Hypertension as a prominent manifestation in pediatric Behcet's disease

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Abstract

Objective:

Hypertension caused by vascular Behcet's disease (BD) is an important prognostic factor of pediatric BD. However, much less is known about its clinical features. The objective of this study is to investigate the clinical characteristics of pediatric BD complicated by hypertension.

Methods:

A retrospective study was carried out in pediatric BD complicated by hypertension hospitalized at the Children's Hospital Capital Institute of Pediatrics from Jan 2009 to Dec 2022.

Results:

Of 65 BD patients, 6 (9.2%) were complicated by hypertension, 4 patients were female, and the median ages of onset and diagnosis were 9.8 years and 11.3 years, respectively. Five of the 6 patients with hypertension had right renal artery involvement, and all of them were treated with glucocorticoids and immunosuppressants. Four patients were treated with biological agents. One patient with severe renal artery stenosis received vascular interventional therapy, but it failed. After 3-6 years of follow-up, five patients were found to have renal atrophy, and one patient was in stable condition.

Conclusion:

Hypertension in pediatric BD is mainly caused by renal artery involvement. Early recognition and treatment of vascular involvement in BD is important to prevent poor prognosis.

1 Introduction

Behcet's disease (BD) is a chronic, recurrent systemic vasculitis syndrome with high heterogeneity. The most common manifestations include recurrent oral aphthous ulcers, genital ulcers, uveitis and cutaneous lesions. [1] More attention has been given to arterial involvement recently, although veins are predominantly involved. [2] In the past, attention was focused on venous involvement in Behcet's disease. Some patients may have hypertension caused by artery involvement as a manifestation, which is difficult to notice. Hypertension is an uncommon manifestation of BD but may cause severe complications that lead to poor prognosis or even death. However, there are limited reports about hypertension in pediatric BD. The aim of this study was to investigate the prominent clinical characteristics of BD patients with hypertension to realize early diagnosis and treatment. The main clinical characteristics, treatment and long-term follow-up of pediatric BD complicated by hypertension were reported.

2 Methods

This retrospective study was conducted at the Children's Hospital Capital Institute of Pediatrics (CIP). Children diagnosed with BD from Jan 2009 to Dec 2022 were included in this study. All participants fulfilled the pediatric criteria for BD (PEDBD) (2015) [3]. Patients diagnosed with hypertension in this study fulfilled the revised criteria of the Clinical Practice Guidelines of the American Academy of Pediatrics [4]. The diagnosis of vascular artery involvement was based on clinical assessments and imaging data: Doppler sonography and/or angio-computed tomography arteriography (CTA), angio-magnetic-resonance imaging (MRI) examinations, etc. Clinical data, including
age, sex, oral and genital ulcerations, blood pressure, cutaneous lesions, ocular lesions, arthritis, vascular lesions, neurological involvement, inflammatory laboratory parameters, treatment, and follow-up, were collected and analysed. This study was approved by ethics committees from the Capital Institute of Pediatrics (SHERLL2021047).

3 Results

In a total of 65 pediatric BD patients in this study, six patients accounted for 9.2% of the BD patients and were complicated by hypertension. The main characteristics of the 6 patients are summarized in Table 1. Four of the 6 patients were female. The median age at diagnosis was 9 years (range: 4-15 years).

3.1 Vascular involvement

In the current study, 15 patients accounting for 23.1% (15/65) were found to have vascular involvement. Vascular lesions in this study included stenosis, dilatation, wall thickening and thrombosis. A total of 10.7% (7/65) of cases were found to have venous lesions, and 18.4% (12/65) were found to have artery lesions. Six cases had both arterial and venous involvement, and eight cases had only arterial involvement. Five cases were complicated with thrombosis. Two patients were found to have intracranial venous sinus thrombosis and pulmonary artery thrombosis.

Of the 12 patients complicated with artery lesions, 8 had renal artery involvement, and 6 presented with hypertension. Six of the 8 patients had involvement of the right renal artery. Six patients were found to have renal artery involvement at the same time as the BD diagnosis, while in the remaining two patients, renal artery lesions were found later after the diagnosis of BD. There were 6 cases of unilateral renal artery involvement and 2 cases of bilateral involvement.

