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Hepatocellular adenoma in the paediatric population: Molecular classification and clinical associations

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Abstract

Hepatocellular adenomas (HCAs) represent rare, benign liver tumours occurring predominantly in females taking oral contraceptives. In children, HCAs comprise less than 5% of hepatic tumours and demonstrate association with various conditions. The contemporary classification of HCAs, based on their distinctive genotypes and clinical phenotypes, includes *hepatocyte nuclear factor 1 homeobox alpha*-inactivated HCAs, *beta-catenin*-mutated HCAs, inflammatory HCAs, combined *beta-catenin*-mutated and inflammatory HCAs, sonic hedgehog-activated HCAs, and unclassified HCAs. In children, there is a lack of literature on the characteristics and distribution of HCA subtypes. In this review, we summarized different HCA subtypes and the clinicopathologic spectrum of HCAs in the paediatric population.

Key words: Paediatric; Hepatocellular adenoma; Malignant transformation; *Beta-catenin*; *HNF1A*; Glycogen storage disorders

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Core tip: Hepatocellular adenomas (HCAs) are uncommon liver tumours with 2 major complications: bleeding and malignant transformation; these lesions are classified based on their distinctive genotypes and clinical phenotypes. HCAs in children may be identified in the setting of conditions such as glycogen storage disorder and familial adenomatous polyposis. However, the molecular subtypes do not always correlate with predisposing risk factors and syndromes. Herein, we will discuss the different subtypes of HCA and the clinicopathological characteristics in children.

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INTRODUCTION

Hepatocellular adenomas (HCAs) are rare benign neoplasms arising from hepatocytes, occurring at a rate of 3-4 per 100000^[1]. There is a female predominance with a strong association with oral contraceptive pill (OCP) use^[2,3]. Other risk factors for the development of HCAs include androgen hormone imbalance, obesity, alcohol intake, liver vascular disease, chronic viral hepatitis, cirrhosis, previous malignancy, and germline genetic susceptibility^[4-6]. Although HCAs are considered benign, these lesions have 2 major complications: severe bleeding and malignant transformation^[4]. The current HCA classification provides considerable benefits in terms of management and prognostication. The literature of HCAs in the paediatric population is still limited. In children, HCAs have been associated with glycogen storage diseases (GSDs), galactosemia, Hurler syndrome (mucopolysaccharidosis type 1), familial adenomatous polyposis syndrome, and Fanconi anemia (FA), among others^[7-10].

In this review, we will discuss the current molecular classification of HCAs, followed by select clinical associations in children.

MOLECULAR SUBTYPES OF HEPATOCELLULAR ADENOMA

HCAs were initially categorized into 4 subtypes based on the genotypes and clinical phenotypes: *hepatocyte nuclear factor 1 homeobox alpha* (*HNF1A*)-inactivated HCAs (HHCAs), inflammatory HCAs (IHCAs), *beta-catenin*-mutated HCAs (bHCAs), and unclassified HCAs (UHCAs)^[11]. Further evaluation using gene expression profiling, RNA sequencing, whole-exome and -genome sequencing, resulted in an expanded classification which includes bHCAs involving exon 3 (b^{ex3}HCAs) and exon 7 or 8 (b^{ex7,8}HCAs), IHCAs with *beta-catenin* mutations (b^{ex3}IHCAs and b^{ex7,8}IHCAs), and a newly defined entity of sonic hedgehog HCAs (shHCAs)^[4]. The clinical and pathological characteristics of these subtypes are summarized in [Table 1](#).

HHCA

HNF1A is a gene located on chromosome 12 (12q24.31) that encodes the protein hepatocyte nuclear factor 1 (HNF1) which acts as a transcription factor, developmentally regulating gene expression through interactions with the promoters of genes expressed in the liver^[12]. Zucman-Rossi *et al*^[11] demonstrated that bi-allelic inactivating mutations of *HNF1A* constituted a homogenous, morphologically distinct subgroup of adenomas (HHCAs). These mutations are exclusive of mutations in genes associated with other subtypes of HCA (*CTNNB1*, *IL6ST*, *JAK1*, *GNAS* and *STAT3*)^[13].

