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Minor salivary gland biopsy in the diagnosis of definite ocular sarcoidosis in paediatric granulomatous uveitis

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Abstract

Background Non-infectious paediatric granulomatous uveitis (PGU) is a rare disease that is idiopathic in more than half of affected children. The diagnosis of definite ocular sarcoidosis (OS) must be supported by the presence of non-caseating granulomas detected in biopsy, and is therefore a challenge in children with PGU. This study investigated the utility of minor salivary gland biopsy (MSGB) in the diagnosis of definite OS in PGU.

Methods Twenty-six consecutive children with PGU diagnosed between 2018 and 2023 and with a systematically performed MSGB within 3 months of the diagnosis were enrolled.

Results The median age at PGU diagnosis was 11.6 (4.2–16.5) years, and 54% of the children were boys. PGU consisted mainly of bilateral (92%) pan-uveitis (96%). MSGB detected non-caseating granulomas (MSGB+) in 12/26 (46%) children. In all, 13 of the 26 (50%) children were diagnosed with definite OS, and 8 (31%) had idiopathic uveitis. MSGB had a sensitivity of 92%, and a NPV of 93% in the diagnosis of definite OS in children with PGU. Compared to MSGB– children, those who were MSGB + were more frequently older than 10 years of age at diagnosis ($p = 0.02$), had a higher rate of general signs ($p = 0.003$), extra-ocular organ involvement ($p = 0.005$) and polyclonal hypergammaglobulinaemia ($p = 0.03$). The most frequent extra-ocular organ involvements at OS diagnosis were renal (46%) and thoracic (46%). First-line therapy was systemic corticosteroids in 88% of the children. During a median follow-up time of 3.1 (0.6–6.3) years after PGU diagnosis, 88% of the children needed methotrexate and/or anti-tumour necrosis factor-alpha therapy to achieve inactive uveitis.

Conclusions MSGB is useful to improve the diagnosis of OS and to reduce the incidence of uveitis considered idiopathic in PGU. MSGB could be considered in PGU patients, particularly those > 10 years of age with general signs and/or hypergammaglobulinaemia.

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Key message

• MSGB performed systematically at PGU diagnosis increased the prevalence of OS and reduced that of idiopathic PGU.

• MSGB could be considered in PGU, particularly in children > 10 years of age with general signs and/or hypergammaglobulinaemia.

• Most children with PGU will need methotrexate and/or anti-TNF-α to achieve inactive uveitis.

Keywords Paediatric granulomatous uveitis, Minor salivary gland biopsy, Ocular sarcoidosis, Sarcoid uveitis, Idiopathic uveitis

Background

Uveitis is characterised by inflammation of the uvea (iris, ciliary bodies, vitreous retina, and/or choroid). Paediatric uveitis (PU) is considerably rarer than adult uveitis, with an annual incidence in Europe of 4–5 new cases per 100,000 children [1, 2]. A long diagnostic delay of PU leads to irreversible structural eye damage that may result in blindness [3, 4, 5, 6].

The aetiologies of uveitis vary widely, but in developed countries non-infectious causes predominate in both adults and children [6, 7]. Juvenile idiopathic arthritis (JIA) is the most frequent cause of PU in children in Europe and the United States, but 25–50% of PU cases remain idiopathic [3, 4, 6, 8]. In paediatric granulomatous uveitis (PGU), a rare subgroup of PU, idiopathic forms are even more frequent, representing 58% of cases [9]. Several diseases are associated with non-infectious PGU, including sarcoidosis, multiple sclerosis, Vogt-Koyanagi-Harada disease, immune deficiency disorders, Crohn's disease, and drug-induced granulomatosis. Rare cases of JIA associated with PGU have also been reported [10, 11]. An aetiological diagnosis is therefore a challenge in patients with PGU, but the early identification of disease associated with PGU is essential to guide specific monitoring and treatment and thereby improve outcomes.

