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Alimentary Tract

Diagnosis and management of children with Blue Rubber Bleb Nevus Syndrome: A multi-center case series

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ABSTRACT

Background: Blue Rubber Bleb Nevus Syndrome (BRBNS) is a rare, severe, sporadically occurring disorder characterized by multiple venous malformations.
Aims: To present and analyze a case series of pediatric patients with BRBNS and to describe diagnostic approaches and management options applied.
Patients and methods: Multicenter, retrospective study, evaluating the diagnosis and management of children with BRBNS.
Results: Eighteen patients diagnosed with BRBNS were included. Cutaneous venous malformations were observed in 78% and gastrointestinal venous malformations in 89%. Lesions were also found in other organs including muscles, joints, central nervous system, eyes, parotid gland, spine, kidneys and lungs. Gastrointestinal lesions were more common in the small intestine than in stomach or colon. The management varied significantly among centers. Endoscopic therapy and surgical therapy alone failed to prevent recurrence of lesions. In younger children and in patients with musculoskeletal or other organ involvement, sirolimus was used with 100% success rate in our series (5 patients treated) although poor compliance with subtherapeutic sirolimus trough levels led to recurrence in a minority.
Conclusions: Considering the multi-organ involvement in BRBNS, diagnosis and management requires a multidisciplinary approach. The treatment includes conservative, medical, endoscopic and surgical options. Prospective multicenter studies are needed to identify the optimal management of this rare condition.

1. Introduction

Blue Rubber Bleb Nevus Syndrome (BRBNS) is a rare, severe, sporadically occurring disorder characterized by multiple venous malformations. Lesions are most commonly found on the skin and the gastrointestinal (GI) tract [1–4] but may also involve

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Table 1
Characteristics of the patients.

General characteristics	N (%)
Patients	18
Gender male	13 (72)
Race	
Caucasian	12 (67)
African America	3 (17)
Asian	2 (11)
European-Maori	1 (6)
Mean age at presentation (years ± SD)	2.8 ± 2.6
Mean age at diagnosis (years ± SD)	5.6 ± 5.4
GI involvement	16 (89)
Stomach	8 (44)
Small bowel	15 (83)
Colon	9 (50)
Skin involvement	14 (78)

other visceral organs [5–8]. The most common clinical presentation is symptomatic anemia due to GI bleeding, both overt and occult [9–11]. Patients with BRBNS may also present with GI complications, such as intussusception, perforation, volvulus with occasional associated mortality [12–15].

Management of BRBNS generally depends on the extent of intestinal involvement and presence of other organ involvement. This includes supportive therapy [16,17], pharmacological [18–21] and endoscopic treatments [22–27]. Surgery is reserved for patients with significant hemorrhage or other complications [28,29]. To date no guidelines are available for diagnosis and management of this rare disorder. In this multicenter, multinational case series we aim to describe the main characteristic features of 18 children with BRBNS, along with successful diagnostic and therapeutic approaches, that can help generate an ideal long-term management strategy.

2. Patients and methods

This was a retrospective chart review of 18 cases with BRBNS from centers in seven countries including Australia, Israel, The Netherlands, New Zealand, Thailand, United Kingdom and the United States of America. Both gastroenterology and dermatology department were involved, in order to include also cases of BRBNS with mainly cutaneous lesions. Data on current age, sex, race, age of presentation, age at diagnosis, clinical and family history, physical and laboratory findings, diagnostic workup and results, treatment, complications and follow up were collected.

Diagnosis of BRBNS was made by the presence of the characteristic venous malformation confirmed histologically and/or by the presence of cutaneous and/or gastrointestinal venous malformations. One of the authors (MT), with a vast experience in endoscopy and vascular malformations, reviewed all the pictures (skin/endoscopic), to ensure diagnostic uniformity. Lesions in other organs were documented if present. Patients already published in other case reports were excluded from the study.

3. Results

3.1. Patient group

Table 1 summarizes the principal characteristics of 18 patients with BRBNS. The diagnostic interval (presentation to diagnosis) was on average 2.2 years (range 1 month to 6 years). Only two patients had a family history of BRBNS (1 mother/1 father).