HHCAs most commonly affect female patients with an average age of 37 years at diagnosis in one series, with 8% of patients demonstrating germline *HNF1A* mutations^[4]. Risk factors for the development of HHCAs include oral contraceptive use, which is especially potent due to the decreased estradiol detoxification in these tumours, and *HNF1A* germline mutations^[4,14]. The familial form of hepatic adenomatosis (multiple HHCAs) secondary to germline mutations of *HNF1A* has been identified in patients with maturity-onset diabetes of the young type 3^[15-19]. Additionally, *HNF1A* contains a poly-cytosine C8-microsatellite, making it susceptible to microsatellite instability; this phenomenon has been observed to result in HHCA development in 3 unrelated children with bi-allelic mutations of *MLH1* and *PMS2*^[20].

Histologically, HHCAs are characterized by intralesional steatosis, along with a lack of inflammation and cytologic atypia^[21]. This phenomenon (intralesional steatosis) is due to increased lipogenesis secondary to *HNF1A* inactivating mutations, occurring via down-regulation of liver fatty acid binding protein (LFABP)^[22]. It is important to note that the degree of steatosis in each lesion varies, and steatosis is not exclusively seen in this subtype of HCA. The diagnosis of HHCA can be confirmed by decreased or absent LFABP immunostaining in the lesional cells^[21]. Although rare, malignant transformation has been associated with this subtype of HCA^[19,23,24].

IHCA

IHCAs are one of the most common subtypes (30%-50% of HCAs) which are

Table 1 Clinicopathologic characteristics of different hepatocellular adenoma subtypes

HCA subtype	Risk factors	Specific clinical features	Histologic features	IHCs
HHCA	<i>HNFI1A</i> germline mutations, MODY type 3, microsatellite instability	Hepatic adenomatosis	Intralesional steatosis	LFABP (absent/decreased)
IHCA	Obesity, alcohol, glycogenosis	Inflammatory syndrome	Sinusoidal dilatation, inflammatory infiltrate	CRP, SAA
b ^{ex3} HCA	Male, liver vascular disease, androgen therapy	Frequent malignant transformation	Pseudoacinar formation, mild nuclear atypia	beta-catenin (nuclear staining), GS (diffuse and strong)
b ^{ex7,8} HCA	No specific risk factors	No specific clinical features	No specific features	GS (weak, heterogeneous)
shHCA	Obesity	Symptomatic bleeding	Intratumoural hemorrhage	Prostaglandin D2 synthase
UHCA	No specific risk factors	No specific clinical features	No specific features	None

HCA: Hepatocellular adenoma; IHCs: Immunohistochemical stains; *HNFI1A*: *hepatocyte nuclear factor 1 homeobox alpha*; HHCA: *HNFI1A*-inactivated hepatocellular adenoma; IHCA: Inflammatory hepatocellular adenoma; b^{ex3}HCA: *Beta-catenin*-mutated hepatocellular adenoma (exon 3); b^{ex7,8}HCA: *Beta-catenin*-mutated hepatocellular adenoma (exon 7/8); shHCA: Sonic hedgehog-activated hepatocellular adenoma; UHCA: Unclassified hepatocellular adenoma; MODY: Maturity-onset diabetes of the young; LFABP: Liver fatty acid binding protein; CRP: C-reactive protein; SAA: Serum amyloid A; GS: Glutamine synthetase.

characterized by *IL6ST* mutations^[4,25]. The gene is located on chromosome 5 (5q11.2) and encodes glycoprotein 130 (gp130), a signal transducer for the JAK/STAT pathway^[26]. Mutations in gp130 lead to sustained activation of the pathway, resulting in hepatocellular proliferation and HCA development^[25,27]. *GNAS* also plays a role in activating this pathway, with somatic mutations leading to the development of HCA and HCC^[25].

IHCAs demonstrate a female predominance, with an average age of diagnosis of 40 years^[4]. Clinically, IHCA patients may present with fever, leukocytosis, and elevated C-reactive protein (CRP), gamma-glutamyl transferase, alkaline phosphatase, and amyloid-associated proteins^[4]. In general, this subtype has been associated with high body mass index, alcohol consumption, GSD type I, and primary sclerosing cholangitis^[21]. IHCAs carry an increased risk of bleeding due to their highly vascularized morphology^[25].