Among 50 children with PGU, Nguyen et al. observed that sarcoidosis was the second most frequent diagnosis after idiopathic PGU, affecting 30% of children [9]. This prevalence was higher than in all previously published series, in which sarcoidosis represented 0–14.8% of the PU cases [12]. However, not all children underwent histological investigation, such that the prevalence of sarcoidosis in PGU may have been underestimated [9]. Indeed, according to the International Workshop on Ocular Sarcoidosis (IWOS) criteria, a diagnosis of definite ocular sarcoidosis (OS) in the context of compatible uveitis must be supported by the presence of non-caseating granulomas detected in biopsy [13].

Several tissues can be sampled to diagnose sarcoidosis, but the lymph nodes, lungs, skin, liver, and kidney are the most common [14, 15]. The minor salivary glands have rarely been biopsied in paediatric patients, although it is an easier biopsy site. Where minor salivary gland biopsy (MSGB) was reported to be of limited use and low sensitivity for the diagnosis of OS in adults with uveitis [16, 17, 18], to the best of our knowledge, there are no published data on the utility of MSGB to diagnose sarcoidosis in PU. Only Adeline et al. investigated the utility of MSGB in children, in Sjogren syndrome [19]. Thus, we investigated the utility of MSGB in the diagnosis of sarcoidosis in PGU. Our monocentric retrospective study was based on 26 children consecutively diagnosed with PGU who underwent systematic MSGB at the time of PGU diagnosis.

Methods

Patients

Children with non-infectious PGU diagnosed before the age of 18 years and referred to the Bordeaux University Hospital Centre between 2018 and 2023 were retrospectively included. Children previously diagnosed with a uveitis-causing disease were excluded. This study was conducted under the French data protection authority MR004 reference methodology, was approved by the local Ethical Committee (reference: CER-BDX 2024 – 302), and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. No signed consent form was necessary, in accordance with French health law. All children and their legal guardians gave their informed consent for the MSGB procedure.

Minor salivary gland biopsy

Since 2018, trained and experienced physicians have systematically and routinely performed MSGB at the University Hospital Centre for the diagnosis of non-infectious PGU. Local anaesthesia consists of applying 2% viscous lidocaine to the labial mucosa, followed by a submucosal injection of 10 mg adrenalized lidocaine/mL. Asepsis is achieved by applying 10% povidone-iodinethe to the labial mucosa. Samples are obtained from three to five labial salivary glands and stored in 4% stabilised, buffered formaldehyde until they are analysed by the anatomopathological laboratory of our hospital. After dehydration, the formalin-fixed tissue is embedded in paraffin and sliced using a microtome into 3 µm serial tissue sections at two section levels to obtain four sections

separated by a 100 µm interval. Then the sections are stained using the haematoxylin-eosin-safran technique. A positive MSGB (MSGB+) is defined as the detection of least one non-caseating granuloma.

Definition

The terminology and diagnosis of PGU were based on the Standard Uveitis Nomenclature [20]. A complete ocular examination was performed by a trained ophthalmologist. Definite/biopsy-proven OS was diagnosed according to the revised IWOS criteria [13]. Clinical manifestations, laboratory results, and organ involvement were considered being present at the time of diagnosis if detected within the first 3 months following a diagnosis of uveitis. General signs were defined as the presence of fever, fatigue, or weight loss. Inactive uveitis and remission (inactive disease for ≥ 3 months after discontinuing all treatments for eye disease) were defined according to the Standard Uveitis Nomenclature [20].

Statistical analyses

Continuous and categorical variables were compared using the non-parametric Wilcoxon–Mann–Whitney test and Fisher's exact test, respectively. All tests were two-sided and $P < 0.05$ was considered to indicate statistical significance. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of MSGB and other parameters for the diagnosis of definite OS were calculated as follows: sensitivity = true positive/(true positive + false negative); specificity = true negative/(true negative + false positive); PPV = true positive/(true positive + false positive); NPV = true negative/(true negative + false negative). Only sensitivity and NPV have been calculated to study the utility of MSGB in the diagnosis of definite OS. According to the IWOS criteria, true positive for MSGB was defined by the presence of non-caseating granulomas in MSGB. Because all the children included in this study had non-infectious uveitis compatible with sarcoidosis (PGU), a MSGB revealing granulomas could not be a false positive [13]. Therefore, specificity and PPV of MSGB in the diagnosis of definite OS were not calculated. A false negative for MSGB was defined as a negative MSGB associated with a biopsy from another site revealing granulomas.