3.2 Hypertension

The majority of patients complicated with hypertension in this cohort suffered from grade 2 hypertension. Two patients developed hypertensive encephalopathy during the course of the disease, and the blood pressure of the 2 patients was over 180/120 mmHg when encephalopathy occurred. In 5 patients, hypertension was found through physical examination during the first hospitalization. In 1 patient, blood pressure was normal in the first physical examination (unilateral limb), and hypertension was found when hypertensive encephalopathy occurred.

3.3 Involvement of extravascular organ systems

Oral aphthous ulceration was observed in 6 patients in this cohort. Other manifestations included cutaneous lesions (nodular erythema, purulent herpes), entral nervous system involvement and arthritis in 5 patients, fever in 4 patients, and gastrointestinal tract lesions in 3 patients. Pathergy reaction was negative in 6 patients. The renal function of 6 patients was normal, and 1 patient had urinary protein.

Compared with patients with nonvasculo-BD, there was no significant difference in the manifestations.

Table 1 Clinical manifestations of 6 BD patients with hypertension
3.4 Laboratory investigations

The leukocyte and platelet counts increased in all 6 cases with hypertension, and hemoglobin decreased in 5 cases. The inflammatory indexes, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were significantly elevated in 6 patients. The average CRP and ESR results were 92.9 mm/h and 100.2 mg/dl, respectively. Two patients were positive for anti-nuclear antibody (ANA), and two were positive for anti-neutrophil cytoplasmic antibody (ANCA). The activity of the renin angiotensin aldosterone system was significantly increased in 4 patients who were tested. The pathogenic examination was positive in all 6 patients, including 2 cases of mycoplasma infection, 1 case of streptococcus infection, and 1 case of parvovirus B19 infection.

Table 2 Laboratory examination of 6 BD patients complicated with hypertension

<table>
<thead>
<tr>
<th>Laboratory examination</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte ↑</td>
<td>5/6(83.3%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5/6(83.3%)</td>
</tr>
<tr>
<td>Platelet ↑</td>
<td>6/6(100%)</td>
</tr>
<tr>
<td>Ferritin ↑</td>
<td>5/6(83.3%)</td>
</tr>
<tr>
<td>ESR ↑</td>
<td>6/6(100%)</td>
</tr>
<tr>
<td>CRP ↑</td>
<td>6/6(100%)</td>
</tr>
<tr>
<td>Cytokines</td>
<td></td>
</tr>
<tr>
<td>−TNF-α†</td>
<td>6(100%)</td>
</tr>
<tr>
<td>−IL-6†</td>
<td>(100%)</td>
</tr>
<tr>
<td>−IL-2R†</td>
<td>6(100%)</td>
</tr>
<tr>
<td>ANA+</td>
<td>2/6(33.3%)</td>
</tr>
<tr>
<td>ANCA+</td>
<td>2/6(33.3%)</td>
</tr>
</tbody>
</table>
3.5 Treatment and follow-up

All patients received treatment with glucocorticoids and immunosuppressants (Table 3). As the most commonly used immunosuppressant, cyclophosphamide (CTX) was used in 5 patients. Other immunosuppressants included thalidomide (n=2), methotrexate (MTX) (n=2), and mycophenolate mofetil (MMF) (n=2). Three patients (Patients 1, 5, and 6) were treated with tumor necrosis factor-α (TNF-α) inhibitors. Five patients were treated with anticoagulant or antiplatelet medications with warfarin or low-dose aspirin. No hemorrhagic complications were observed under anticoagulant or antiaggregant therapy. Six patients were followed up for 3 years to 6.4 years. Patients 1 and 6 were found to have renal atrophy at the time of diagnosis. For patient 1, during the follow-up, the size of the right kidney progressively decreased 3 years after the first CT scan (Fig. 1A and Fig. 1B). She underwent balloon dilatation of the right renal artery but failed due to severe stenosis of the renal artery. Patient 4 relapsed because she stopped treatment without authorization. She had hypertension caused by stenosis of the renal artery and renal atrophy, and an incomplete renal cortex was found 2.5 years after diagnosis (Fig. 2A and Fig. 2B). However, there was no corresponding clinical manifestation except the increase in blood pressure until she manifested sudden convulsion caused by hypertensive encephalopathy.

