viscomi C, Bottani E, Zeviani M. Emerging concepts in the therapy of mitochondrial disease. Biochim Biophys Acta 2015 Jun-Jul;1847:544–57. https://doi.org/10.1016/j.bbabio.2015.03.001. Epub 2015 Mar 10. Review. PubMed PMID: 25766847.