Results

Population

Between 2018 and 2023, 59 children with non-infectious uveitis were consecutively referred to our University Hospital Centre, 28/59 (47%) of whom had PGU. An infectious aetiology was excluded in all children, and all had a negative interferon-gamma release assay. None of the children with PGU had previously been diagnosed with a disease associated with uveitis. Two children refused MSGB. Among the remaining 26 children with PGU who underwent systematic MSGB, 14 (54%) were boys. The median age at PGU diagnosis was 11.6 (4.2–16.5) years. PGU mainly consisted of pan-uveitis (96%), was bilateral (92%), and complicated by papillary oedema (81%).

Utility of MSGB in the diagnosis of definite ocular sarcoidosis

In all children, MSGB was performed within the first 3 months following PGU diagnosis, with a median delay of 17 days (2–86) after the diagnosis, and after systemic corticosteroid (CS) initiation in 8/26 (31%) children. No acute or long-term complications related to MSGB were observed. MSGB revealed non-caseating granulomas (MSGB+) in 12/26 (46%) children. The final diagnosis was definite OS in 13/26 (50%) children, and idiopathic uveitis in 8/26 (31%). Only one child with a diagnosis of definite OS had no granuloma according to MSGB. Other diagnoses were anti-nuclear antibody-positive JIA ($n = 2$), Vogt-Koyanagi-Harada disease ($n = 1$), tubulointerstitial nephritis and uveitis syndrome ($n = 1$), and uveitis arising from signal transducer and activator of transcription 3 gain-of-function ($n = 1$). The two children with JIA were girls, and the youngest at diagnosis, 4.2 and 6 years, respectively. They initially had asymptomatic uveitis and positive anti-nuclear antibodies, and later developed oligo arthritis during follow-up.

The characteristics of the children at uveitis diagnosis according to the presence (MSGB+) or absence (MSGB–) of non-caseating granuloma on MSGB are reported in Table 1. Compared to the MSGB– children, those who were MSGB + were more frequently ≥ 11 years of age at uveitis diagnosis ($p = 0.02$), with the highest incidence of uveitis diagnosed in children 11–13 years of age (10/12, 83%) (Fig. 1). Macular oedema was observed in 6/14 (43%) children with MSGB–, and in none with MSBG+ ($p = 0.02$). MSGB + children more frequently had general signs ($p = 0.003$), extra-ocular organ involvement ($p = 0.005$), and polyclonal hypergammaglobulinaemia ($p = 0.03$). There were no other significant differences.

Characteristics of the 13 children with biopsy-proven ocular sarcoidosis

Among the 13 children with definite, biopsy-proven OS, 12 were MSGB + and 1 was MSGB– but with granulomas according to renal biopsy. Two MSGB + children had also undergone biopsy at another site (bronchial biopsy), which also demonstrated non-caseating granulomas. The characteristics of these children at uveitis diagnosis are reported in Additional Table 1. All children had bilateral pan-uveitis, revealed by eye redness and/or pain, and 62% had general signs. The most frequent anomalies in laboratory results were an increased C reactive protein level and/or erythrocyte sedimentation rate

Table 1 Characteristics of the children at uveitis diagnosis according to the presence (MSGB+) or absence (MSGB–) of granuloma on minor salivary gland biopsy (MSGB)