Microscopically, IHCAs are characterized by display inflammatory infiltrates (predominantly lymphocytes and histiocytes, admixed with plasma cells and neutrophils), sinusoidal dilatation, dystrophic arteries, and variable ductular reaction in the periphery of the lesions^[4,21]. By immunohistochemistry, the tumours are positive for CRP and serum amyloid A^[4]. Malignant transformation occurs in 5-10% of IHCAs, with coexisting *beta-catenin* mutations implicated in the pathogenesis^[28].

bHCA

CTNNB1 (catenin, beta-1) is a gene located on chromosome 3 (3p22.1) that encodes the protein beta-catenin, an adherens junction protein^[29]. This protein anchors the actin cytoskeleton between epithelial cells, communicating a contact inhibition signal, regulating normal cell growth and behaviour^[29]. The Wnt/beta-catenin pathway regulates hepatocellular development, growth, and regeneration^[30]. Mutations in *CTNNB1* may result in uncontrolled hepatocyte proliferation. These mutations can occur in exon 3, 7, or 8, giving rise to HCAs and HCC^[4]. b^{ex3}HCAs has the highest malignant transformation potential^[4]. In one series, approximately half of all bHCAs co-demonstrated inflammatory phenotypes with mutations affecting genes implicated in IHCAs (6% of all HCAs being classified as b^{ex3}IHCAs and 4% as b^{ex7,8}IHCAs)^[4].

bHCAs occur in younger patients than the other subtypes, with an average age of 27.5-28.5 years at diagnosis, and a female predominance, although a higher proportion of males are affected than in other subtypes^[4]. An association with androgen therapy is well-described.

The characteristic morphological features include mild cytologic atypia and pseudoacinar formation in addition to typical HCA findings. In b^{ex3}HCAs, the lesional cells demonstrate diffuse and strong immunohistochemical expression of glutamine synthetase (GS) and aberrant, nuclear positivity for beta-catenin^[4]. Meanwhile, b^{ex7,8}HCAs are characterized by perivenular and heterogeneous staining of GS without nuclear beta-catenin expression.

shHCA

A subset of HCAs demonstrates small deletions of *INHBE* (inhibin, beta-E) which lead to *INHBE-GLI1* fusions^[4]. *INHBE* is a gene located on chromosome 12 (12q13.3) that

encodes a protein which plays a role in pancreatic exocrine growth and proliferation^[31]. *GLI1* is a gene located on chromosome 12 (12q13.3) as well; it is involved in signal transduction in the sonic hedgehog signaling pathway, and activates transcription of target genes^[32]. In the liver, the sonic hedgehog pathway leads to growth of progenitor hepatocyte populations, thereby promoting regeneration, with accompanying compensatory reparative changes, including inflammation, fibrosis and vascular remodeling^[33]. These changes are classically associated with cirrhosis but can play a role in the pathogenesis of shHCAs, HCC, and cholangiocarcinoma^[33]. *GLI1* fusions have been observed in other benign neoplasms, as have other mutations affecting the sonic hedgehog pathway^[34-36]. In one series, shHCAs accounted for 4% of previously unclassified HCAs^[4].

shHCAs have a strong female predominance, with an average age of diagnosis of 43 years^[4]. This subtype shows intratumoural hemorrhage on microscopic examination^[4]. By immunohistochemistry, the lesional cells are positive for prostaglandin D2 synthase, while argininosuccinate synthetase 1, albeit molecularly enhanced in shHCAs, shows non-specific staining in this subtype as well as others^[4,37]. Currently, the malignant potential of shHCAs is unknown^[4].

UHCA

UHCA accounted for approximately 7% of HCAs in one large series^[4]. These lesions occur with a female predominance at an average age of 38 years^[4]. The microscopic and immunohistochemical analysis is non-specific, aside from showing typical morphologic features of HCA^[4,21].

HEPATOCELLULAR ADENOMAS IN CHILDREN

HCAs represent < 5% of all paediatric hepatic tumours^[8]. In addition to sex hormone disturbances as seen in adults, HCAs in children may arise in the background of FA, GSDs type I, III, and IV, galactosemia, immunodeficiency, congenital portosystemic shunts (CPSS), cardiac hepatopathy status-post Fontan procedure, Hurler syndrome, familial adenomatous polyposis, germline *HNF1A* mutations and maturity-onset diabetes of the young type 3, among others^[7-10,38]. HCAs may also occur spontaneously in the paediatric setting. In one series, up to 30% of HCAs developed without risk factors^[9]. **Table 2** highlights different conditions which have been associated with HCAs in the paediatric population.

The average age of HCA presentation in children is 14 years, although HCAs may be detected as early as prenatally^[10,39,40]. The lesions most commonly present in the right lobe of female patients^[7]. Clinically, patients present with HCAs found incidentally on imaging or with abdominal pain, which can be related to bleeding and rupture which occur in 27.2% and 17.5% of patients, respectively^[9,41].

