ORIGINAL ARTICLE

AG-2019-167
doi.org/10.1590/S0004-2803.202000000-44

Peutz-Jeghers syndrome in resource-limited scenario

Natascha Silva **SANDY**[1], Elizete Aparecida **LOMAZI**[2], Maria de Fátima **SERVIDONI**[2] and Maria Angela **BELLOMO-BRANDÃO**[2]

Received: 2 December 2019
Accepted: 6 March 2020

ABSTRACT – **Background** – Peutz-Jeghers Syndrome (PJS) is a rare, autosomal dominant disease, caused by deletions in the chromosome 19p33.3/ gene LKB1/STK11. These mutations inactivate a serine/threonine kinase and predispose to carcinogenesis. In PJS, tumors of the gastrointestinal, testicles, pulmonary, breast, pancreas, uterus and ovaries can be found. **Objective** – To evaluate demographics, clinical presentation and complication/outcomes of pediatric patients presenting with Peutz-Jeghers syndrome (PJS), as well as to present and discuss management in the context of limited resources. **Methods** – We conducted a retrospective chart review of a cohort of six patients, who were diagnosed and/or followed at the Clinics Hospital, University of Campinas – Sao Paulo/Brazil, between 2000 and 2018. Data analyzed included gender, age of presentation, age of diagnosis, family history, PJS complications. **Results** – Median age of diagnosis of 6.7 years, with a mean time of follow-up of 8.1 years. Mucocutaneous pigmentation was universally present. Half of the patients had a known family history at the time of diagnosis. On follow up, intestinal intussusception was documented in four out of six patients, in most (three), in different locations and in multiple occasions. The active investigation of siblings and parents of the index case led to the diagnosis of three first-degree relatives in the present case series. **Conclusion** – In this first pediatric PJS Brazilian case series, we report a wide spectrum of PJS manifestations and complications. In a resource limited scenario, despite limitations for the surveillance of complications, the relative frequency of complications was not higher than historically reported.

HEADINGS – Peutz-Jeghers syndrome. Intussusception. Demographic data. Child.

INTRODUCTION

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant inherited disorder characterized by the association of gastrointestinal hamartomatous polyps, mucocutaneous hyperpigmentation (most commonly in the lips and oral mucosa), and predisposition to carcinogenesis[1]. Even though a causative gene for this syndrome has been identified (LKB1, in chromosome 19p13.3, that encodes a serine-threonine kinase, STK11)[2], there is no genotype-phenotype correlation[3] and some patients remain without a detectable STK11 mutation – therefore, a negative genetic study, does not exclude the diagnosis of PJS. With a reported incidence of 1 in 120 thousand births[4], the medical literature on PJS consists mainly of case series, single center experiences, and/or historical cohorts, especially in pediatrics. Despite this scarce evidence, there are available guidelines for the management of PJS in adults, and, most recently, recommendations for its diagnosis and management in the pediatric population were published by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)[5].

The ESPGHAN position paper[5] gives recommendations for diagnosis, gastrointestinal and extra-intestinal surveillance and management of PJS. Genetic testing for diagnosis of children at risk is recommended from age 3 years if the child remains asymptomatic, and earlier in a symptomatic child, with the caveat that lip and mucosal freckling are not pathognomonic for PJS. In terms of surveillance, it is stated that gastrointestinal screening should start no later than 8 years of age in an asymptomatic PJS patient, with upper endoscopy, colonoscopy and video capsule endoscopy (VCE), and obviously, earlier for symptomatic patients – as a general rule, these procedures would be repeated every 3 years, however individualization of care is advised. And for extra-intestinal manifestations, clinical vigilance is advised for gonadal tumors in both genders, with special attention for feminizing manifestations in male patients (e.g. gynaecomastia), given the risk of Large-cell calcifying Sertoli cell tumours of the testis (LCCSCTs), associated with the syndrome. Finally, in regards to treatment, no pharmacological intervention is indicated, elective polypectomy should indicated to avoid polyp-related complications, with the suggested size cut-off of 1,5-2 cm for small bowel polyps, and urgent surgical reduction for the treatment for symptomatic intussusception (with intraoperative enteroscopy and removal of other polyps).