3.2. Clinical presentation

Cutaneous venous malformations were present in 14/18 patients at the time of presentation and during the follow-up (78%). The distribution of the lesions was: generalized in 3 (17%); limbs in 4 (22%); extremities/lower back in 2 (11%); face in 2 (11%); face/neck in 1 (6%); perianal area/leg/scalp in 1 (6%); and thorax/neck in 1 (6%). Two (11%) presented with angiokeratoma.

Eleven (61%) presented with anemia manifesting as pallor, lethargy or poor exercise tolerance. Overt GI bleeding occurred in 7/18 (39%) — 2 with melena and 5 with hematochezia. Overt GI bleeding was associated with cutaneous vascular malformation in 6 (33%). Four (22%) presented with occult bleeding, identified by stool testing, in whom 3 (16%) had skin involvement.

Other organ involvement included intra-muscular in 4 (22%), central nervous system (CNS) in 3 (17%), intra-articular in 3 (17%), ocular in 1 (6%), parotid gland in 1 (6%), spine in 1 (6%), kidney in 1 (6%) and pulmonary in 1 (6%).

Significant co-morbidities were found in 5/18 patients including: dysplastic cystic kidneys; hydronephrosis; tetralogy of Fallot; epilepsy; posterior fossa cystic lesions, right hemiplegia; subdural hemorrhage; hydrocephalus; plexiform neurofibroma of the lumbar spine; factor XII deficiency; Abernethy-type vascular malformation with porto-systemic shunt; hepatopulmonary syndrome; and cardiomegaly with pulmonary hypertension.

Non-therapy related complications included: severe muscle pain in two patients (one severe enough to cause intermittent immobility requiring wheelchair); intussusception (2 episodes in the same patient); knee pain requiring morphine; recurrent bleeding of a toe lesion; and psychological problems related to chronic illness.

4. Diagnostic findings

4.1. Laboratory results

Blood tests revealed microcytic anemia in 16 (89%) of whom 10 (56%) reported severe, symptomatic anemia requiring more than one blood transfusion. The lowest hemoglobin (Hb) values recorded in these patients varied from 18 g/L to 114 g/L (mean value 59.5 g/L). Consumptive coagulopathy was recorded in 2 patients (11%). Albumin values ranged from 20 to 43 g/L (mean value 33.5 g/L).

Faecal occult blood was positive in all 6 anemic patients who were tested.

4.2. Radiological investigations

Five patients had an abdominal Magnetic Resonance Imaging (MRI), demonstrating vascular malformations in 4 (80%). Abdominal ultrasound (US) was performed in 7 patients, of whom 4 (57%) had vascular malformations identified and 2 underwent abdominal computed tomography (CT) angiography which showed vascular malformations in both (100%).

4.3. Endoscopic procedures

The endoscopic procedures performed, and diagnostic yield are shown in Table 2. Sixteen patients underwent conventional GI endoscopy – upper GI endoscopy in 13 and ileo – colonoscopy in 15. Children underwent an average of 1.25 upper GI endoscopy (range 0–3) and 2.25 ileo-colonoscopies (range 0–12) each. Wireless capsule endoscopy (WCE) was performed in 12/18 patients, with an average of 1.4 WCE per patient (range 0–3). WCE provided a 100% positive diagnostic yield for BRBNS lesions. Enteroscopy was performed in 9/18 patients, 5 patients had an intra-operative enteroscopy (IOE), 2 patients had double balloon enteroscopy (DBE)

Table 2
Endoscopic diagnostic procedures performed and yield.

Procedures	Diagnosis/n° of procedures	Diagnostic yield (%)
OGD	8/13	62
IC	13/15	87
WCE	12/12	100
DBE/SBE	4/4	100
IO enteroscopy	5/5	100

OGD: oesophagogastrodudenoscopy; IC: ileo-colonoscopy; WCE: wireless capsule endoscopy; BE: double balloon enteroscopy; SBE: single balloon enteroscopy; IO enteroscopy: intra-operative enteroscopy.

and 2 patients had a single balloon enteroscopy (SBE): on average 2 enteroscopies were performed per patient and all demonstrated BRBN lesions. The distribution of lesions in the GI tract were: stomach in 8/18 (44%); small bowel in 15/18 (83%) — specifically duodenum in 6/18 (33%), jejunum in 11/18 (61%), and ileum in 5/18 (28%); and colon in 9/18 (50%). Two children did not undergo any endoscopic procedures because they had only cutaneous manifestations and no GI symptoms or anemia or occult bleeding; although they received a radiologic evaluation (abdominal MRI and abdominal US in one, and abdominal US in the other, all with a negative result).

