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Analysis of the etiology, clinical characteristics and treatment outcomes of choroidal neovascularization in Chinese children and adolescents

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Abstract

Background This study aimed to investigate the etiology, clinical characteristics and treatment outcomes of choroidal neovascularization (CNV) in Chinese children and adolescents.

Methods A retrospective analysis was conducted on the clinical data, multimodal imaging and treatment outcomes of pediatric patients with CNV at Beijing Tongren Hospital from May 2014 to October 2024.

Results 72 children with CNV were included. The average age was 12.1 ± 3.5 years and 36 (50.0%) were male. The most common etiologies of pediatric CNV were idiopathic (37.50%), inflammatory chorioretinopathy (31.94%) and congenital or hereditary abnormalities (16.67%). Age distribution analysis showed that CNV most commonly occurred in adolescence (13–17 years, 48.61%) and school age (7–12 years, 45.83%). Idiopathic CNV was the main cause of CNV in children ≤ 12 years (43.24%), followed by inflammatory chorioretinopathy (21.62%) and congenital or hereditary abnormalities (18.92%), while the main cause of CNV in children > 12 years was inflammatory chorioretinopathy (42.86%). Most of the CNVs were subfoveal (56.3%) and all of the CNVs with complete fundus fluorescein angiography (FFA) images were classic type. Of the 58 eyes (72.5%) with complete optical coherence tomography (OCT) data, all of the CNVs were type 2. Analysis of 26 eyes treated with intravitreal anti-VEGF drugs showed that the best corrected visual acuity (BCVA) significantly improved from 0.75 ± 0.46 logMAR at baseline to 0.63 ± 0.46 logMAR at the last follow-up ($p = 0.021$), with 38.5% patients achieved ≥ 2-line BCVA improvement. These eyes with active CNV required a mean of 2.12 ± 0.80 injections during the follow-up period.

Conclusion The etiology and clinical characteristics of CNV in children differed from those in adults. Idiopathic, inflammatory, and congenital or hereditary CNV were the three most common etiologic factors in children. Most pediatric CNV were unilateral, type 2 and subfoveal. Pediatric CNV responded well to anti-VEGF medication and anti-VEGF drugs can significantly improve the visual acuity of children with CNV.

Keywords Choroidal neovascularization, Chinese children, Etiology, Multimodal imaging, Anti-VEGF

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Introduction

Choroidal neovascularization (CNV) is a common pathological change that occurs in various choroidal and retinal diseases. The most common cause of CNV in the population over 50 years old is age-related macular degeneration (AMD), followed by pathologic myopia [1]. However, in younger patients, the diseases associated with CNV are more complex [2–4]. Currently, there is little research on the etiology and characteristics of CNV in children, especially in Asian children. Zhang et al. [5] reported the etiology of CNV in 30 Chinese patients under the age of 18, and found that congenital or developmental abnormalities, inflammatory retinochoroidopathy, and idiopathic were the most common causes. However, the sample size was small.

Due to the lack of clear complaints and poor cooperation during examination and treatment in children, the management of pediatric CNV is challenging. Early diagnosis and standardized treatment are of great significance for the prognosis and reducing complications of CNV [6, 7], especially in pediatric patients, which may have a significant impact on their lifelong vision and visual quality [5]. The analysis of clinical and multimodal imaging characteristics of CNV is helpful for the diagnosis and treatment monitoring of CNV, so as to formulate personalized prevention and treatment strategies in children. Anti-vascular endothelial growth factor (VEGF) medications are the first-line option for CNV treatment. Other treatment options include photodynamic therapy (PDT), observation, or a combination of anti-VEGF and PDT. However, due to the rarity of pediatric CNV, there is currently no large-scale clinical study describing the clinical and imaging characteristics in detail, as well as confirming the optimal treatment regimen, efficacy and outcome of anti-VEGF drugs in children and adolescents with CNV.

This study retrospectively analyzed the etiology, clinical characteristics and treatment outcomes of CNV in children under 18 years old in China, in order to provide a basis for guiding the diagnosis and treatment of pediatric CNV.

Materials and methods

Study population

Children aged under 18 years old with CNV who visited Beijing Tongren Eye Center, Beijing Tongren Hospital from May 2014 to October 2024 were retrospectively analyzed. To identify the initial cohort, we searched for patients who underwent FFA and/or ICGA at our center from 2014 to 2024 based on Heidelberg system, the diagnosis was set to "choroidal neovascularization", and patients < 18 years of age were selected. Then, we retrieved the corresponding patients' medical records and multimodal images from our center's FFA/ICGA Imaging Report Library and Picture Archiving and Communication System for further analysis. This study adhered to the tenets of the Declaration of Helsinki and approval was obtained from the Ethical Review Committee of Beijing Tongren Hospital, Capital Medical University. Due to the invasive nature of FFA and ICGA, written informed consent was obtained from each patient's parents before the examination.

The inclusion criteria were as follows: (1) age < 18 years; (2) diagnosed with CNV. The diagnosis of CNV was confirmed by FFA and ICGA. In some patients, spectral domain optical coherence tomography (SD-OCT) or optical coherence tomography angiography (OCTA) was performed to assist the diagnosis of CNV.

