

REVIEW ARTICLE

Schnitzler syndrome: validation and applicability of diagnostic criteria in real-life patients

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Abstract

Background: Schnitzler syndrome is characterized by an urticarial rash, a monoclonal gammopathy, and clinical, histological, and biological signs of neutrophil-mediated inflammation. The aim of this study was to assess the applicability and validity of the existing diagnostic criteria in real-life patients.

Methods: This multicentric study was conducted between 2009 and 2014 in 14 hospitals in which patients with Schnitzler syndrome or controls with related disorders were followed up. We compared the sensitivities and specificities and calculated the positive and negative predictive values of the Lipsker and of the Strasbourg criteria for the patients with Schnitzler syndrome and for the controls. We included 42 patients with Schnitzler syndrome, 12 with adult-onset Still's disease, 7 with cryopyrin-associated periodic disease, 9 with Waldenström disease, and 10 with chronic spontaneous urticaria.

Results: All patients with Schnitzler syndrome met the Lipsker criteria. According to the Strasbourg criteria, 34 patients had definite Schnitzler syndrome, five had probable Schnitzler syndrome, and three did not meet the criteria. One control met the Lipsker criteria and had probable Schnitzler syndrome according to the Strasbourg criteria. Sensitivity and specificity of the Lipsker criteria were 100% and 97%, respectively. For the Strasbourg criteria, sensitivity for definite and probable diagnosis was 81% and 93%, respectively, with a corresponding specificity of 100% and 97%.

Conclusion: Diagnostic criteria currently in use to diagnose Schnitzler syndrome are reliable. More investigations must be done to attest their efficiency in patients with recent-onset manifestations.

Schnitzler syndrome was first described in 1972 by a French dermatologist, Liliane Schnitzler (1). Its main features include urticarial rash, recurrent fever, bone or joint pain, monoclonal IgM or rarely IgG gammopathy, and elevated

acute-phase reactants such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). The first cases were described in Europe, but now, Schnitzler syndrome has been reported all over the world including Japan (2) and Australia

(3) with approximately 300 cases reported to this day, mostly in case reports.

Since 1972, the definition of this entity has evolved, but there is still no known marker that would allow an unequivocal diagnosis. Therefore, the diagnosis relies on a set of clinical, biological, histological, and morphological signs. In 2001, Lipsker et al. (4) suggested diagnostic criteria (Table 1) that were based on a review of literature and their own experience with four patients. The main clinical findings in 52 patients were analyzed, and the more common signs were included in the criteria system. Since this landmark publication, authors of almost every subsequently published case referred to this set of criteria. Nevertheless, their validity has never been formally evaluated. In 2012 (5), an expert conference was held in Strasbourg and allowed the elaboration of new set of diagnostic criteria known as the 'Strasbourg criteria', summarized in Table 2. The Strasbourg criteria formally allowed the presence of a monoclonal IgG component, which the previous criteria did not, and introduced the notion of dermal neutrophilic infiltrate on skin biopsy. Indeed, in 1995 the first case of Schnitzler syndrome with a monoclonal IgG component was described (6). The experts also felt the need to have the possibility to distinguish between patients with definite Schnitzler syndrome and probable Schnitzler syndrome (5).

The aim of this study was to validate and to test in real-life patients the Strasbourg criteria, but also the former diagnostic criteria ('Lipsker criteria'), which had never been evaluated. The sensitivity and specificity of these criteria were thus tested in a series of patients suffering from Schnitzler syndrome and in controls suffering from clinical relevant differential diagnoses or related diseases such as adult-onset Still's disease (AOSD), cryopyrin-associated periodic syndrome (CAPS), Waldenström disease (WD), or chronic spontaneous urticaria (CSU).

Material and methods

Study population

We included 42 patients with a Schnitzler syndrome, between 2009 and 2014 in 14 hospitals in France and Italy (Strasbourg University Hospital, Nantes University Hospital,

Table 1 Lipsker diagnostic criteria of Schnitzler syndrome (*Medicine (Baltimore)* 2001;80:37–44)

Urticarial rash and monoclonal IgM component and at least two of the following criteria:
Fever
Arthralgia or arthritis
Bone pain
Palpable lymph nodes
Liver or spleen enlargement
Elevated ESR
Leukocytosis
Abnormal findings on bone morphologic investigations

Table 2 Strasbourg diagnostic criteria of Schnitzler syndrome (*Allergy* 2013;68:562–568)

Obligate criteria
Chronic urticarial rash and
Monoclonal IgM or IgG
Minor Criteria
Recurrent fever*
Objective findings of abnormal bone remodeling with or without bone pain†
A neutrophilic dermal infiltrate on skin biopsy‡
Leukocytosis and/or elevated CRP§
Definite diagnosis if
Two obligate criteria AND at least two minor criteria if IgM and three minor criteria if IgG
Probable diagnosis if
Two obligate criteria AND at least one minor criteria if IgM and two minor criteria if IgG

*Must be >38°C, and otherwise unexplained. Occurs usually—but not obligatory—together with the skin rash.

†As assessed by bone scintigraphy, MRI or elevation of bone alkaline phosphatase.

‡Corresponds usually to the entity described as 'neutrophilic urticarial dermatosis' (*Medicine* 2009;88:23–31); absence of fibrinoid necrosis; and significant dermal edema.

§Neutrophils >10 000/mm³ and/or CRP >30 mg/l.