4.4. Non-GI investigations

Six patients underwent neuroimaging, (4 facial and brain MRI, 1 brain CT, 1 cranio-facial ultrasound, 1 neck ultrasound, 1 spine ultrasound) which showed a vascular malformation in 3. Three patients had radiological investigations for muscoloskeletal lesions (knee, ankle, femur) that were positive in all cases. One patient with frank hematuria underwent renal ultrasound, cystoscopy and micturating cystoureterogram, all of which were inconclusive. One child had a pulmonary CT angiography and CT venography that showed lung involvement. One patient had a CT angiography of abdomen and pelvis, which identified renal involvement.

5. Management and follow up

Patients were followed for 1–18 years (median 9.5 years). The main characteristics of the patients, management and clinical course are summarized in Table 3.

5.1. No active intervention

Two patients did not require any therapy during their follow up of average 2.7 years (range 2.5–3). One only had skin lesions at follow up. The other one with skin lesions and vascular malformations throughout the small bowel, with hematochezia as the presenting symptom, had spontaneous resolution of the symptoms and stable Hb at follow-up.

5.2. Supportive therapy

Supportive therapy included initial oral iron supplementation in 11/18 (61%) and intravenous iron infusions in 3/18 (17%). Ten patients (56%) reported a history of severe microcytic anemia needing more than one blood transfusion (on average 0.9 transfusions per month) with 2 requiring port-a-cath insertion due to the need for recurrent blood transfusions. Only one patient (6%) received supportive therapy, while the remaining (94%) also received radiologic, endoscopic, surgical, medical therapy or a combination of these.

5.3. Endoscopic treatment

Ten children (56%) received endoscopic treatment. Several endoscopic techniques were employed according to instrument availability at different centres and the endoscopist's experience, including: argon plasma coagulation (APC) in 6; snare mucosectomy in 1; APC, band ligation and sclerotherapy in 1; and sclerotherapy only in 3. All reachable lesions were treated. A great variation in the number of lesions founded and, therefore, treated was observed among patients (form 1 to more than 100, average 21). A transient rise in Hb (average 9.7 months, range 4–16 months) was recorded in all patients following endoscopic treatment, regardless of the technique used. Only one patient retained a persistently stable Hb after therapy (10%); GI bleeding relapsed in all others (90%). The patient who did well after endoscopic therapy was a post-pubertal boy, who underwent to 3 DBE with APC treatment of all small bowel and colonic lesions (16, 13, 4 lesions founded/treated during each procedure). Two of the remaining patients, required further endoscopic treatments. Seven children required additional therapies: 1 surgery; 1 medical; and 5 both medical and surgery.

5.4. Surgical treatment

GI surgery was performed in 8 patients (44%) and included: IO enteroscopy with surgical wedge excision of all GI lesions founded in 3; IO enteroscopy with snare mucosectomy and APC treatment of all GI lesions founded in 1; ileo-cecectomy in 1 (lesions concentrated in that segment); and surgical wedge excision of all small bowel and colonic lesions founded in 2; small bowel resection and reanastomosis in 1 (lesions concentrated in that segment). Number of lesions founded and, therefore, treated varied from 1 to 47, average 11. Surgery resulted in stabilization of Hb with temporary remission of symptoms in all. After surgery, normal Hb levels were recorded for an average of 11.6 months (range 6–20 months). However, all but one subsequently deteriorated, requiring other active therapies. Four had medical treatment (see below); 1 had APC via endoscopy; and 1 underwent 4 endoscopic APC of multiple lesions in the stomach, duodenum and colon with, plus 2 surgical excision of 7 vascular lesions in jejunum and 2 in the ileum. The patient who did well after surgical therapy was a post-pubertal boy, who underwent to intra-operative enteroscopy with surgical wedge resections of all GI lesions found (6 small bowel lesions and 2 colon lesions).