Even thought the guideline provides such recommendations for the diagnosis and surveillance for pediatric patients affected by Peutz-Jeghers syndrome, the reality is that, in a resource limited scenario, such as the public health system in Brazil, some of the recommendations are simply not feasible, due to lack of resources.

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] University of Toronto, Hospital for Sick Children, Department of Pediatrics, Division of Gastroenterology, Hepatology and Nutrition, Toronto, ON, Canada. [2] Universidade Estadual de Campinas (UNICAMP), Faculdade de Ciências Médicas, Departamento de Pediatria, Campinas, SP, Brasil.
Corresponding author: Natascha Silva Sandy. E-mail: natascha.silvasandy@sickkids.ca

The aim of this study is describe the experience of a Brazilian tertiary center in the diagnosis and follow-up of pediatric patients with PJS. Although there were some case reports and adult case series[6-10], there has been no similar casuistic described in Brazil or even South America. We face the challenges of prolonged waiting time for outpatient elective tests and procedures, as well as unavailability of genetic testing for the diagnosis of PJS, and capsule endoscopy/ double balloon enteroscopy/ push enteroscopy expertise for surveillance of the small bowel in children.

METHODS

A retrospective chart review of all pediatric patients with Peutz-Jeghers syndrome, who were diagnosed and/or followed at the Clinics Hospital, University of Campinas – São Paulo, Brazil, from 2000 to 2018, was conducted. Subjects were identified from a patient registry kept by the senior author.

All included patients were initially screened to confirm that they met criteria for clinical diagnosis of PJS, defined by the presence of any of the following: 1) Two or more histologically confirmed Peutz-Jeghers polyps; 2) Any number of PJ polyps detected in an individual who has a family history of SPJ in a close relative; 3) Characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in a close relative; 4) Any number of PJ polyps in an individual who also has characteristic mucocutaneous pigmentation[5,11]. These criteria are recognized in the ESPGHAN[5] position paper for the clinical diagnosis of a single individual, even though there is the recommendation to offer genetic diagnosis for children at risk. Because there are clinical and histology-based criteria for the diagnosis of PJS, at our instution genetic testing cannot be performed routinely – this type of request is reserved for selected/ atypical cases, upon clear justification of its need, and approval of the indication.

Clinical and demographic data were collected, including age, gender, presenting symptoms, endoscopic findings, histological features, treatment modalities and clinical course during follow-up. The present study was approved by the Research Ethics Committee of the State University of Campinas (Unicamp) under Certificate number 64427114.9.0000.5404.

RESULTS

Demographics and clinical presentation

Initially eight cases were identified, two were excluded for not meeting the criteria for clinical diagnosis. Six cases were included: four were male; with a mean age of presentation of 4.7 years, while the mean age of diagnosis was 6.7 years. Mean time of follow-up was 8.1 years. Mucocutaneous pigmentation was universally present. Half of the patients had a known family history at the time of diagnosis, two of them representing internal referral after a sibling was diagnosed. One case led to the detection of maternal disease. TABLE 1 presents a summary of patient demographics, presentation, reason for referral, family history, and time of follow-up time.

TABLE 1. Demographics, presentation, reason for referral and family history.