	Total ***N*** **= 26**	**MSGB+** ***N*** **= 12**	**MSGB–** ***N*** **= 14**	***P***
Girls/boys	12/14	6/6	6/8	1
Age at uveitis onset, years, median (min–max)	11.6 (4.2–16.5)	12.2 (6.1–13.7)	10.6 (4.2–16.5)	0.09
Age > 10 years at uveitis onset, *n* (%)	15 (58%)	10 (83%)	5 (36%)	**0.02**
Delay between uveitis diagnosis and onset, days, median (min–max)	28 (2–394)	22 (2–394)	30 (2–245)	0.81
Familial history of autoimmune and/or inflammatory disease, *n* (%)	6 (23%)	4 (33%)	2 (14%)	0.37
Uveitis characteristics, *n* (%)				
Redness and/or pain	23 (88%)	12 (100%)	11 (79%)	0.22
Bilateral uveitis	24 (92%)	12 (100%)	12 (86%)	0.48
Pan-uveitis	25 (96%)	12 (100%)	13 (93%)	1
Synechiae	16 (62%)	6 (50%)	10 (71%)	0.42
Papillary oedema	21 (81%)	10 (83%)	11 (79%)	1
Macular oedema	6 (23%)	0 (0)	6 (43%)	**0.02**
Visual acuity of the weaker eye, median (min–max)	8.5(1–10)/10	9(1–10)/10	6.5(2–10)/10	0.22
Visual acuity of the weaker eye ≤ 4	8 (31%)	2 (17%)	6 (43%)	0.22
Extraocular involvement, *n* (%)				
General signs	9 (35%)	8 (67%)	1 (7%)	**0.003**
Organ involvement	13 (50%)	10 (83%)	3 (21%)	**0.005**
Laboratory results, *n*, positive/performed				
Lymphopenia < 1.5 10^9/L	3/25 (12%)	1/12 (8%)	2/13 (15%)	1
Elevated CRP and/or ESR	10/25 (40%)	7/12 (58%)	3/13 (23%)	0.11
Polyclonal hypergammaglobulinaemia	9/24 (36%)	7/11 (64%)	2/13 (15%)	**0.03**
Elevated ACE	0/22	0/11	0/12	1
Time to MSGB after uveitis diagnosis, days, median (min–max)	17 (2–86)	7 (2–69)	21 (4–86)	0.24
MSGB performed after systemic corticosteroid initiation, n (%)	8 (31%)	5 (42%)	3 (21%)	0.4

Legend: ACE, angiotensin conversing enzyme; CRP,C reactive protein; ESR, erythrocyte sedimentation rate

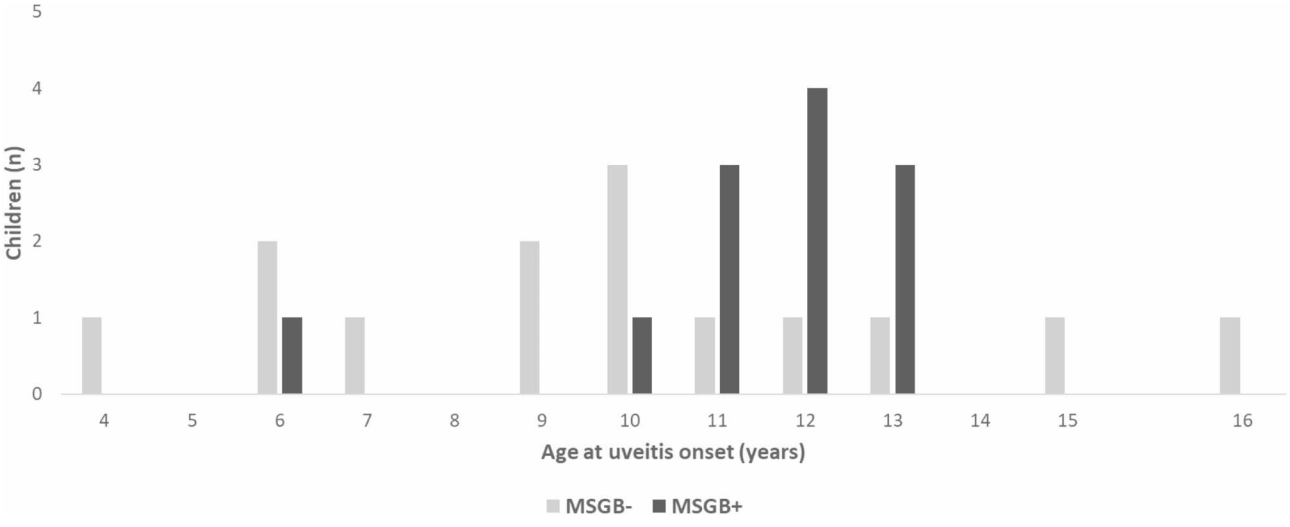

Fig. 1 Age at uveitis onset according to the presence (MSGB+) or absence (MSGB–) of granuloma on minor salivary gland biopsy (MSGB)