5.5. Non-GI surgical interventions

Non-GI surgical management were excision of skin lesions in 5 and a left nephrectomy in 1 patient, with good outcomes defined as bleeding stop, reduction of blood transfusion requirement, in all the patients and in addition resolution of consumptive coagulopathy in one.

5.6. Medical treatment

Seven children (39%) received a medical treatment including: sirolimus mono-therapy in 4; prednisolone in 1; thalidomide, interferon alpha-2a, prednisolone, propranolol and octreotide in 1; thalidomide, tranexamic acid and sirolimus in another.

5.6.1. Sirolimus therapy

Table 4 summarizes the principal characteristics of 5 patients treated with sirolimus, the response to the therapy and the follow up. Children treated with sirolimus remained stable and asymptomatic. A relapse with lesion regrowth was recorded with poor compliance, reducing the dose or stopping therapy. All of them had

Table 3
Main characteristics of the patients, management and clinical course.

Patient n°	Sex	Age at diagnosis (Y)	Skin	GI	Other	Blood transfusions requirement prior to treatment	Treatment	Treatment description	Outcome	Age at last follow up (Y)
1	F	2	++	+	–	0	None	None	Stable, asymptomatic	10
2	M	0	+	–	–	0	None	None	Stable, asymptomatic	13
3	M	2	++	+++	–	0–2/year	Supportive therapy	Iron infusions	Blood transfusions requirement 0–2/year	5
4	M	11	+++	++	CNS	0–2/year	8 interventional radiology + supportive therapy	8 embolizations of CNS lesions, iron supplements	Blood transfusions requirement 0–2/year	13
5	M	16	–	++	–	2–3/month	1 surgery	Intra-operative enteroscopy with surgical wedge resections of small bowel and colon	Stable, asymptomatic	17
6	M	12	++	–	Muscles	0	1 surgery	Resection of skin lesions	stable, asymptomatic, consumption coagulopathy resolved	26
7	M	4	+++	++	Angiokeratoma of left thigh	0,5–1/month	21 endoscopic	17 APC, 2 band ligation, 2 sclerotherapy	Blood transfusions requirement decreased (2–4/year)	12
8	F	15	–	+	–	0,5–1/month	1 endoscopic	1 APC	Blood transfusions requirement decreased (2–3/year)	22
9	M	1	+	++	Muscle	1	4 endoscopic + 2 surgery	4 APC, wedge excisions of small bowel lesions, skin lesions resection	Stable, asymptomatic	9
10	M	5	++	++	–	1	3 endoscopic + 1 surgery	3 APC, 1 skin lesion resection	Stable after endoscopic therapy; remission of discomfort after surgical removal of skin lesion	23
11	M	12	+	++	–	1	1 endoscopic + 1 surgery	Snare mucosectomy, intra-operative enteroscopy with snare mucosectomy and APC	Still anemic, iron infusions dependent, plan to start on sirolimus	14
12	M	0	+++	++	Muscles	2-3/month	1 surgery + medical	Ileocaecectomy, sirolimus	Stable, asymptomatic, no further blood transfusions required, sirolimus side effects	14
13	M	12	–	++	–	0	1 surgery + medical	Small bowel resection and reanastomosis, sirolimus	Stable, asymptomatic, relapse when compliance to sirolimus was scarce	16