N	Gender	Age of presentation (years)	Presentation	Reason for referral	Age at diagnosis	Time of followup	Known family history at time of diagnosis	Case led to diagnosis in a relative
1	Male	6.2	Intussusception	Post surgery for intususception, multiple hamartomatous polyps	6.2	15.8	No	Yes (patient #3)
2	Male	5.5	Sertoli cell tumor	Sertoli cell tumor in association with mucocutaneous pigmentation	5.8	13.5	No	Yes (mother)
3	Male	3.4	Asymptomatic, with family history	Sibling diagnosis (patient #1) in association with mucocutaneous pigmentation	3.4	7.83	Yes (sibling)	No
4	Male	0.1	Rectal polyp as neonate	Genetic diagnosis	2*	7.75	No	No
5	Female	9.8	Worsening mucocutaneous pigmentation	Characteristic pigmentation	13.8	1.9	Yes (father)	Yes (patient #6)
6	Female	3	Asymptomatic, with family history	Sibling diagnosis (patient #5) in association with mucocutaneous pigmentation	9	1.83	Yes (sibling)	No
TOTAL 6	04/06 male	Mean: 4.7 years	02/06 Asymptomatic, 02/06 with known complications	02/06 had a sibling followed by our team	Mean: 6.7 years	Mean: 8.1 years	03/06 with positive FH	03 cases

Surveillance

All patients underwent physical examination with a complete blood count to detect iron deficiency anemia due to occult bleeding from gastrointestinal tract polyps or cancer every 6 months to every year. Male patients underwent testicular ultrasonography annually, and testicular microlithiasis was detected without other findings in one of the four male patients.

Mean age of first endoscopic evaluation was 6.6 years, ranging from the first month of life to 14 years of age. Endoscopic evaluation, including upper and colonoscopy, was universally done at time of the diagnosis. In half of the cases, colorectal polyps were detected in the initial colonoscopy, and in one of them the presence of low-grade dysplasia tubular adenoma was already present at the time of the first evaluation. On successive endoscopic evaluation, the presence of characteristic colonic or rectal Peutz-Jeghers polyps was universally verified.

As video capsule endoscopy, double balloon enteroscopy and push enteroscopy were not available, none of the patients underwent these forms of evaluation at age 14. Two patients underwent Ileoscopy while they had stomas. As magnetic resonance enterography (MRE) is considered an alternative imaging modality for individuals with PJS in whom capsule endoscopy cannot be performed[12], this was the modality of choice most recently adopted, with a change from old fashion Small bowel follow through (SBFT) to the adoption of MRE as the preferred small bowel imaging modality since 2016, when this test became routinely available for pediatric patients at our center – however, with the limitations of prolonged waiting time for outpatient procedure (average 6 months) and technical limitations of this modality of imaging.

Clinical course and follow-up

While one patient was referred after curative unilateral orchiectomy due to Sertoli cell tumor, cancer development was not verified during follow up in any of the cases. Intestinal intussusception was documented in four out of six patients – three patients had multiple episodes and different locations. All patients who had documented intussusception at any point, eventually required surgical treatment: three patients underwent intestinal resection (one of them multiple times and with the need of a colectomy), while one patient underwent only polyp removal without intestinal resection.

Data regarding endoscopic surveillance, intussusceptions and surgeries are summarized in TABLE 2.

DISCUSSION

In a country of continental dimensions but limited resources, we present the first pediatric series of cases of a rare disease of unknown prevalence in our population. Early diagnosis of Peutz-Jeghers allows adequate surveillance over its complications and early treatment. In the present series, there was a clear gap between the first reported manifestation and PJS clinical diagnosis. According to ESPGHAN recommendations, genetic testing for an asymptomatic at risk child should be considered from the age 3 years old and should be done even earlier in a symptomatic at risk child. In our cohort, genetic study was only done in one case – as it is not routinely covered by the public health system. Therefore PJS diagnosis relies on clinical criteria, following previous described definitions. Despite those limitations, the first documented diagnosis in one family led to the recognition of the diagnosis in another family member in a significant fraction of the cases (three out of six).

Although uncommon, the first intussusception as complication of the polyposis may occur in first few years of life[13] – and in our series intussusception was first detected in the first month of life. In PJS, more than just intussusceptions, the presence of polyps in the gastrointestinal tract may lead to obstruction, as well as abdominal pain associated with vascular distress, acute or chronic GI bleeding, and ulceration or extrusion of the polyp through

TABLE 2. Endoscopic surveillance, intussusception and surgical treatment.