Definition of diseases and etiologies

The diagnostic criteria for the etiology of CNV were as follows. Pathologic myopia (PM) was defined as refractive error ≤-6 diopters (D) and presented fundus changes associated with PM (such as chorioretinal atrophy, lacquer crack and posterior staphyloma) [8]. Punctate inner choroidopathy (PIC) was defined as multiple, punctate, yellow white inflammatory lesions or scars involving the deep retina and inner choroid. The lesions often presented in the posterior pole and diameter of each lesion was less than 250 μm. It was often associated with moderate to high myopia and usually had no signs of uveitis or vitritis [9–11]. Multifocal choroiditis (MFC) was defined as the presence of yellow-white round or oval multifocal chorioretinal lesions larger than 250 μm, accompanied by punched-out atrophic chorioretinal scars with or without pigmentation. The lesions could be located in the peripheral retina or involved the posterior pole [9, 10]. The diagnosis of Best vitelliform macular dystrophy (BVMD), autosomal recessive vitelliform dystrophy (ARB), Bietti crystalline dystrophy (BCD) and retinitis pigmentosa (RP) were all diagnosed by typical clinical manifestations combined with genetic test results [12–14]. The diagnosis of traumatic choroidal rupture required a history of ocular blunt trauma and typical fundus manifestations. The diagnosis of laser-induced retinopathy was based on the fact that the affected eye had gazed at or been irradiated by laser. Other causes of CNV, such as multiple transient white dot syndrome (MEWDS), choroidal osteoma (CO), ocular toxoplasmosis (OT) and other types of uveitis and retinal vasculitis were defined based on specific clinical features, laboratory tests and fundus multimodal imaging. If CNV cases could not be attributed to any cause, they were defined as idiopathic.

Clinical data collection and multimodal imaging examinations

Demographic data, etiologic factors, laterality, location and multimodal imaging characteristics of each

CNV lesion were recorded. Best corrected visual acuity (BCVA) was recorded using Snellen charts and converted to logarithm of minimum angle of resolution (logMAR) for statistical analyses. Color fundus photographs (CFP) were captured by FF450 plus (Carl Zeiss Meditec, North America) or CX-1 (Canon, Tokyo, Japan) color fundus camera. FFA and ICGA images were acquired using Spectralis HRA (Heidelberg Engineering, Heidelberg, Germany). Fundus autofluorescence (AF) images were taken before FFA and ICGA. SD-OCT/OCTA image acquisition was performed applying RTVue XR Avanti (Optovue, Fremont, CA) or Spectralis HRA (Heidelberg Engineering, Heidelberg, Germany). Diagnosis of CNV and multimodal imaging analysis were conducted by two experienced ophthalmologists (SS Yan and YZ Liu), and in case of uncertainty, the final decision was made by another fundus specialist (HY Zhou).

The location of CNV was determined by the distance between the outer boundary of CNV in early phase FFA and the center of foveal avascular zone (FAZ). According to the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study Group, CNVs were classified as follows: extra foveal (200 mm outside the center of the foveal avascular zone), juxtafoveal (1–199 mm from the center of the foveal avascular zone), and subfoveal (under the center of the foveal avascular zone) [15]. CNVs were classified into classic or occult based on FFA according to TAP group criteria [16]. In ICGA, CNVs were classified into focal spots (CNV hypercyanescence no greater than one optic disc area) and plaques (CNV hypercyanescence greater than one optic disc area) [17]. Based on the location of hyperreflective lesions in relation to the retinal pigment epithelium (RPE) on OCT/OCTA, CNVs were categorized into type 1 and type 2. If the hyperreflective CNV lesion was located within the sub-RPE space, it was type 1 CNV (corresponding to occult CNV in FFA); if the hyperreflective CNV lesion was located in the subretinal space, it was type 2 [18]. CNV was determined to be active if any of the following were present: clinical evidence of exudate, fluid or hemorrhage on fundus examination, hyperfluorescence and late leaking on FFA, and presence of subretinal or intraretinal fluid on OCT. CNV lesions were considered to be inactive if there was no clinical evidence of hemorrhage or exudate, no fluorescence leakage on FFA, and no subretinal or intraretinal fluid on OCT. Intravitreal anti-VEGF medication was recommended as first-line treatment for eyes with active CNV.

Table 1 Clinical and multimodal imaging features of pediatric CNV

Patients/eyes (*n*)	72/80
Sex, male (n, %)	36 (50.0%)
Age (year)	
Total	12.1 ± 3.5
Female	13.3 ± 3.0
Male	11.0 ± 3.6
Bilateral eye affected (n, %)	8 (11.1%)
BCVA at first visit (LogMAR)	0.83 ± 0.51 (-0.1 ~ 2.4)
Multimodal imaging features	
Location of CNV (n, %)	80 (100%)
Subfoveal	45 (56.25%)
Juxtafoveal	19 (23.75%)
Extrafoveal	16 (20.00%)
FFA (n, %)	75 (100%)
Classic	75 (100%)
Occult	0 (0%)
ICGA (n, %)	65 (100%)
Focal spot	56 (86.15%)
Plaque	9 (13.85%)
OCT/OCTA (n, %)	58 (100%)
Type 1	0 (0%)
Type 2	58 (100%)
CNV activity	80 (100%)
Active	46 (57.5%)
Inactive	34 (42.5%)

CNV, choroidal neovascularization; BCVA, best corrected visual acuity; FFA, fundus fluorescein angiography; ICGA, indocyanine green angiography; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography

Statistical analysis

All statistical analyses were performed using SPSS version 26.0 (SPSS, Inc., Chicago, USA). Continuous variables with normal distribution were presented as mean ± standard deviation (SD), continuous variables with skewed distribution were presented as median (25th, 75th percentile), and categorical variables were presented as number/percentage (n/%). Comparisons between groups were made using the Student's t-test (normally distributed variables) or Mann-Whitney U test (non-normally distributed variables). Chi-square test or Fisher's exact test was used for frequency comparisons. A *P*-value of < 0.05 was considered statistically significant.

Results

A total of 72 children were included in this study, of which 36 (50%) were males. The mean age of onset was 12.1 ± 3.5 years (5–17 years). There was a significant difference in the age between males (11.0 ± 3.6 years) and females (13.3 ± 3.0 years) ($p = 0.005$). The majority of patients had unilateral CNV (88.9%, $n = 64$), while 8 (11.1%) patients had CNV in both eyes. There was no significant difference between males and females in the presence of unilateral or bilateral CNV ($p = 0.684$). BCVA of the affected eye at first visit was 0.83 ± 0.51 (-0.1 ~ 2.4) LogMAR. The demographic data and clinical characteristics of the patients and affected eyes were presented in Table 1.