14	M	1	–	++	CNS, eyes	0	1 endoscopic + medical	1 APC, sirolimus	Stable, asymptomatic	2
15	F	2	++	+++	Joints, angiokeratoma of second left toe and right thigh	2/month	2 endoscopic + 1 surgery + medical	2 APC, skin lesions resection, sirolimus	Scarce response to endoscopic and surgical treatment, good response to sirolimus, relapse when compliance to sirolimus was scarce	14
16	F	7	+	+++	Joints, parotid glands, left kidney	2–3/month	1 endoscopic + medical + 6 surgery	Sclerosing agents for GI and parotid lesions, thalidomide, interferon alpha-2a, prednisolone, propanolol, octreotide, 5 intraoperative-enteroscopy with surgical wedge excision of small bowel lesions, left nephrectomy	Still blood transfusion dependent, consumptive coagulopathy, Interferon alpha-2a side effects,	22
17	F	5	+	+++	CNS, spine, muscles, joints	3–6/year	1 endoscopic + medical + 5 surgery	Sclerosing agents, thalidomide, tranexamic acid, sirolimus, 3 intraoperative-enteroscopy with surgical wedge excision of small bowel lesions, 2 resections of skin lesions	Further surgeries for 2 active intussusceptions, thalidomide side effects, good response to sirolimus, relapse when the drug was stopped, required surgery, then occasional blood per rectum, no blood transfusion requirement	17
18	M	1	+	++	Lungs	Dependent	1 endoscopic + medical + 1 surgery	Sclerosing agents, prednisolone, surgical wedge excision of small bowel lesion	Blood transfusions requirement decreased, awaiting surgery for the occlusion of portosystemic shunt	19

CNS: central nervous system; APC: argon plasma coagulation.

Table 4
Main characteristics of patients treated with sirolimus, response to the therapy and follow up.

Patient no	Sex	Clinical presentation	Disease involvement	Blood transfusion requirement prior to treatment	Previous unsuccessful treatments (n)	Outcome on sirolimus	Sirolimus trough levels monitored (yes/no, average)	Follow up
12	M	Hematochezia, symptomatic anemia requiring blood transfusions, leg cramps	Skin (generalized), colon, ileum, muscles	2–3/month	Ileo-caecectomy (1)	Stable, asymptomatic	Yes, 5.2 ng/mL	Stable, asymptomatic for 7 years. Then he developed mouth ulcers and complained of mood swings with drug trough levels recorded 9.2 ng/mL. Symptoms resolved after the dose of the drug was diminished, but then the patient became non-compliant over time with drug levels going from 6.8 ng/mL to undetectable at the most recent follow up. The patient was having occasional abdominal pain at that time, but not hematochezia, and the WCE did not demonstrate any vascular lesions.
13	M	Hematochezia, symptomatic anemia, abdominal pain	Ileum, colon	None	Small bowel resection and reanastomosis (1)	Stable, asymptomatic	No	Stable, asymptomatic for 10 months. Then he experienced a symptomatic relapse when compliance to sirolimus was scarce.
14	M	Melena, symptomatic anemia	Stomach, duodenum, jejunum, CNS, eyes	None	Endoscopic APC therapy (1)	Stable, asymptomatic	Yes, 6.9 ng/mL	Stable, asymptomatic.
15	F	Occult GI bleeding symptomatic anemia requiring blood transfusions	Skin (limbs, angiokeratoma of second left toe and right thigh), stomach, duodenum, jejunum, colon, joints	2/month	Endoscopic APC therapy (2), skin lesions resection (1)	Stable, asymptomatic	Yes, 4 ng/mL	Stable, asymptomatic for 3 years. Then she developed symptomatic anemia requiring transfusions. At that time drug trough levels were low (average 2.5 ng/mL), and the patient admitted poor adherence to therapy.
17	F	Hematochezia, symptomatic anemia requiring blood transfusions, joint pain that forced her on a wheelchair	Skin (thigh), stomach, ileum, colon, CNS, spine, muscles, joints	3–6/year	Endoscopic sclerotherapy (1), thalidomide, tranexamic acid, resections of skin lesions (2)	Stable, asymptomatic	No	Stable, asymptomatic for 5 years. Later, she had poor adherence to therapy, and the drug was stopped, with recurrence of rectal bleeding in few months. Subsequently, she had 28 small bowel lesions excised, removal of several skin lesions and 2 operations for complications related to BRBNS (two episodes of intussusception). After the surgery, she reported occasional blood per rectum, but remained stable and required no blood transfusions.

CNS: central nervous system; APC: argon plasma coagulation.

previous treatment failure/relapse on other therapy (two surgical, two endoscopic, one endoscopic and medical).