N	Age at first endoscopic evaluation	Findings of first endoscopic evaluation	Histology	Total number of endoscopic evaluations	Location of hamartatous polyps on follow up	Documented intussusception	Surgery needed	Intestinal ressection
1	6.3	Small gastric polyps, normal colonoscopy	Hyperplastic gastric polyps	11	Duodenal, ileal, colonic	Yes, multiple	Yes, once	Jejunal (20 cm)
2	6.1	Chronic gastritis, normal colonoscopy	Mild chronic gastritis	8	Rectal	No	No	No
3	9.7	Gastric and duodenal polyps, normal colonoscopy	Hyperplastic gastric polyps, hamartomatous duodenal polyps (x2)	7	Duodenal, colonic, rectal	Yes, once	Yes, once	No
4	0.1	Multiple colonic polyps	Multiple hamartomatous polyps identified in colectomy	3	Ileal, colonic	Yes, multiple	Yes, multiple	Colectomy and multiple enterotomies
5	14.1	Small gastric polyps, mulitple colorectal polyps	Hyperplastic gastric polyps, tubular adenoma in the ascending colon, hamartomatous polyp in the transverse, rectal tubular adenoma with low grade dysplasia.	2	Colonic, rectal	No	No	No
6	3.6	Chronic gastritis, normal colonoscopy	Mild chronic gastritis	2	Ileal, colonic	Yes, multiple	Yes	Ileal (6 cm)

the rectum or ostomies. In our series, four out of six patients had at least one episode of intussusception during their lifetime. The high overall percentage of patients that undergone laparotomy for intussusception in this study – 50% – is in keeping with previous historical data[14,15].

Although the mechanism of carcinogenesis remains to be elucidated, the increased risk of cancers in PJS is very well documented. The reported frequency of any cancer in PJS ranges from 37% to 93%, representing a relative risk that is 9.9 to 18 higher than the general population, with a peak incidence in the fourth and fifth decades of life[16]. The most common cancers are colorectal, breast, stomach, small intestine, pancreatic and gonadal tumors. But, because the risk of cancer is age dependent, it is limited to 2% in the first 2 decades of life[17]. In the pediatric age range, one of the main concerns is Sertoli cell tumours of the testis: the association between Sertoli cell tumour and PJS is well documented, but its prevalence remains unknown. The presence of this tumor was the presenting manifestation in one of the cases in this series. All male patients in the series underwent testicular ultrasonography, annually or biannually – as this test has been previously recommended in the surveillance of PJS[16], although the latest pediatric guideline argues that there is no evidence to justify this strategy, and recommends only clinical assessment for feminizing manifestations, including gynaecomastia, and vigilance over precocious puberty.

For the gastrointestinal surveillance, upper endoscopy, VCE and colonoscopy are recommended, starting not later than the age of 8 years; and furthermore, elective polypectomy to prevent polyp-related complications is endorsed[5]. Elective endoscopic polypectomy was routinely performed in patients in this series via upper endoscopy and colonoscopy, but other modalities, such as push enteroscopy and double balloon enteroscopy were not available for our pediatric population. Timing for GI surveillance was individualized, with investigations repeated no longer then every 3 years. Whether the "sub-optimal" small intestine investigation/surveillance (capsule/enteroscopy) has significant consequences to patient care or long term outcomes is a question that remains to be answered. The ESPGHAN current recommendation for the use of VCE is justified on previous findings that small bowel polyps larger than 15 mm in diameter were identified as the most important risk factor for small bowel intussusception, and that the great majority of intussusceptions in PJS occur in the small bowel[5], however to this date, there is no pediatric data that proves that surveillance of the small bowel followed by elective polypectomy decreases the risk of urgent laparotomy for intussusception – there are only studies in the adult population, in whom for anatomical reasons, small bowel surveillance is relatively easier. In the current study, although patients did not undergo the recommended modalities for small bowel vigilance, as discussed above, we did not see an increase in the rate of emergency surgery to treat symptomatic intussusception.