Similar to adults, HCAs predominantly manifest as solitary lesions, while multiple lesions are more frequently observed in children with predisposition, such as GSD and Hurler syndrome^[8,42]. Currently, there are no published recommendations about screening protocols for HCA in patients with predisposing factors except for children with GSD^[10]. In children with GSD type I, liver imaging is routinely performed every 12-24 mo^[43]. Computed tomography or magnetic resonance imaging with contrast should be considered in older children to look for evidence of increasing lesion size, poorly defined margins, or hemorrhage^[43].

Histologic evaluation of the tumor should be considered in sporadic cases with no known predisposing factor for diagnostic confirmation and evaluation of the background liver^[10]. The molecular classification is currently the same as in adults. The main differential diagnoses of HCAs in the paediatric population include focal nodular hyperplasia, hemangiomas, fibrolamellar carcinoma, and HCCs; the detailed clinicopathological features of these entities are beyond the scope of this review. Selected entities associated with paediatric HCAs are discussed below.

Sex hormone dysregulation

Sex hormone dysregulation is a shared pathway for development of HCAs, across all subtypes and age groups. Besides OCP, sex hormone dysregulation in the paediatric population can occur with obesity, polycystic ovarian syndrome (PCOS), Klinefelter's syndrome, sex hormone producing tumours, such as Sertoli-Leydig cell tumours, and in the treatment of other diseases, such as hormone therapy for Turner's syndrome, steroid therapy for FA and Glanzmann's thrombasthenia, and oxcarbazepine therapy for seizures^[10,44-51]. Oxcarbazepine and other sodium ion channel modulating antiepileptic drugs have been found to cause reproductive endocrine dysfunction, and this is the proposed pathogenesis of HCAs in these cases^[51].

The molecular subtype of these tumours is not well-described. There is one report

Table 2 Various clinical associations of pediatric hepatocellular adenomas

Sex hormone dysregulation
Oral contraceptive use
Obesity
Klinefelter's syndrome
Polycystic ovary syndrome
Sex hormone producing tumours (<i>e.g.</i> , ertoli-Leydig cell tumours)
Androgen therapy (Turner's syndrome, Fanconi anemia, Glanzmann's thrombasthenia)
Antiepileptic therapies with sodium ion channel modulation
Metabolic disorders
Glycogen storage diseases type I, III, and IV
Galactosemia
Hurler syndrome (mucopolysaccharidosis type 1)
Fanconi Anemia (with or without androgen therapy)
Diabetes mellitus type II
Immunodeficiency
Congenital portosystemic shunts
Cardiac hepatopathy (status-post Fontan procedure)
Other syndromes
Alagille syndrome
Familial adenomatous polyposis syndrome
Maturity-onset diabetes of the young type 3
McCune-Albright syndrome
Noonan syndrome with multiple lentigines
Prader Willi syndrome
Wolf-Hirschhorn syndrome

of a 13 year old girl, with obesity, PCOS, and diabetes mellitus type II who had a HCA that demonstrated a variant of unknown significance in *HNFI1A* with accompanying characteristic prominent lesional steatosis, along with acinar growth and conspicuous nucleoli^[48]. Conversely, there are reports of bHCAs (including coexisting inflammatory phenotype) arising in obese adolescents, a large UHCA (GS positive, beta-catenin negative) in an 8-year-old girl without predisposing risk factors, and an IHCA in a 30-year-old woman with Turner's syndrome^[45,52-54].

FA

FA is a rare autosomal recessive disorder (1 in 90000), which is characterized by pancytopenia and dysmorphic features, and treated with anabolic steroids^[55,56]. Patients affected by FA have increased development of liver tumours, including HCAs and HCC^[57]. In a study that reviewed 32 patients with FA and associated hepatic lesions, 32% of neoplasms were determined to be HCAs^[58]. Additionally, androgen therapy and iron overload increase the risk of HCA development in these patients^[49,59]. HCC in FA patients may develop as a malignant transformation of HCA^[49,59,60].

Glycogen storage diseases

There is a strong link between GSDs and HCAs, occurring in GSD types I, III, and IV^[61]. Additionally, Roshcer *et al*^[62] reported a likely hepatic adenoma detected on ultrasound in a patient with GSD type VI. HCAs are seen in approximately 16%-75% of patients with GSD type I, and are usually detectable by age 15^[63]. GSD-associated HCAs are frequently multiple, and, in contrast to the hormone-related etiologies, these occur without female predominance and with metabolic control leading to regression of lesional size and burden^[64].