The etiology of CNV in children was diverse (Table 2). In our cohort of 72 patients, idiopathic choroidal neovascularization (ICNV) accounted for the highest percentage of 37.50% (27/72, 28 eyes; Figs. 1a-d). Inflammatory chorioretinopathy accounted for 31.94% (23/72, 25 eyes), including PIC in 8 patients (11.11%, 9 eyes; Figs. 1i-l), MFC in 7 patients (9.72%, 7 eyes; Figs. 1e-h), MEWDS in 1 patients (1.39%, 1 eye), toxoplasmic retinochoroiditis in 1 patient (1.39%, 1 eye), and other types of uveitis and retinal vasculitis in 6 patients (8.33%, 7 eyes). Congenital or hereditary diseases accounted for 16.67% (12/72, 16 eyes), including BVMD in 8 patients (11.11%, 12 eyes; Fig. 2a-f), ARB in 1 patient (1.39%, 1 eye; Fig. 2g-j), BCD in 1 patient (1.39%, 1 eye; Fig. 2k-p), RP in 1 patient (1.39%, 1 eye), and other types of macular dystrophy in 1 patient (1.39%, 1 eye). Traumatic choroidal retinopathy accounted for 8.33% (6/72, 6 eyes), including laser injury in 4 patients (5.56%, 4 eyes; Figs. 3a-d) and choroidal rupture in 2 patients (2.78%, 2 eyes; Fig. 3e-h). Intraocular tumor accounted for 4.17% (3/72, 4 eyes), all of which were choroidal osteomas (Fig. 3i-n). Only 1 patient (1.39%, 1 eye) had pathologic myopic CNV (PM-CNV). Overall, there were 8 patients with bilateral CNV, of which 4 had BVMD, 2 had chorioretinal inflammation, 1 had choroidal osteoma, and 1 was idiopathic. These data indicated that the etiologies of CNV in Chinese children were diverse, with idiopathic, inflammatory, and congenital or hereditary diseases being the three most common etiologic factors.

Table 2 Etiology and prevalence of CNV in Chinese children and adolescents

Etiology	*N* (%)	Age (year)	Female/Male
Idiopathic	27 (37.50%)	11.6 ± 3.1	12/15
Inflammatory	23 (31.94%)	13.3 ± 2.7	18/5
PIC	8 (11.11%)	13.1 ± 2.7	8/0
MFC	7 (9.72%)	12.6 ± 3.1	4/3
MEWDS	1 (1.39%)	14.0	1/0
Toxoplasma	1 (1.39%)	14.0	1/0
Others	6 (8.33%)	11.5 ± 2.9	4/2
Congenital/Hereditary	12 (16.67%)	11.6 ± 4.3	2/10
BVMD	8 (11.11%)	10.0 ± 4.0	2/6
ARB	1 (1.39%)	11.0	0/1
BCD	1 (1.39%)	17.0	0/1
RP	1 (1.39%)	14.0	0/1
Others	1 (1.39%)	17.0	0/1
Traumatic	6 (8.33%)	11.3 ± 4.8	3/3
Laser injury	4 (5.55%)	8.5 ± 2.5	2/2
Choroid Rapture	2 (2.78%)	17.0 ± 0.0	1/1
Tumorous	3 (4.17%)	11.0 ± 5.2	1/2
Choroidal osteoma	3 (4.17%)	11.0 ± 5.2	1/2
PM	1 (1.39%)	16.0	0/1
Total	72 (100%)	12.1 ± 3.5	36/36

PIC, punctate inner choroidopathy; MFC, multifocal choroiditis; MEWDS, multiple transient white dot syndrome; BVMD, Best vitelliform macular dystrophy; ARB, autosomal recessive vitelliform dystrophy; BCD, Bietti crystalline dystrophy; RP, retinitis pigmentosa; PM, pathologic myopia

Patients were categorized into 4 groups according to their age: early childhood (1–3 years), preschool age (4–6 years), school age (7–12 years) and adolescence (13–17 years). Overall, the majority of CNV presented in adolescence ($n = 35$, 48.61%), followed by school age ($n = 33$, 45.83%), with fewer patients in preschool age ($n = 4$, 5.56%), and no patient in early childhood ($n = 0$). CNV in male children occurred more often during school age ($n = 22$, 61.11%), whereas in female children, CNV occurred more often during adolescence ($n = 24$, 66.67%). The most common etiology of CNV in children ≤ 12 years was idiopathic (16/37, 43.24%), followed by inflammatory chorioretinopathy (8/37, 21.62%) and congenital or hereditary diseases (7/37, 18.92%), while the main cause of CNV in children older than 12 years of age was inflammatory chorioretinopathy (15/35, 42.86%), followed by idiopathic (11/35, 31.43%) and congenital or hereditary diseases (5/35, 14.29%).

For children with idiopathic CNV, the peak age of onset was school age ($n = 15$, 55.56%), followed by adolescence ($n = 11$, 40.74%). All children with CNV secondary to PIC were female ($n = 8$, 100%) and all presented in adolescence. In children with CNV secondary to MFC, the peak age of onset was school age ($n = 4$, 57.14%) and adolescence ($n = 3$, 42.86%), with male children more likely to occur in school age ($n = 3$) and female children were more likely to occur in adolescence ($n = 3$). Most of the children with CNV secondary to BVMD were males ($n = 6$, 75.0%), and most of the children were preschool and school age at the time of presentation.