In conclusion, Peutz-Jeghers syndrome is a rare autosomal dominant disorder, characterized by multiple gastrointeintestinal hamartomatous polyps, typical mucocutaneous pigmentation, and increased risk of cancer. This case series reports on clinical characteristics, follow-up and surveillance of six cases followed at a tertiary center in Brazil over the period of 18 years. Recently, ESPGHAN has published a society paper with recommendations for the management of PJS in children – unfortunately we do not have the resources to follow ESPGHAN's recommendations in their totality – specifically, genetic testing is not routinely offered for children at risk (diagnosis relies mainly on clinical presentation, family history and histology of polyps) and the small bowel surveillance is done with magnetic resonance enterography, as video capsule endoscopy and push enteroscopy were not available in our institution – one of the biggest tertiary centers in the country (however such resources may be more available in other public tertiary centers or in the private health system). This study is the first to report management of Peutz-Jeghers syndrome in a resource limited scenario, where despite the impossibility and limitations in following some of those recommendations, the relative frequency of complications was not higher than historically reported, and even in the absence of genetic testing for PJS, the active investigation of siblings and parents of the index case led to the diagnosis of three first-degree relatives in the present case series.

Authors' contribution

Sandy NS conceptualized the article, obtained REB approval, collected the data, drafted the initial manuscript, reviewed and revised the manuscript, approved the final draft as submitted. Lomazi EA, Servidoni MF and Bellomo-Brandão MA supervised Sandy NS throughout all the different phases of this study, analyzed the data, reviewed and revised the manuscript, and approved the final draft as submitted.

Orcid

Natascha Silva Sandy: 0000-0002-7744-8984.
Elizete Aparecida Lomazi: 0000-0001-5504-4746.
Maria de Fátima Servidoni: 0000-0002-5237-7227.
Maria Angela Bellomo-Brandão: 0000-0002-1145-2606.

Sandy NS, Lomazi EA, Servidoni MF, Bellomo-Brandão MA. Manejo da síndrome de Peutz-Jeghers no contexto de recursos limitados. Arq Gastroenterol. 2020;57(3):227-31.

RESUMO – **Contexto** – A síndrome de Peutz-Jeghers (SPJ) é uma doença autossômica dominante rara, causada por deleções no cromossomo 19p33.3/gene LKB1/STK11. Essas mutações inativam uma serina/treonina quinase e predispõem à carcinogênese. Na SPJ, podem ser encontrados tumores do trato gastrointestinal, testicular, pulmonar, de mama, de pâncreas, de útero e de ovários. **Objetivo** – Avaliar dados demográficos, apresentação clínica e complicações de pacientes pediátricos que se apresentam com SPJ, além de apresentar e discutir o manejo no contexto de recursos limitados. **Métodos** – Realizamos uma revisão retrospectiva de prontuários de uma coorte de seis pacientes, diagnosticados e/ou acompanhados no Hospital das Clínicas da Universidade de Campinas – São Paulo, Brasil, entre 2000 e 2018. Os dados analisados incluíram sexo, idade de apresentação, idade do diagnóstico, história familiar, complicações da SPJ. **Resultados** – Idade média de diagnóstico de 6,7 anos, com tempo médio de seguimento de 8,1 anos. A pigmentação mucocutânea estava universalmente presente. Metade dos pacientes tinha um histórico familiar conhecido no momento do diagnóstico. Intussuscepção intestinal foi observada em quatro dos seis pacientes durante o período de acompanhamento, sendo que em três ocorreram vários episódios em diferentes múltiplas localizações. A investigação ativa de irmãos e pais do caso-índice levou ao diagnóstico de três parentes de primeiro grau na presente série de casos. **Conclusão** – Nesta primeira série de casos brasileiros de SPJ pediátrica, relatamos um amplo espectro de manifestações e complicações da SPJ. Em um contexto de recursos limitados, apesar das limitações para a vigilância de complicações, a frequência relativa de complicações não foi maior do que o relatado historicamente.