Figure 1A and 1B. Patient 1, a 8-year-old girl, axial contrast-enhanced CT imaging. A showed the narrowing of the right renal artery (arrow). Note the accompanying small renal size and deficient enhancement in the renal parenchyma. B 3 years later, follow-up CT image demonstrated that the right kidney became further smaller.

Figure 2A and 2B. Patient 3, a 12-year-old girl, axial contrast-enhanced CT imaging. A showed accessory renal artery stenosis of the right kidney; the renal volume was normal with smooth margin. B After 31 months, the edge of right kidney became irregular due to focal thinner renal cortices.

Table 3 Blood pressure and treatment in children with BD with renal artery involvement
<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Blood pressure(L/R)</th>
<th>RAS activation</th>
<th>Renal artery stenosis</th>
<th>Renal atrophy</th>
<th>Abnormal renal function (urinalysis, serum creatinine)</th>
<th>Markers of renal injury elevation</th>
<th>Anti-hypertension drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L 146/116 R 144/16</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>2</td>
<td>L 136/52 R 133/50</td>
<td>ND</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>ND</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>3</td>
<td>L 128/102 R 140/108</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Amlodipine Captopril Metoprolol</td>
</tr>
<tr>
<td>4</td>
<td>L 120/70 R 137/80</td>
<td>ND</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Amlodipine Captopril Metoprolol</td>
</tr>
<tr>
<td>5</td>
<td>L 138/94 R 148/98</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Amlodipine Captopril Metoprolol Prazosin</td>
</tr>
<tr>
<td>6</td>
<td>L 149/97 R 154/77</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Benazepril metoprolol nifedipine</td>
</tr>
</tbody>
</table>

L left; R right; ND no data; RAS renin-angiotensin system

4 Discussion

BD is a multisystem vasculitis syndrome that can involve blood vessels of all types and sizes and affect any tissue or organ. Sixty-five BD patients were analysed, and 6 patients manifested hypertension in the current study. The common feature of these patients is renal artery stenosis as the cause of hypertension. This study expanded the spectrum of childhood Behcet’s disease and revealed important prognostic factors.

Vascular BD has been adopted for patients in whom vascular manifestations are present and often dominate the clinical features. Vascular lesions, with an incidence of 12.8%, are one of the main clinical manifestations of BD and may represent a life-threatening condition. Male sex and young age were reported to increase the risk of vascular complications. Vascular lesions occur in 1.8–32.1% of pediatric patients. In China, the incidence of vascular lesions in adult BD is 7.7%. In the past, venous involvement was frequently reported in many studies, while reports about arterial lesions in patients with BD are rare and often lack awareness. It was reported that the frequency of
arterial lesions ranges from 1–33.5%. In the current study, the frequency was 18.5% (12/65). All 6 patients with hypertension suffered from stage 2 hypertension and hypokalaemia caused by the increased production of renin due to stenosis of the renal arteries. For those patients with hypertension caused by renal artery involvement, hypertension is a progressive process. During the early stage of artery wall thickening, blood pressure could be normal. With the progression of the disease, lumen stenosis may develop and lead to renin-angiotensin-aldosterone system activation, resulting in hypertension.