In all the affected eyes, CNVs were most frequently located in the subfoveal area (45 eyes, 56.25%), followed by juxtafoveal (19 eyes, 23.75%) and extrafoveal (16 eyes, 20.00%) (Table 1). In autofluorescence images, CNV appeared as a patch of hypoautofluorescence that could be partially surrounded by hyperautofluorescence. Of all the 72 patients, 5 patients (5 eyes) were allergic to sodium fluorescein and did not undergo FFA, thus a total of 67 patients (75 eyes, 93.75%) with CNV had complete FFA data. According to FFA images, all the CNVs were classic type (100%). A total of 65 affected eyes (81.25%) had complete ICGA images, and the proportions of "focal spots" and "plaques" CNVs were 86.15% (56 eyes) and 13.85% (9 eyes) respectively. A total of 58 eyes (72.5%) had OCT or OCTA data, including 35 eyes with OCT images and 23 eyes with OCTA images. All of the OCT/OCTA B-scan images showed hyperreflective lesions in the subretinal space (type 2 CNV) with 30 eyes showed subretinal fluid (SRF). Abnormal blood flow signals were seen in CNV on OCTA images. There were no type 1 or type 3 CNVs among the children in this study. Analysis of the multimodal images revealed that 46 (57.5%) CNVs

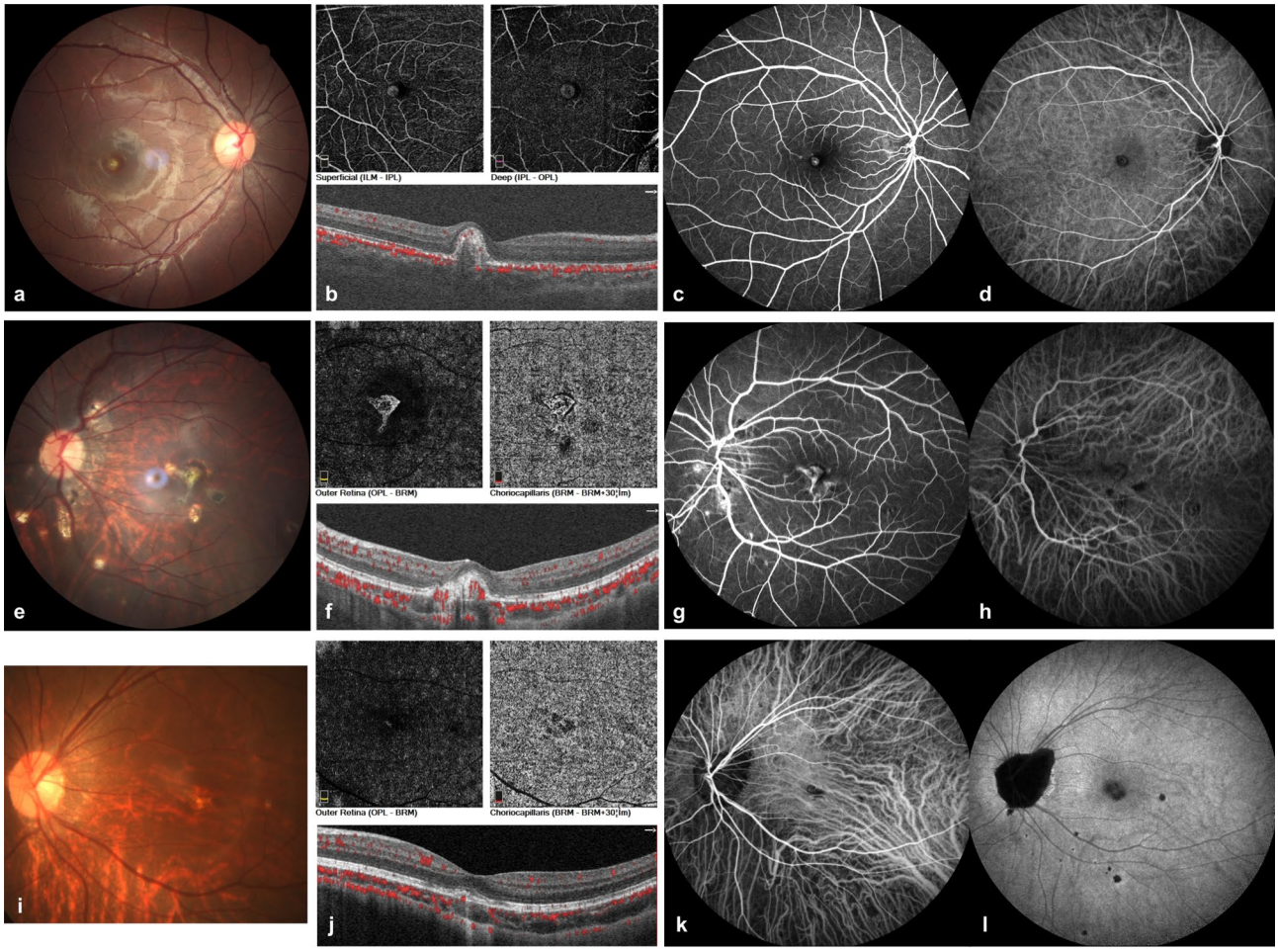

Fig. 1 Multimodal images of idiopathic and inflammatory CNV in children. **a**-**d** An 11-year-old boy with idiopathic CNV in the right eye. Color fundus photography showed a small round yellow-white lesion in the macula. OCTA showed a hyperreflective CNV lesion growing above the RPE in the macula. Early-phase FFA and ICGA demonstrated a small patch of hyperfluorescence in the macular area. **e**-**h** A 16-year-old girl with CNV secondary to MFC. Fundus examination found multiple yellow punched-out foci in the posterior pole, and some of the lesions were hyperpigmentation. OCTA showed a subfoveal CNV with blood flow signals. The CNV was hyperfluorescent on both FFA and ICGA with slight leakage. The MFC lesions showed hyperfluorescent staining on FFA and hypocyanescence on ICGA. **i**-**l** A 16-year-old girl with PIC and secondary CNV. Fundus photography showed small yellow-white dots in the macula area and CNV was hard to recognize. OCTA demonstrated an irregular RPE with small CNV blood signals visible in the outer retinal and choroidal capillary layers. CNV hypercyanescence was noted in early-phase ICGA and PIC lesions showed dot-like hypocyanescence in late-phase ICGA

were active and 34 (42.5%) CNVs were quiescent or scarred.