In a large series of GSD-related HCAs, the majority (52%) were classified as IHCAs, harbouring *IL6ST* or *GNAS* mutations, with the remainder classified as bHCAs (28%, with 57% b^{ex3}HCA and 43% b^{ex7,8}HCA) or UHCAs (20%)^[65]. At the Hospital of Sick Children, we encountered an adolescent with GSD type IA who developed a HHCA (Figure 1) despite no previous reports of this subtype in GSD patients.

Chromosomal aberrations affecting chromosome 6 (gain of 6p and loss of 6q) have been observed in 60% of GSD I-related HCAs^[66]. The high frequency of bHCAs, in

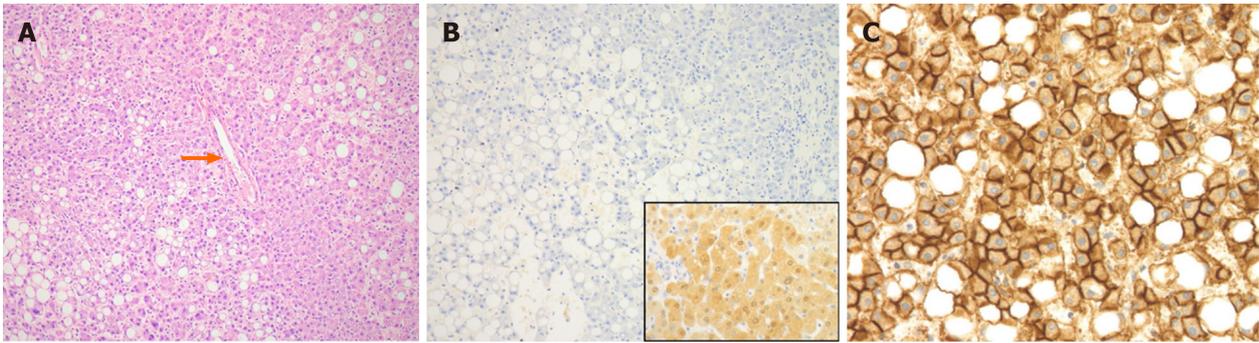


Figure 1 Hepatocellular adenoma in a child with glycogen storage disease type 1A. A: a well-differentiated hepatocellular lesion with scattered macrovesicular steatosis and unpaired arterioles (arrow), while complete portal tracts are not identified (hematoxylin and eosin, 4 ×); B: the lesional hepatocytes are negative for fatty acid binding protein immunohistochemical stain (4 ×); inset shows normal hepatocytes with immunohistochemical expression of liver fatty acid binding protein (10 ×); C: Moreover, the lesion demonstrates absence of nuclear beta catenin immunostaining (membranous staining is identified; 10 ×). The overall pathologic findings are in keeping with an *hepatocyte nuclear factor 1 homeobox alpha*-inactivated hepatocellular adenoma.

particular b^{ex3} HCA, in this population, as well as shared abnormalities of chromosome 6 with HCC, correlates with our understanding of the behaviour of these neoplasms and the increased frequency of malignant transformation of GSD I-related HCAs, which occurs through the adenoma-carcinoma sequence^[66,67].

HCAs are seen in 4%-25% of patients with GSD type III^[68,69]. Compared to GSD I-related HCAs, malignant transformation is less frequently observed in GSD type III, and almost exclusively in the setting of cirrhosis^[68]. GSD type IV has documented association with HCAs and HCC development, however the pathologic progression is also not well understood^[70].

Alagille syndrome

Alagille syndrome is an autosomal dominant condition caused by mutations in *JAG1* (94% of cases) and *NOTCH2* (1.5% of cases)^[71]. Alagille syndrome is pathologically characterized by a paucity of intrahepatic bile ducts, with other syndromic sequelae, including cardiac malformations, vascular malformations, vertebral abnormalities, and abnormal facies^[72]. The association with HCA development is tenuous. In one series of 20 patients with AS who received imaging, 6 were found to have nodular hepatic masses, and of the 5 that underwent pathological evaluation, none met the criteria for diagnosis as HCAs^[73]. However, there is a reported case of a 9 year old boy with AS, with a proven mutation in *NOTCH2*, who was incidentally found to have a HCA on abdominal ultrasound for portal hypertension, which was consistent with a HHCA upon histologic evaluation^[74].