(54%) and polyclonal hypergammaglobulinaemia (54%). Only one child had lymphopaenia and none had hypercalcaemia or an elevated angiotensin-converting enzyme (ACE) level. Lysozyme levels were not investigated. Renal and thoracic involvement were the most frequent types of extra-ocular organ involvement determined at uveitis diagnosis. Renal involvement consisted of elevated α1- and/or β2-microglobulinuria (4/6), acute renal failure (3/6), and significant proteinuria (2/6). Thoracic involvement consisted of restrictive ventilatory disorders in pulmonary function tests (3/6), mediastinal adenopathy and/or parenchymal involvement as determined via

thoracic computed tomography (4/6). Among the six children with thoracic involvement, three had respiratory symptoms (cough and/or dyspnoea) at PGU diagnosis. Other forms of extra-ocular involvement were peripheral facial paralysis ($n=1$), arthralgia ($n=1$), and erythaemia nodosum ($n=1$). No child had liver involvement.

Removing the only child with OS who was not MSGB + from the analysis, the two other children with extra-ocular organ involvement in the MSGB– group had renal involvement: one with idiopathic uveitis had isolated elevated α1- and/or β2-microglobulinuria and one with tubulointerstitial nephritis and uveitis syndrome had elevated α1- and/or β2-microglobulinuria and acute renal failure. No MSGB– child had thoracic involvement, although chest thoracic computed tomography was performed in only 9/14 (64%) children.

Finally, in the diagnosis of definite OS in children with PGU, MSGB had a sensitivity of 92%, and a NPV of 93%. Among several parameters tested alone or in combination, the combination of general signs and/or hypergammaglobulinaemia had a sensitivity, specificity, PPV, and NPV of 85% (Additional Table 2).

Evolution and treatment

All children received local CSs. Systemic treatment details are provided in Table 2. First-line therapy was systemic CSs in most of the children (88%), with treatment initiated after a median delay following PGU diagnosis of 17 (1–91) days. In only 5/26 (19%) children were methotrexate (MTX) and/or anti-tumour necrosis factor-α (anti-TNF) administered as first-line therapy (Fig. 2A). CSs were administered for a median duration of 8 (1–20) months, with a significantly longer duration in MSGB + than in MSGB– children ($p=0.04$). Only 3 children achieved inactive uveitis when treated with CSs alone, and all were in the MSGB– group. At the last follow-up, 23/26 (88%) children had needed MTX and/or anti-TNF to achieve inactive uveitis, with no significant difference between the MSGB + and MSGB– groups (Fig. 2B). The anti-TNF agents were adalimumab ($n=11$), and infliximab ($n=5$). At a median follow-up of 3.1 (0.6–6.3) years after PGU diagnosis, all children had inactive uveitis, but only 6/26 (23%) were in remission.

Discussion

In this short retrospective monocentric study, non-infectious PGU in our 26 patients was mostly bilateral pan-uveitis, revealed by eye redness and/or pain. Young adolescents around the age of 11 were most often affected, with no difference between boys and girls. PGU is therefore very different from PU associated with JIA, which is the most common form of PU in children. JIA-associated PU mainly consists of asymptomatic anterior uveitis and more often occurs in young girls [3, 4, 5, 6, 7, 8]. PGU is a rare subgroup of a rare disease in which idiopathic PU, accounting for more than half of all cases, appears to be much more prevalent than in PU in general [3, 4, 5, 6, 7, 8, 9]. An aetiological diagnosis is therefore a major challenge in PGU, but to the best of our knowledge, only the study of Nguyen et al. [9] focussed

Table 2 Treatments used during follow-up according to the presence (MSGB+) or absence (MSGB–) of granuloma on minor salivary gland biopsy (MSGB)