5.6.2. Other therapies

One patient with complex GI and non-GI manifestation (parotid, kidney) of BRBNS and poor response to endoscopic therapy received several therapies including thalidomide, interferon alpha-2a, prednisolone, octreotide, and propranolol. These therapies were not maintained due to lack of efficacy or excessive side effects. Subsequently, she underwent surgery with wedge excision of up to 100 small bowel lesions and a left nephrectomy for kidney involvement. She responded well initially, however, she recorded a new lower GI bleeding episode few months after the surgery.

Another patient also received multiple therapies due the to a complex BRBNS involvement: firstly, he was treated with endoscopic sclerotherapy, then with predisolone, with no improvement of Hb levels. Surgical excision of the small bowel mesenteric arteriovenous malformation subsequently led to a decrease in blood transfusion requirement.

5.7. Interventional radiology

None of the patients had radiological therapy for GI lesions. One patient had 8 radiological embolizations of CNS lesions, and remained subsequently on supportive therapy, requiring 0–2 blood transfusions per year. Another patient had a successful radiologic sclerotherapy of neck and parotid lesions.

5.8. Treatment complications and adverse events

No complications secondary to endoscopic treatment were recorded, regardless of the technique used. Complications related to surgical treatment were recorded in one patient, who developed adhesions after two laparotomies for small bowel resection and re-anastomosis. Adverse events related to medical treatment were: peripheral neuropathy in a patient treated with thalidomide; hair loss in a patient treated with interferon alpha-2a (symptom resolved after discontinuation of the drug); mouth ulcers and mood swings in a patient treated with sirolimus (symptoms resolved after diminishing of the dose).

6. Discussion

BRBNS is a rare vascular disorder characterized by multiple venous malformations primarily affecting the skin and the GI tract. To date, etiopathology of BRBNS is still unknown. According to the study published by Soblet and colleagues, BRBNS is considered as sporadic disorder, caused by somatic double (cis) mutations in the TEK gene causing a ligand-independent receptor hyperphosphorylation in vitro [30]. However, cases of autosomic dominant inheriting have been described [31,32], and two of our patients presented with a family history of BRBNS (1 mother/1 father). No guidelines are currently available for BRBNS management in adults or children. Since Gascoyen firstly described the disease in 1860 [33] and William Bean named it as BRBNS a century later [34], there have been only around 200 cases reported. As previously described [35,36], in our series most were Caucasian. We observed male predominance (72%), though this was not reported in other series [37].

Generally, venous malformations are detectable at birth or early in infancy but can develop later in life [38] and usually increase in size and number over time.

Clinical manifestations in BRBNS may vary depending on the organs involved. The most common finding is microcytic anemia [10], and in our series 89% of the patients were anemic with 56% requiring more than one blood transfusion.

Skin lesions are almost universal but not always reported [9]. Angiokeratoma can rarely be seen [39] — 11% in our series. Our findings support the high incidence of small bowel involvement [2,3], present in 83%. A positive correlation between the number of GI venous malformations and the number of cutaneous lesions has been described [40]. We failed to find any correlation between number of GI lesions and patient's age. Neverthless, we noticed a slower regrowth of GI lesions after endoscopic/surgical treatment in older children.

As previously reported [41], overt GI bleeding was a common presenting symptom in our series.

In larger adult series the most commonly affected organ, after skin and GI tract, is the CNS, followed by the liver, muscle, vagina and spine [42]. In our series, after skin and GI tract, skeletal muscle was most commonly involved (22%). Muscle involvement alone did not interfere with motor function, but CNS lesions led to mechanical compromise in some. Pulmonary involvement has been described in a minority (only 1 in our series) manifesting as chronic cough due to endobronchial lesions [5] and spontaneous hemothorax due to sub-pleural lesions [43]. Other organ involvement in our cohort included eyes, parotid gland and kidney, all rarely reported in literature.

Complications associated with this syndrome include intussusception, volvulus, hemorrhage, postoperative disseminated intravascular coagulation (DIC) and occasionally even death [12–15]. We recorded 2 episodes of intussusception and 2 of DIC.