Congenital portosystemic shunts

Congenital portosystemic shunts (CPSS) are rare vascular malformations, affecting approximately 1 in 30000 children^[75]. These shunts can be evident on prenatal ultrasounds, and are classified as intrahepatic or extrahepatic. Patients with CPSS are at risk for the development of HCAs and HCCs, in addition to other complications, such as cholestasis, hepatopulmonary syndrome, and encephalopathy^[75,76]. The CPSS-related hepatic lesions generally respond well to shunt correction^[76]. CPSS-associated HCAs can occur in the presence of other hereditary syndromes, such as Noonan syndrome with multiple lentigines (LEOPARD syndrome) and other undiagnosed multisystem syndromes^[76]. The patients included in one series displayed a variety of dysmorphic features in addition to CPSS-related HCAs, which may indicate that multiple genetic signaling pathways are involved in HCA development in these patients, in addition to hepatic and systemic blood flow abnormalities^[76].

Other syndromes

Terracciano *et al*^[77] reported a child with a family history of Carney complex who underwent enucleation of a HCA at the age of 9. She re-presented at the age of 14 with fibrolamellar carcinoma, which has not been well-documented to develop from HCAs^[77]. An association between IHCA and McCune-Albright syndrome has been described in adults, both driven by *GNAS* mutations^[25,78]. Additionally, HCAs have been described in Wolf-Hirschhorn syndrome, a rare contiguous gene deletion syndrome involving the short arm of chromosome 4^[79].

MALIGNANT TRANSFORMATION OF HEPATOCELLULAR ADENOMA IN CHILDREN

In a large meta-analysis, 4.2% of HCAs were found to undergo malignant transformation, with 4.5% of resected HCAs containing focal malignancy^[80]. The highest risk of malignant transformation is seen in b^{ex3}HCAs, although the phenomenon has been identified in other subtypes as well^[4,81]. In b^{ex3}HCAs, the initial *CTNNB1* mutation is sufficient for development of benign HCAs, with accompanying telomerase reverse transcriptase (*TERT*) mutations required for malignant transformation^[82-84]. Other risk factors for malignant transformation include large size (> 5 cm), male sex, high alcohol intake, diabetes mellitus type II (DMII), fibrosis of the background liver, and acquired *TP53* mutations^[4,85]. Malignant transformation of HCAs is a rare phenomenon in the paediatric population; it has been described in association with GSD type I, FA, CPSS, and Wolff-Hirschhorn syndrome^[49,67,76,79].

Rare cases of malignant transformation from HCA into hepatoblastoma have also been reported. Louie *et al*^[86] reported hepatoblastoma arising in a pigmented bHCA of a 4-year-old male patient, while Gupta *et al*^[87] reported 3 children with familial adenomatous polyposis syndrome who developed hepatoblastoma in the background of hepatic adenomatosis^[86,87].

Determining malignant transformation is often challenging pathologically, as the distinction between HCA and well-differentiated HCC is not always straight forward. Current pathological features that are helpful in this distinction include assessment for architectural distortion, HCC with a rim of residual HCA, cytologic atypia, loss of reticulin staining, and increased immunohistochemical staining for CD34^[85,88]. Even after workup this distinction may still be difficult, prompting the suggestion of a separate diagnostic category of atypical hepatocellular neoplasm or hepatocellular neoplasm of uncertain malignant potential^[89,90]. Some have recommended chromosomal analysis of adenomas with atypical features for abnormalities shared by HCC, namely those affecting chromosomes 1, 8, and 6, in an attempt to elucidate their potential behaviour^[91,92].

The assessment of malignant transformation in children should be based on the histopathology and its molecular subtyping, similar to the diagnostic approach in adults.

CONCLUSION

The current molecular classification of HCAs demonstrates a reliable correlation to risk factors and prognosis. When it comes to the paediatric population, the molecular subtypes are identifiable, however, often do not correlate with predisposing risk factors and syndromes. Our understanding of the molecular pathways involved in liver tumourigenesis, paediatric HCC, and neoplasia in general, will play a large role in our approach to patients with liver lesions, predisposing risk factors, and seemingly unrelated syndromes with molecular aberrations in associated genes. Better documentation of HCA subtypes in this age group and further study of these lesions, patients, and tumours will continue to illuminate pathogenesis. HCAs remain an area of future study and a clinical entity best managed with a multidisciplinary approach.

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