	Total ***N*** **= 26**	**MSGB+** ***N*** **= 12**	**MSGB–** ***N*** **= 14**	***P***
Systemic corticosteroids				
Total, *n* (%)	23 (88%)	10 (83%)	13 (93%)	0.58
Intravenous bolus, *n* (%)	5/23 (22%)	2/10 (20%)	3/13 (23%)	1
Delay of initiation after diagnosis, days, median (min–max)	17 (1–91)	18 (4–51)	15 (1–91)	0.57
Duration of treatment, months, median (min–max)	8 (1–20)	13 (3–20)	7 (1–16)	0.04
Children with inactive uveitis at last follow-up with corticosteroids alone, *n* (%)	3/23 (13%)	0	3/13 (23%)	0.22
Methotrexate				
Total, *n* (%)	22 (85%)	12 (100%)	10 (71%)	0.10
Delay of initiation after diagnosis, months, median (min–max)	5 (0.5–35)	7 (0.5–35)	4 (2.5–12)	0.57
Initiated without anti-TNF, *n* (%)	11/22 (50%)	6/12 (50%)	5/10 (50%)	1
Initiated with anti-TNF, *n* (%)	11/22 (50%)	6/12 (50%)	5/10 (50%)	1
Children with inactive uveitis at last follow-up with methotrexate alone (without anti-TNF), *n* (%)	7/11 (64%)	4/6 (67%)	3/5 (60%)	1
Anti-TNF				
Total, *n* (%)	16 (62%)	8 (67%)	8 (57%)	0.70
Delay of initiation after diagnosis, months, median (min–max)	7 (0.5–35)	8 (0.5–35)	7 (2–33)	0.78
Associated with methotrexate, *n* (%)	15/16 (94%)	8/8 (100%)	7/8 (88%)	1
Children with inactive uveitis at last follow-up with anti-TNF, *n* (%)	16/16 (100%)	8/8 (100%)	8/8 (100%)	1
Uveitis in remission at last follow-up, *n* (%)	6 (23%)	2 (17%)	4 (29%)	0.65
Follow-up time after uveitis onset, years, median (min–max)	3.1 (0.6–6.3)	3.2 (0.6–6.3)	3.1 (1.3–5.6)	0.83

Legend: Anti-TNF, anti-tumour necrosis factor-α

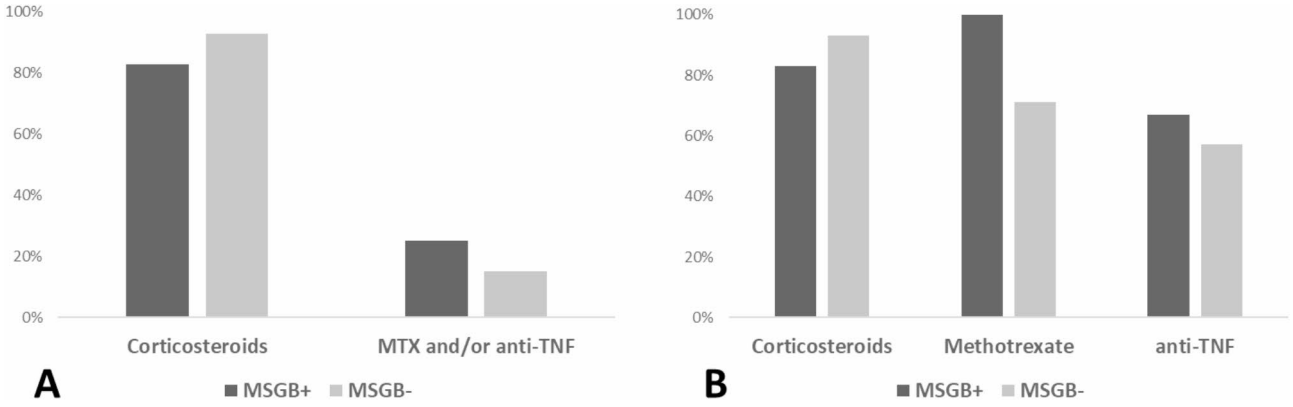

Fig. 2 Treatments used according to the presence (MSGB+) or absence (MSGB–) of granuloma on minor salivary gland biopsy (MSGB): first-line treatments (**A**) and treatments used during follow-up (**B**). MTX, methotrexate; anti-TNF, anti-tumour necrosis factor-α

specifically on PGU. In our study, MSGB, systematically performed in 26 children at PGU diagnosis, successfully identified non-caseating granuloma in roughly half of the children, thus allowing a diagnosis of definite/biopsy-proven OS according to IWOS criteria [13]. These results suggest that systematically performing MSGB at PGU diagnosis will increase the prevalence of OS in PGU. Indeed, the prevalence of OS in our study was higher than in the 50 children with PGU in whom MSGB was not routinely performed (30%), and higher than in PU in general (0–14.8%) [9, 12]. Furthermore, systematically performing MSGB at PGU diagnosis reduced the prevalence of idiopathic PGU in our study from 58 to 31% [9].