Considering the multi-organ involvement of BRBNS, the diagnostic work up and management of BRBNS patients should be multidisciplinary. An algorithm summarizing our suggested management of children with BRBNS is described in Fig. 1. In addition to the initial history, examination full blood count (FBC), clotting and fecal occult blood (FOB), GI tract evaluation is mandatory if BRBNS is suspected.

GI radiological investigations may include barium contrast studies, tagged RBC nuclear scans, abdominal CT and MRI [44–46]. In our series both abdominal MRI and CT revealed a good sensitivity. Abdominal US succeeded to identify GI vascular malformations in 57% (all confirmed at WCE), however a false-negative result was detected in one: subsequent WCE revealed the presence of multiple small bowel lesions. One patient with a negative radiological finding both at MRI and US, and 1 patients with negative finding at US, never underwent WCE evaluation due to non-availability at their referral centers; however, these patients did not show neither gastrointestinal symptoms, nor anemia, nor occult bleeding during follow up.

We believe that endo-luminal investigation with GI endoscopy should be mandatory in patients with BRBNS, and WCE is a non-invasive, highly sensitive and specific technique to evaluate the small bowel and to identify the distribution of BRBNS lesions [47]. GI conventional endoscopy is a highly sensitive diagnostic tool but can offer a therapeutic alternative in addition [22,23].

Most of the patients with BRBNS generally become blood transfusion-dependent during paediatric age. It is conceivable that symptomatic anemia and repeated blood transfusions deeply affect quality of life. Therefore, treatment should be individualized according to symptoms and organ involvement, firstly ensuring a good quality of life to those patients and aiming at preventing regular invasive treatments. When GI bleeding is mild, some authors advise conservative treatment with iron supplementation and blood transfusions [16]. In our series, only one young adult patient (6%) remained stable and asymptomatic on iron supplements alone. In general, BRBNS lesions are extensive, requiring multiple interventions, therefore this would be an unlikely course. GI lesions can be safely treated with endoscopic techniques such as APC, sclerotherapy, band ligation, snare mucosectomy, electrocauterization or endoscopic laser (Nd:YAG) photocoagulation

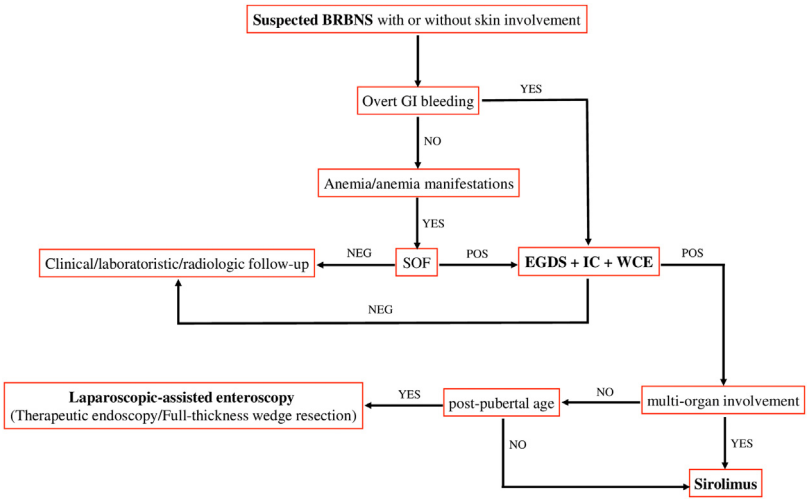

Fig. 1. Suggested management algorithm for gastrointestinal involvement in children with Blue Rubber Bleb Nevus Syndrome.

[22–27,48,49]. Some authors suggest avoiding endoscopic interventions such as APC in the small bowel due to its thin wall: one case of perforation reported [50,51]. Even if it has not been further confirmed [52], it seems reasonable to strikes a cautionary note on the application of APC technique to treat bigger – and thus deeper – lesions. To date, no clinical studies comparing various endoscopic techniques have been reported. In our series, endoscopic technique adopted was chosen according to instrument availability at different centers and to endoscopist's experience; we did not record any advantages between techniques, nor complications. Considering that GI bleb are fragile with a propensity to bleed easily, all the reachable lesions were treated, even if not actively bleeding at the time of the evaluation. Although, GI bleeding frequently relapsed after endoscopic interventions.