DESCRITORES – Síndrome de Peutz-Jeghers. Intussuscepção. Dados demográficos. Criança.

REFERENCES

1. Boardman LA, Thibodeau SN, Schaid DJ, Lindor NM, McDonnell SK, Burgart LJ, et al. Increased risk for cancer in patients with the Peutz-Jeghers syndrome. Ann Intern Med. 1998;128:896-9.
2. Hemminki A, Markie D, Tomlinson I, Avizienyte E, Roth S, Loukola A, et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. Nature. 1998;391:184-7.
3. Mehenni H, Gehrig C, Nezu J, Oku A, Shimane M, Rossier C, et al. Loss of LKB1 kinase activity in Peutz-Jeghers syndrome, and evidence for allelic and locus heterogeneity. Am J Hum Genet. 1998;63:1641-50.
4. McGarrity TJ, Kulin HE, Zaino RJ. Peutz-Jeghers syndrome. Am J Gastroenterol. 2000;95:596-604.
5. Latchford A, Cohen S, Auth M, Scaillon M, Viala J, Daniels R, et al. Management of Peutz-Jeghers Syndrome in Children and Adolescents: A Position Paper From the ESPGHAN Polyposis Working Group. J Pediatr Gastroenterol Nutr. 2019;68:442-52.
6. Silva VC, Takano GHS, Medeiros BPC, Freitas BC, Ornelas CAR, Fontes W. [The Peutz-Jeghers syndrome: new data and molecular bases on a rare disease]. [Article in Portuguese]. Implant News Perio. 2017;2(3):521-5.
7. Loureiro J, Menegazzo GL, Vergamini L, Pestana RC, Formiga FB, Sousa MGC, et al. Diagnostic difficulty in Peutz–Jeghers syndrome. J Coloproctol (Rio J.). 2015;35:67-71.
8. Torres Neto JR, Santiago RR, Prudente ACL, Mariano DR, Torres FAP, Torres JAP, et al. Peutz-Jeguers syndrome: case report and literature review. J Coloproctol (Rio J.) 2012;32:75-8.
9. Andrade AC, Carvalho Junior E, Dantas KS, Sousa JS, Morais RKP. Peutz-Jeghers syndrome - case report. Rev Col Bras Cir. 2008;35:210-1.
10. Matos Silva CDC, Pitanga JP, Oda DA, França AM. Peutz-Jeghers Syndrome: case report and literature review. Rev Bras Oncol Clin. 2010;7:28-32.
11. Beggs AD, Latchford AR, Vasen HFA, Moslein G, Alonso A, Aretz S, et al. Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut. 2010;59:975-86.
12. Gupta A, Postgate AJ, Burling D, Ilangovan R, Marshall M, Phillips RKS, et al. A prospective study of MR enterography versus capsule endoscopy for the surveillance of adult patients with Peutz-Jeghers syndrome. AJR Am J Roentgenol. 2010;195:108-16.
13. Sado T, Nakayama Y, Kato S, Homma H, Kusakari M, Hidaka N, et al. Extremely young case of small bowel intussusception due to Peutz-Jeghers syndrome with nonsense mutation of STK11. Clin J Gastroenterol. 2019;12:429-33.
14. Hinds R, Philp C, Hyer W, Fell JM. Complications of childhood Peutz-Jeghers syndrome: implications for pediatric screening. J Pediatr Gastroenterol Nutr. 2004;39:219-20.
15. Vidal I, Podevin G, Piloquet H, Le Rhun M, Frémond B, Aubert D, et al. Follow-up and surgical management of Peutz-Jeghers syndrome in children. J Pediatr Gastroenterol Nutr. 2009;48:419-25.
16. Van Lier MG, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol. 2010;105:1258-64; author reply 1265.
17. Hearle N, Schumacher V, Menko FH, Olschwang S, Boardman LA, Gille JJP, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 2006;12:3209-15.