Finally, in the diagnosis of definite OS in PGU, MSGB had a sensitivity of 92%, and a NPV of 93%. These results are probably overestimated due to the limited number of false negatives in our study. Indeed, only one child with MSGB– had a biopsy from another site revealing granulomas. Furthermore, we were unable to determine the specificity and PPV of the MSGB as there was no possibility of a false positive for MSGB+, and the results would have given an uninterpretable value of 100% for specificity and PPV. Indeed, a positive MSGB result necessarily classified as definite OS in our non-infectious PGU cohort [13].

Among children with sarcoidosis, OS is diagnosed in 29–74% and is the presenting symptom in 30–40% of patients with systemic sarcoidosis [14, 15, 21]. The diagnosis of definite OS in PGU patients is a major challenge as it must be supported by the presence of non-caseating granulomas on biopsy [13]. Among the many tissues that can be biopsied, MSGB is very rarely performed to support the diagnosis of biopsy-proven sarcoidosis in children, although the minor salivary glands can be easily biopsied [14, 15]. In French recommendations, MSGB is considered useful at PGU diagnosis but it is not systematically recommended [5]. To the best of our knowledge, the MSGB positivity rate in PGU, and in PU in general, had not previously been examined. The high prevalence of MSGB + in our study is in sharp contrast with the low prevalence among adult uveitis patients. Blaise et al. found a 24% positivity rate of MSGB in granulomatous uveitis in patients who also had a chest X-ray compatible with sarcoidosis, with MSGB + determined in only 41% of those with sarcoidosis [16]. In Bernard et al., the MSGB positivity rate in uveitis was 5.2%, and MSGB had a sensitivity of only 18.8% in sarcoidosis [17]. However, the mean delays between the diagnosis of uveitis and MSGB were 3.3 years and 1 year, respectively, and thus much longer than in our study, such that systemic treatments initiated in the meantime could have caused false negatives MSGB results [16, 17]. In our study, MSGB was performed after systemic CSs initiation in roughly one third of the children, with no influence on the result. However, the short delay between uveitis diagnosis and MSGB (about 2 weeks) suggests that a recent CS treatment does not adversely affect the results of MSGB.

Although the utility of MSGB in the diagnosis of OS has been challenged, and non-caseating granuloma is not specific to sarcoidosis, MSGB + children in our study had a sarcoidosis-like phenotype [8]. Only one child with definite OS was MSGB–. The characteristics of the children who were MSGB + were comparable to those of the children with sarcoidosis evaluated in previous studies, as just as many girls as boys were affected, the age at onset was typically between 11 and 13 years and general signs predominated [14, 15, 22]. Given the age of onset, these children with OS more likely had adult-type sarcoidosis than early-onset sarcoidosis (also called Blau syndrome). The latter is an autosomal-dominant genetic disease caused by a mutation in NOD2 [12]. However, the non-investigation of the NOD2/CARD15 mutation is a limitation of our study. Furthermore, these children had no macular oedema, in contrast to the MSGB– children. Macular oedema is significantly more frequent in idiopathic uveitis [23]. Polyclonal hypergammaglobulinaemia