The patient could be asymptomatic, and the urine test and serum creatinine levels could be normal in the early stage of disease. Without careful and systemic physical examination, it is difficult to detect hypertension and vascular involvement. It will be more difficult and confusing, especially in situations in which the blood pressure is normal at the beginning, which easily leads to ignorance of regular monitoring of blood pressure. In fact, the blood pressure of some patients was normal at the first hospitalization but ignored monitoring after discharge, such as patient 1 and patient 3 in this cohort. The blood pressure of the two patients was normal at the beginning and was not monitored regularly in the course of disease until they developed hypertensive encephalopathy years later, and vascular involvement was detected to screen for the reasons for hypertension. What should be noted and easy to ignore is regular bilateral blood pressure monitoring. There may be two reasons for this: on the one hand, the blood pressure was indeed normal at the beginning, and the other reason may be that the patient's bilateral blood pressure was asymmetric, and the normal blood pressure value was obtained by measuring the blood pressure on the normal side. Therefore, it is important to measure bilateral blood pressure routinely for vascular BD patients. Vascular ultrasound or CTA could help determine whether vascular involvement is present. Once vascular lesions occur, blood pressure should be closely monitored, and hypertension should be treated in a timely manner to prevent damage to important target organs, such as the eyes, heart, brain and kidneys. This reminds us that systematic screening for asymptomatic arterial lesions should be performed in BD rather than venous lesions only to find artery involvement in the early stage and treat in time to avoid important organ involvement. Careful physical examination is crucial in discovering hypertension and vascular murmur, which indicates vascular involvement.

Eight patients in this study had renal artery lesions, and five of them were found to have renal atrophy. Pyknosis related to hypertension and reduced renal blood supply may contribute to this phenomenon. What needs special attention is that five of the six patients had right artery involvement, and the pathogenic association between BD and right renal artery involvement needs to be clarified in future studies. It has been reported that in patients with fibromuscular dysplasia (FMD), which often causes right artery stenosis, the right renal artery is more prone to be involved than the left renal artery, which may be due to renal mobility when assuming an upright position being greater in the right than in the left kidney, therefore, it has been suggested that repeated stretching of the renal artery may cause microtraumas that predispose patients to FMD. Therefore, we speculate that the susceptibility of BD to right renal artery stenosis may also be related to this factor.

According to vascular involvement, the prevalence in this study was 18.5% (12/65), of which renal artery involvement accounted for 12.3% (8/65). Other involved vessels cover the main arteries and veins of intracranial, limbs and organs, with a wide range of lesions. Previous studies have found that veins are more prone to be involved in BD and that vascular involvement, especially thrombosis, is common in men. In this study, the proportions of patients with arterial and venous involvement were similar, and most of the patients were female, which is different from previous studies. A study involving 796 Chinese patients with Behçet's syndrome reported that 12.8% of the patients were affected by blood vessels, in which the male/female ratio was 4:1 and the average age of onset was 29.5. In addition, 54.9% of patients with BD had arterial involvement, 70.6% of patients had venous lesions, and 25.5% had both arterial and venous involvement. This may be related to ethnic differences and the small number of cohorts.
In summary, children with BD should not only be given attention to venous involvement but also arterial involvement and thrombosis. Patients 2 and 4 were detected to have multiple venous thromboses.

According to the laboratory examination, leukocytes increased slightly in 5 patients, and elevated platelets and mild anemia were found in 6 patients. It should be noted that the inflammatory indexes (CRP and ESR) increased in all patients; the average ESR was 90 mm/h, and the average level of CRP was 98.06 mg/dl. It is suggested that when the inflammatory index is significantly increased, attention should be given to vascular involvement. Pathergy reaction was negative in all patients. This might be related to the application of glucocorticoid therapy before the diagnosis. In this study, 5 patients were positive for etiology, suggesting that infection may be the cause of the disease.

All children in this study were treated with glucocorticoids combined with cyclophosphamide, and other immunosuppressants included thalidomide and methotrexate. Three patients with nervous system involvement were treated with methylprednisolone pulse therapy, and two of them were treated with infliximab. Except for one patient who was lost to follow-up, the other patients were followed up for 3.3 years to 6.3 years. The symptoms and laboratory examinations improved, and the average time of clinical remission was 6 months. All three patients were complicated with severe renal artery stenosis. One patient stopped treatment one year after diagnosis and showed manifestations of hypertension and convulsion. Two years later, her kidneys significantly shrank, the renal cortex became thinner, and some renal cortex was discontinuous (Fig. 2A and Fig. 2B). This may be related to long-term hypertension and insufficient blood supply to the kidney. Three patients with venous thrombosis were treated with glucocorticoid pulses combined with TNF-α inhibitors, and one patient was treated with IL-6 inhibitors. Two of the patients were treated by steroid pulse therapy combined with cyclophosphamide. It is concluded that thrombosis in BD is mainly mediated by inflammation and that immunosuppressive therapy should be the core of treatment, including immunosuppressive drugs. Anticoagulant therapy may significantly increase the risk of aneurysm rupture and fatal hemorrhage, and immunosuppressive therapy is important for patients with thrombosis. Hence, patients with venous thrombosis should undergo relevant examinations to detect the existence of pulmonary artery aneurysms.