In this study, 26 out of 46 eyes (57.5%) with active CNV were treated with intravitreal injection of anti-VEGF drugs, the follow-up data were incomplete or missing for the remaining 20 eyes. Analysis was conducted on the 26 eyes receiving treatment. The average follow-up time was 14.65 ± 8.55 months (3–44 months), 23 eyes (88.5%) were treated with ranibizumab 0.5 mg/0.05 ml and 3 eyes (11.5%) were treated with conbercept 0.5 mg/0.05 ml. The baseline BCVA was 0.75 ± 0.46 logMAR, which significantly improved to 0.63 ± 0.46 logMAR at the final follow-up ($p = 0.021$). The proportion of patients achieving ≥ 2-line BCVA improvement was 38.5% (10/26). During the follow-up period, the total number of anti-VEGF injections was 2.12 ± 0.80 (1–4 injections), and most of the CNVs (15 eyes, 57.7%) were stabilized after two injections. Recurrence of CNV occurred in 3 eyes (11.5%) and all of them were stabilized after one additional anti-VEGF injection. The etiology of these 3 cases of CNV was PIC. There were no ocular or systemic complications in all the children treated with anti-VEGF therapy.

Discussion

CNV is one of the most important causes of visual impairment in children and adolescents and can seriously impact their growth and quality of life. Pediatric patients often do not have clear complaints and are difficult to cooperate well with examinations, which poses challenges to the early diagnosis and monitoring of CNV. An in-depth understanding of the etiology and clinical characteristics of CNV in children is a prerequisite for