Fishman et al. reported effective control of bleeding lesions in 90% of cases after several surgical techniques over a five-year period [29]; recent reports suggest that wedge or segmental resection are safe and effective [28]. These studies are in contrast with our results that show only a temporary benefit from surgery, with a relapse of symptoms in all the patients but one (a young adult patient) within 1 year. Nevertheless, a pre-operative investigation of the GI tract with DBE/WCE is a reasonable choice to identify the number and the distribution of lesions as they are not commonly identified by visualization of the serosal surface of the bowel alone; intraoperative enteroscopy at the time of surgery is helpful [53].

Given the relatively high rate of lesion recurrence after surgical excision [54] and endoscopic treatment [27], several medical therapies have been proposed to treat BRBNS. Anti-angiogenetic agents such as steroids, interferon α-2a, propanolol and thalidomide have been used in attempts to reduce the occurrence of the bleeding episodes [20,21], however they universally failed in our series.

A newer agent, sirolimus, acting against angiogenesis has shown effective control of symptoms in our patients. Yuksekkaya et al. showed its potential efficacy where other medical therapies had failed with apparent complete remission of GI and musculoskeletal lesions and consequent bleeding, with no side effects in the 20 months follow up period [20]. Subsequent case reports have substantiated this effect [55–60]. Considering the multiorgan involvement in patients with BRBNS, medical therapy should be advisable, with sirolimus currently the best option [61]. Of course, further studies are needed for verification. Treatment begins at 1.6 mg/m^2/day divided into two doses given every 12 h, with subsequent doses adjusted to maintain a goal drug trough levels at 1–5 ng/mL [26,62]. In our series, all 5 patients treated with sirolimus remained stable and asymptomatic during the follow up and relapse of symptoms or decrease in Hb levels were recorded with poor compliance or with subtherapeutic sirolimus trough levels. However, we cannot exclude a primary loss of response of the drug, or other factors affecting the result. Further study of sirolimus seems warranted, although the rarity of this condition may mitigate against large placebo-controlled studies going forward. Table 5

Table 5
Overview of the common therapies for Blue Rubber Bleb Nevus Syndrome.

Therapy	Advantages	Disadvantages
Sirolimus	Oral administration Trough levels Delay surgery Treatment of non-GI lesions	Treatment compliance Possible side effects
Therapeutic laparoscopic-assisted enteroscopy	Preservation of bowel length Complete eradication	Invasiveness Repeated treatment sessions Hospitalization General anaesthesia Adhesions formation
Therapeutic endoscopy	Preservation of bowel length	Possible perforation Residual small bowel lesions Invasiveness Repeated treatment sessions Hospitalization General anaesthesia
Surgical full-thickness wedge resection	Preservation of bowel length	Invasiveness Repeated treatment sessions Hospitalization General anaesthesia Adhesions formation
Segmental bowel resection	Useful only if confined lesions	Invasiveness Short bowel syndrome Malnutrition Nephrolithiasis Repeated treatment sessions Hospitalization General anaesthesia Adhesions formation

offers an overview of the advantages and disadvantages of the common therapies for BRBNS.

In conclusion, there exists significant variation of care among centers in managing children with BRBNS, and the experience is evolving over time. Variable results have been achieved with surgical resections that can potentially lead to short gut syndrome. Endoscopic treatment when carried out well and appropriately with pan-enteroscopic approaches can be beneficial to treat GI venous malformations, and less invasive compared to surgery. A combined endoluminal and surgical approach may be more promising. However, both surgery and endoscopy seem ineffective on a long-term period, especially in young children. Historically, drug therapies have not worked for BRBNS, except recent promising data on sirolimus. Sirolimus could be considered a good option in young patients in order to delay surgical or endoscopic treatment until lesions have fully emerged, and in those with multiorgan involvement. Future studies should address adequate dosing, drug levels, duration of therapy and long-term side effects with sirolimus and factors that are associated with a more severe phenotype. Children with BRBNS have multisystem and multiorgan involvement that require invasive and supportive therapies and a multi-disciplinary approach.

Conflicts of interest

None declare.

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