A study showed that tumor necrosis factor inhibitors associated with other immunosuppressive drugs seem to be effective in the management of major vessel involvement and could reduce the risk of relapse. In the current study, anti-TNF-α agents achieved an ideal therapeutic effect on BD accompanied by pulmonary artery aneurysm and venous thrombosis, and the long-term prognosis should be discussed in further studies. For the treatment of hypertension, it is difficult to achieve the ideal effect. Usually, more than two kinds of antihypertensive drugs are needed (Table 3). Once renal artery stenosis occurs, it may lead to the activation of the renin-angiotensin system, and blood pressure is more difficult to control. The blood pressure of children with renal artery involvement but limited to the thickening of the wall was normal. Timely and effective treatment may prevent renal artery stenosis to protect important target organs. Therefore, routine examination of renal artery ultrasound or CTA in children with BD is as important as monitoring blood pressure.

The limitation of the current research is the small number of patients due to the low incidence. In the long run, multicenter research is needed to identify genes that predispose patients to the condition and improve the detection and quantification of renal artery stenosis.

5 Conclusions
In conclusion, hypertension in children with BD is mainly caused by renal artery stenosis, and early diagnosis is difficult. Renal artery involvement in BD in children is a serious complication and an important factor determining the prognosis of the disease. A long course of disease and lack of treatment may lead to renal atrophy. Patients with renal artery involvement should be closely monitored for blood pressure and regularly evaluated for important target organs. Early recognition of vascular involvement is important to evaluate prognosis.

**Abbreviations**

ANA: anti-nuclear antibody  
ANCA: anti-neutrophil cytoplasmic antibody  
BD: Behcet's disease  
CRP: C-reactive protein  
CT: computed tomography  
CTX: cyclophosphamide  
EL: eye lesions  
EN: erythema nodosum  
ESR: erythrocyte sedimentation rate  
FMD: fibromuscular dysplasia  
GU: genital ulcers  
ITI: intestinal tract involvement  
MMF: mycophenolate mofetil  
TNF-α:  
MTX: methotrexate  
N: no  
NI: neurologic involvement  
ND: no data  
OAU: oral aphthous ulcers  
PN: patient number  
PL: papulopustular lesions  
PR: pathergy reaction
Declarations

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Authors' contributions

XW wrote the draft of the manuscript and contributed to patient management. GS and XL designed the study, revised the manuscript and supervised patient treatment. JL and ZZ contributed greatly to patient management. All the authors have read and approved the final version of the manuscript.

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Data availability

All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

Parental informed consent for publication was obtained from all participants. This study was approved by the Ethics Committee of Capital Institute of Pediatrics.

Consent for publication

Written informed consent was obtained from the patient’s legal guardians for the publication and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

References


Figures

Figure 1A

Figure 1B

Figure 1

A and B, Patient 1, a 8-year-old girl, axial contrast-enhanced CT imaging. A showed the narrowing of the right renal artery (arrow). Note the accompanying small renal size and deficient enhancement in the renal parenchyma. B 3 years later, follow-up CT image demonstrated that the right kidney became further smaller.
A and B. Patient 3, a 12-year-old girl, axial contrast-enhanced CT imaging. A showed accessory renal artery stenosis of the right kidney; the renal volume was normal with smooth margin. B After 31 months, the edge of right kidney became irregular due to focal thinner renal cortices.