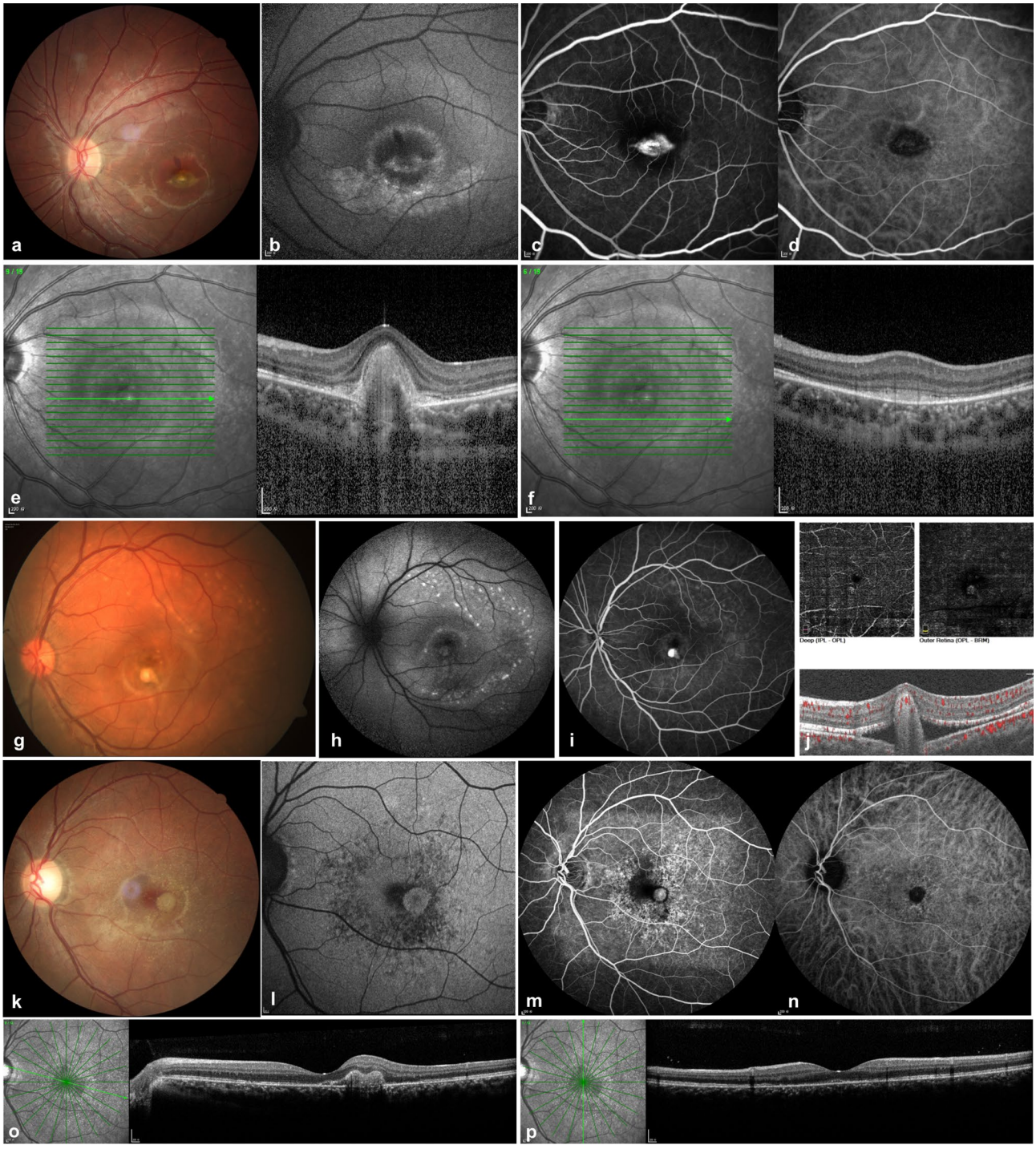

Fig. 2 Multimodal images of CNV secondary to hereditary diseases. **a**-**f** A 6-year-old boy with bilateral BVMD and CNV membrane in the left eye. Fundus examination of the left eye revealed a subfoveal yellow-gray fibrotic CNV membrane with hemorrhage. In AF image, the vitelliform material surrounding the CNV was hyperautofluorescent (vitelliruptive stage). Early-phase FFA showed hyperfluorescence of CNV, and the simultaneous ICGA showed hypercyanescent neovascular network surrounded by hypocyanescence. OCT images demonstrated a type 2 CNV. Hyperreflective material could be seen in the subretinal space with a loss of outer retinal layers. **g**-**j** An 11-year-old boy was diagnosed with ARB due to the biallelic pathologic mutation of BEST1 gene. Fundus examination revealed a yellow-white juxtafoveal CNV and yellow dots around the fovea. AF image demonstrated multiple hyperautofluorescent extramacular punctate deposits. CNV had significant fluorescence leakage in FFA. OCTA showed a type 2 CNV with subretinal fluid (SRF). **k**-**p** A 17-year-old boy with BCD showed numerous glittering crystalline deposits in the posterior pole on fundus examination. The CNV appeared as a round light grey lesion temporal to the fovea. AF image showed diffuse hypoautofluorescence interspersed with hyperautofluorescence in the macular region. FFA showed hyperfluorescent window defects around the macula and the CNV showed mild fluorescence leakage. OCT images demonstrated a type 2 CNV located inferotemporal to the fovea with RPE irregular, interdigitation zone (IZ) and ellipsoid zone (EZ) interruption and loss