is seen more frequently in MSGB + children. Nguyen et al. similarly observed more frequent polyclonal hypergammaglobulinaemia in children with OS than in those with idiopathic PGU [9]. In a study of 37 adults with proven or possible OS, polyclonal antibody activation tests were useful for supporting a diagnosis of OS [24]. Concerning other laboratory tests, no child in our study had an elevated ACE level or hypercalcaemia and only one child had lymphopaenia; lysozyme levels were not investigated. However, in 15 previously described children with OS, ACE elevation was rare and of low sensitivity (27%) in the diagnosis of OS in adult uveitis [9, 24]. Moreover, normal ACE values are more frequent in paediatric than in adult sarcoidosis [21]. Finally, extra-ocular organ involvement was much more frequent in MSGB + than in MSGB– children. Renal and thoracic involvement were the most common types of extra-ocular involvement and were observed in slightly less than half of the children. Renal tests are simple (blood and urine tests) and should be performed in all patients with PGU whereas an irradiating exam, such as thoracic computed tomography, should be limited to MSGB + children, based on our finding that none of the MSGB– children had thoracic involvement. However, we cannot formally recommend limiting thoracic computed tomography to MSGB + children, as this exam was not performed in one third of our MSGB– patients.

All patients required systemic therapy. While there were no significant differences in the treatments used according to the MSGB results, our sample size was small. CSs were the first-line therapy in almost all children but only three achieved inactive uveitis with this treatment alone. Most of the children needed MTX and/or anti-TNF to achieve inactive uveitis, probably due to the severity of PGU in our study population. Indeed, most of the children had bilateral pan-uveitis complicated by synechiae, papillary oedema, and visual acuity loss. The severity of pan-uveitis in both PU not associated with JIA and in PGU has been examined in previous French studies [9, 25]. MTX and particularly anti-TNF were more widely used in our patients than in those in previous studies performed in the era of biologic therapy and focussing on patients in whom JIA was the predominant cause of PU, suggesting severe PGU in our patients [4, 6, 23, 26, 27, 28]. According to French recommendations, the management of PU not associated with JIA, including OS and idiopathic PGU, should follow that used in patients with PU associated with JIA [5]. However, due to their different origins and greater severity, PGU management would likely improve with the development of specific recommendations. For example, the recommendations for the management of OS in adults could be applied to OS in children, albeit with the limited use of CSs, commonly prescribed for adults, given their side effects [29]. The longer duration of CS use in children with MSGB + compared with children with MSGB– could be the consequence of the application of these recommendations for the management of adult OS to children in our study. We suggest that children with PGU will benefit from early treatment with MTX and/or anti-TNF, as most of children in our study needed these treatments to achieve inactive uveitis. The early use of disease-modifying anti-rheumatic drugs and/or anti-TNF in adults with non-anterior uveitis and in paediatric panuveitis not associated with JIA was suggested in previous studies [25, 30]. CS monotherapy should be avoided, as it is rarely sufficient to achieve inactive uveitis.

Conclusions

The prevalence of OS in PGU is probably underestimated. Thus, at PGU diagnosis a biopsy could be considered to avoid a misdiagnosis of sarcoidosis, particularly in children older than 10 years of age with general signs, hypergammaglobulinaemia, or extra-ocular involvement compatible with sarcoidosis. MSGB is a simple, minimally invasive procedure with few complications and it does not require the use of general anaesthesia. It could be preferred over biopsy performed at another, more invasive site. A normal ACE value should not rule out a diagnosis of OS in patients with PGU.

Abbreviations

ACE	Angiotensin conversing enzyme
CS	Corticosteroids
IWOS	International Workshop on Ocular Sarcoidosis
JIA	Juvenile idiopathic arthritis
MSGB	Minor salivary gland biopsy
MTX	Methotrexate
NPV	Negative predictive value
OS	Ocular sarcoidosis
PGU	Paediatric granulomatous uveitis
PPV	Positive predictive value
PU	Paediatric uveitis
TNF	Tumor necrosis factor

Supplementary information

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Additional Table 1

Additional Table 2

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Author contributions

L.E. and M-N.M. collected data. JG helped with data management. L.E., M-N.M. and J.G. wrote the manuscript. S.K., C.C., and G.C. analysed MSGB. O.R., C.B., M-B.R., J.C., P.P., and J.G. were involved in patients care. All authors reviewed and approved the manuscript. All group members fulfil ICMJE criteria for authorship.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted under the French data protection authority MR004 reference methodology, was approved by the Ethical Committee of the Bordeaux university hospital centre (reference: CER-BDX 2024 – 302), and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. No signed consent form was necessary, in accordance with French health law.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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