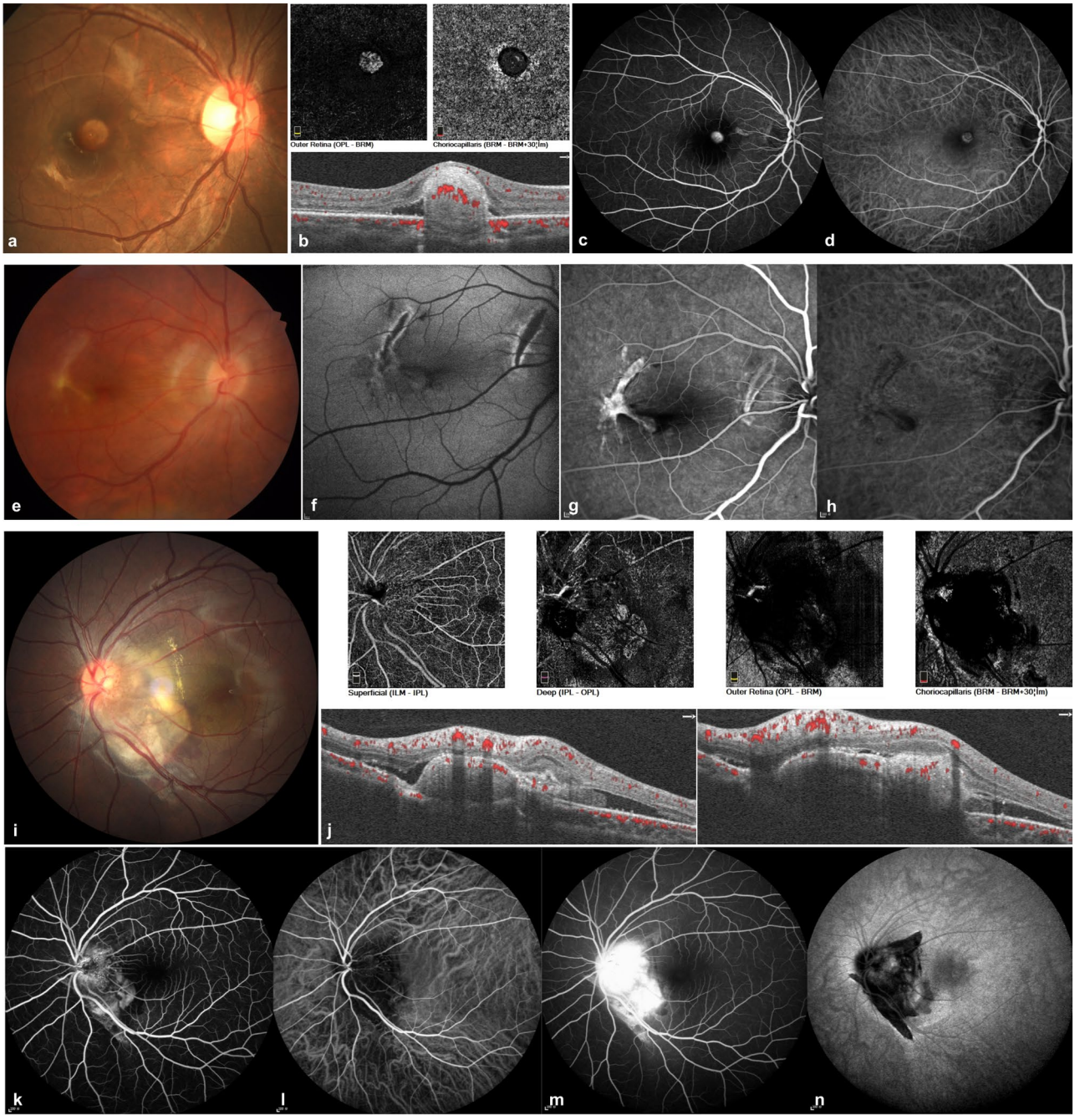

Fig. 3 Multimodal images of CNV secondary to ocular trauma and tumor. **a**-**d** Laser-induced CNV in a 9-year-old boy. Fundus photography showed a yellow-white subfoveal CNV with subtle subretinal fluid. OCTA of the outer retina layer depicted the CNV. Early-phase FFA and ICGA demonstrated hyperfluorescence CNV lesion with fluorescence leakage. **e**-**h** A 17-year-old boy with a history of ocular blunt trauma 5 months prior to the presentation of CNV. Arcuate choroidal rupture could be seen temporal to the optic disc and macula in color fundus photography. AF, FFA and ICGA showed that the CNV was adjacent to the margin of the arcuate choroidal rupture in the macular area. **i**-**n** A 17-year-old girl with choroidal osteoma in her left eye. Fundus photography showed a yellowish, peripapillary and sharply demarcated lesion of choroidal osteoma. Hard exudate and subretinal hemorrhage were noted at the temporal margin of the tumor. OCTA revealed a CNV in the deep retinal layer. FFA showed large patches of hyperfluorescence and marked leakage around the optic disc, whereas the corresponding ICGA showed choroidal osteoma as hypocyanescence. ICGA demonstrated hypercyanescence of CNV at the inferotemporal margin of the choroidal osteoma

appropriate and timely intervention. At present, there are few studies on the etiology, clinical characteristics and treatment outcomes of CNV in children, and most of them are conducted in Western populations. In this study, we evaluated the etiology, clinical and multimodal imaging features, and treatment outcomes of CNV in Chinese children and adolescents to further support the diagnosis and treatment strategies of CNV in pediatric patients.

In this retrospective study, we found that the etiology of CNV in Chinese children and adolescents was diverse, with the three most common etiologies being idiopathic, inflammatory, and congenital or hereditary diseases. The most common cause of inflammatory CNV was PIC, and the most common cause of CNV secondary to congenital or hereditary disease was BVMD. These results differed from those in young adults, which idiopathic, pathologic myopia and PIC were the top three etiologies [2, 4]. Pathologic myopia CNV was relatively rare in children, whereas congenital or hereditary diseases accounted for a certain percentage. In addition, inflammatory CNV had a high proportion in both children and adults.

Moosajee et al. [19] firstly conducted a prospective observational study of 27 children aged under 16 years with CNV, and found that the most common etiologies were inflammatory chorioretinopathy (33.3%), optic disc abnormalities (33.3%), and idiopathic (18.5%). Padhi et al. [20] retrospectively analyzed 35 patients with CNV under 18 years old and found retinal dystrophies to be the most common etiology of CNV in children (39.53%), with BVMD accounting for the largest proportion (32.6%), followed by idiopathic CNV (27.9%) and inflammatory CNV (9.3%). Zhang et al. [5] retrospectively analyzed 30 cases of CNV in Chinese children under 18 years old and concluded that the most common etiologic factors were congenital/developmental abnormalities (30.0%) and inflammatory chorioretinopathy (30.0%), followed by idiopathic CNV (26.7%). Due to the rarity of CNV in children, the sample sizes of the above studies are relatively small. Our study is currently the largest study on the etiology and multimodal imaging characteristics of CNV in Chinese children. The results of our study were in agreement with Padhi et al. [20] and Hoyek [21]. However, CNV caused by PIC had a higher prevalence among Chinese adolescents, and there were more cases of CNV secondary to optic disc abnormalities in Western cohort. In addition, we reported rare cases of pediatric CNV secondary to RP, BCD, and ARB. Furthermore, traumatic CNV in pediatric patients should not be overlooked. For pediatric patients, it is important to carefully inquire about their history of laser exposure and ocular blunt trauma. Moreover, we found that pathologic myopic CNV was relatively rare in the pediatric population, which differed from previous findings in case series of Chinese children [5], but consistent with research results in Western populations [21, 22].

This study also conducted an age distribution analysis of the etiology of CNV in children, and the results showed that the most common etiology of CNV in children aged 12 years and younger was idiopathic, followed by congenital or hereditary diseases; while the main cause of CNV in children aged 12 years and over was inflammatory chorioretinopathy, followed by idiopathic. Given the racial and regional differences, as well as the differences in patient populations across medical centers, there are some differences in the etiology of pediatric CNV among studies, but overall, idiopathic, inflammatory, and congenital or hereditary diseases are the three main etiologies of CNV in children. We also noticed that there was a significant difference in the age between male and female children with CNV ($p = 0.005$), of which the average age was younger in males than females. We speculated that it was due to the fact that women had more inflammatory CNVs, while men had more congenital or hereditary CNVs. Patients with inflammatory CNV were older than those with congenital CNVs.

In our study, the overall proportion of females to males was comparable, which was consistent with the results of IRIS registry study [23]. Previous studies found a higher proportion of females in idiopathic CNV in adults, but the reason was unclear. However, in our study, the proportion of females in idiopathic CNV was lower in pediatric patients (46.4%), which differed from that in adults. Ocular inflammation-mediated angiogenesis is involved in choroidal neovascularization in patients with inflammatory CNV. In this study, the proportion of inflammatory CNV was 31.25%, with 72% occurring in female patients, which was similar to previous studies in adults [4, 24]. Thus, inflammatory CNV is an important component of CNV in Chinese pediatric patients. Given that more than half of PIC and MFC patients have CNV [25, 26], the high prevalence of CNV in uveitis children requires the attention of ophthalmologists.

CNV is most commonly located in the macula area, with subfoveal CNV having the greatest impact on vision and being the most difficult to control [27]. In our study, subfoveal CNV accounted for 56.3% of pediatric CNV, which was higher than the percentage of subfoveal CNV in young adults (52%) [2]. Zhang et al. [5] found that up to 84.8% of the CNVs in children were located subfoveally. These results suggest that CNV in children is more likely to occur in the subfoveal area than in adults, posing a serious threat to vision and visual development of children. However, CNV located near or outside the central fovea may be overlooked by patients due to their smaller impact on vision. In addition, in our study, all pediatric CNVs were type 2, which was different from adult CNVs. Liu et al. [4] found in their study of CNV in Chinese

adults under 50 years that 94.2% of CNV presented as classic type in FFA, and the remaining occult CNVs were seen in patients with polypoidal choroidal vasculopathy (PCV). Furthermore, type 1 CNV is commonly found in neovascular age-related macular degeneration (nAMD), PCV and pachychoroid neovasculopathy, and type 3 CNV is a subtype of nAMD. Since these diseases do not occur in children, all pediatric CNVs in our study are classic/type 2, which is similar to the results of previous studies [5, 21].

Our study also found that CNV in children had a good response to anti-VEGF treatment. Hoyek et al. [21] analyzed long-term follow-up data of 21 children (25 eyes) with CNV membrane, and the average follow-up time was 56.46 months. They found that 23 eyes (92%) received anti-VEGF (bevacizumab) medication, with a CNV retreatment rate of 52%. The overall frequency of anti-VEGF treatment was 2.56 ± 2.53 injections, and the final follow-up BCVA after treatment was 0.51 ± 0.59 logMAR, which was significantly improved compared to baseline BCVA (0.81 ± 0.56 logMAR). Kozak et al. [28] analyzed data from 45 children with CNV treated with intravitreal injections of either bevacizumab or ranibizumab, with a mean follow-up time of 12.8 months. The average number of injections was 2.2, and BCVA improved in 22 eyes (49.0%). Our study found that an average of 2.12 ± 0.80 anti-VEGF injections were required for the regression or stabilization of CNV in children. The baseline BCVA was 0.75 ± 0.46 logMAR, and the BCVA significantly improved to 0.63 ± 0.46 logMAR after anti-VEGF treatment ($p = 0.021$). Our results were similar to those of the above studies, and we noted that the number of anti-VEGF injections for pediatric CNV was significantly lower than that for adult CNV. Currently there are relatively few studies on the treatment and prognosis of pediatric CNV. Although some studies recommend a 1 + PRN treatment plan, we speculate that 2 + PRN seems to be better for the treatment of active CNV in children. Large-scale, multicenter clinical trials are needed to confirm which regimen is more suitable for pediatric CNV.

In addition, we often see children with severely reduced BCVA due to CNV, which could also be due to a long disease duration. Children may either not notice their deterioration in vision or it may not be taken seriously. Therefore, mydriatic fundus examinations are necessary when children report visual decline for prompt diagnosis and treatment of CNV. Mydriatic fundus examinations are necessary when children report visual decline instead of just fitting new glasses.

There are some limitations in this study. Firstly, due to the retrospective nature of the study, more detailed clinical information on some patients are lacking, such as refractive status, symptoms, time of onset, et al. OCT/OCTA has not been performed in some patients, and not all patients have follow-up data. Retrospective design could also introduce potential selection bias. Further studies with more detailed clinical data are needed to determine the risk factors of pediatric CNV and to identify systemic and ocular risk factors for idiopathic CNV. Secondly, due to the rarity of CNV in children, the number of subjects included in this study is still limited. Thirdly, the patients in this study are only from a single center. Since our eye center is a tertiary referral institution that receives a large number of difficult cases, there may be a selection bias in the patient population. Therefore, there might be higher prevalence of rare etiologies in our center (e.g. BCD, ARB, et al.). In the future, multicenter prospective clinical studies will provide more detailed information for diagnosis and treatment monitoring of CNV in children. In addition, although age- and sex-stratified analyses provided valuable insights into demographic trends of pediatric CNV, we did not perform multivariate analyses to adjust for potential confounders such as etiology subtypes, blood test results and treatment protocols due to the limitation of retrospective study and insufficient clinical data. This limits our ability to establish independent associations between age/sex and clinical outcomes, as unmeasured variables may have influenced the observed differences. Future studies incorporating multivariate models are warranted to explore interactions between demographic and clinical factors and identify independent predictors of CNV outcomes. Moreover, we haven't included an adult CNV control group to study the differences in imaging characteristics between adult and pediatric CNV, and this will be the direction of our future research.

Conclusions

In conclusion, the most common etiologies of CNV in Chinese children and adolescents are idiopathic, inflammatory, and congenital or hereditary diseases. Most pediatric CNVs are unilateral and are most commonly located in the subfoveal area. CNV in children appears as classic/type 2 CNV on multimodal imaging. The highest incidence of CNV in children is between the age of 7 and 17. Age-stratified analysis shows that idiopathic is the main etiology of CNV in children under 12 years of age, while inflammatory chorioretinopathy is the most common etiology in children older than 12 years. Pediatric CNV has a good response to anti-VEGF treatment and anti-VEGF drugs can significantly improve the visual acuity of children with CNV.

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Author contributions
Shenshen Yan contributed to the study design, data analysis, drafting and revising of the manuscript. Haixia Ji contributed to data analysis and interpretation. Yuzhu Liu and Xuan Jiao contributed to data acquisition and

data collection. Haicheng She and Haiying Zhou designed the study, revised the manuscript and supervised the project. All authors approved the final version of the manuscript.

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Data availability
All data generated or analyzed during this study are included in this article. Further inquiries are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This retrospective observational study adhered to the tenets of the Declaration of Helsinki. Approval was obtained from the Ethical Review Committee of Beijing Tongren Hospital, Capital Medical University. The requirement for written informed consent was waived by the Ethical Review Committee of Beijing Tongren Hospital due to the retrospective design of this study. However, as FFA and ICGA are invasive examinations, all patients' parents had signed informed consent forms for invasive examinations before FFA and ICGA.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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