Montpellier University Hospital, Le Mans Hospital, Valenciennes Hospital, Marseille University Hospital, Toulon Military Hospital, Niort Hospital, Dax Hospital, Besançon University Hospital, Saint-Louis University Hospital and Tenon University Hospital in Paris, Genova University Hospital, and Bari University Hospital). Thirty-three of them were part of an ongoing study about the potential genetic predisposition in patients with Schnitzler syndrome (<https://clinicaltrials.gov/ct2/show/NCT00933296>). Patients signed a written informed consent to participate in the study. Two authors (LG and DL), experienced in the diagnosis and management of Schnitzler syndrome, reviewed in depth the medical files of these patients to ascertain that they had Schnitzler syndrome according to the clinical and biological findings, exclusion of differential diagnoses and disease course. In case of disagreement with the diagnosis of Schnitzler syndrome, a contact was made with the investigator to have more information about the patient. The final diagnosis was reached by consensus.

As controls, we also included 38 patients presenting with clinical manifestations similar to those experienced by patients with Schnitzler syndrome: AOSD fulfilling Yamaguchi criteria (7) (12 patients), CAPS (seven patients, with genetic confirmation in six patients), WD (nine patients), or CSU (10 patients).

Data collection and analysis

We collected clinical, biological, histological, and morphological data from the patients using a standardized anonymized questionnaire. We then applied the Lipsker diagnostic criteria (with the possibility of IgM or IgG monoclonal component)

and the Strasbourg criteria to this series of patients and to the controls. The primary end point was the proportion of patients and controls fulfilling each set of diagnostic criteria. Accuracy measures (sensitivity, specificity, and predictive values) were calculated from two-by-two tables and their confidence intervals estimated using logit transformation and Bayesian arguments with an *a priori* Jeffreys distribution, according to Rubin and Schenker's method (8). For comparing these accuracy measures, we performed exact binomial tests for differences in the specific case of binary diagnostic tests in a paired study design (9).

As this is a real-life study, the lacking data were considered as 'not present'.

Results

Patients with Schnitzler syndrome

The diagnosis of Schnitzler syndrome was accepted in 42 patients by consensus between the two senior authors. There were 31 males and 11 females with a mean age of disease onset of 56 years and a mean delay before diagnosis of 31 months. The mean duration of follow-up between the first clinical signs and the last news of the patients was 12.5 years [5–28 years]. All patients had urticarial rash and it was the first clinical sign in 32 patients. The frequency of skin flares varied between patients (data available in 26): daily rash in 19 patients, more than once a week in 4 patients, once a week in 2 patients, and less than once a month in one patient. Elementary lesions were mostly macules and slightly elevated papules in 24 patients. Target-shaped lesions could be observed (one patient) as well as edematous plaques (two patients), dermatographism (four patients), and angioedema (one patient). Among the 19 patients with available data, the maximum duration of each elementary lesion was less than 24 hours in 15 patients and between 24 and 48 hours in 4 patients. Lesions could occur on every part of the body, but most frequently on the trunk (37 patients) and limbs (36 patients). Eighty-six percent of the patients had recurrent fever (data available in 36). The mean temperature was 39.5°C and usually lasted less than 12 hours. Sixteen patients (38%) had joint and/or bone pain, mostly on lower limbs. Five patients had splenomegaly or hepatomegaly and 16 patients had enlarged lymph nodes, mostly in axillar and inguinal area. Other common clinical signs were asthenia, loss of weight, myalgia, or headache.

All patients had a monoclonal component, which was a monoclonal IgM gammopathy in 37 patients (88%) predominantly associated with a kappa light chain (32 patients). Five patients had a monoclonal IgG gammopathy. The mean level of the monoclonal component was 9 g/l, but it could be present at very low level (trace) in 4 patients, or very high levels (up to 41 g/l). Elevated ESR was observed in 36 patients (86%). Elevated CRP was present in 29 patients, and it was not measured in 8 patients. The mean CRP value was 95 mg/l [34–215 mg/l]. Increase in neutrophils count was found in 18 patients but it was not specified in 10 patients.

A cutaneous biopsy was performed in 31 patients (74%) showing a neutrophilic dermal infiltrate in 10 patients. The other biopsies were interpreted as urticaria, vasculitis, or 'minimal inflammatory lesions'.

Skeletal examinations were performed in 39 patients and showed bone lesions in 23 (59%) of them. Some patients had several types of bone investigations. Conventional X-rays were performed in 21 patients and showed osteocondensation of proximal tibias in only 2 patients. Five patients had a bone scan, which showed lesions in three. Bone technetium scanning revealed an increased radiotracer uptake in 22 patients, mainly on lower limbs. Results were normal or aspecific in 8 patients (not specified in 2). Magnetic resonance imaging was performed in 12 patients and was abnormal in 6 patients, although the details of the signal abnormalities were not specified. Positron emission scanning was performed in three patients. It showed an increased FDG uptake of axial skeleton or the mid-third femurs in 2 patients and a diminished FDG uptake in one patient.

Twenty-five patients were treated with the IL-1 receptor antagonist anakinra, which allowed complete remission of all symptoms within hours after the first injection in all patients except for two, who still complained of joint pain, possibly not related to Schnitzler syndrome.

Waldenström disease occurred in 6 patients with Schnitzler syndrome with a mean delay of 11.4 years [4–20 years] between the first clinical symptoms of Schnitzler syndrome and the diagnosis of WD.

All patients with a Schnitzler syndrome met the Lipsker diagnostic criteria. According to the Strasbourg criteria, 34 patients had a definite Schnitzler syndrome, 5 had a probable Schnitzler syndrome and 3 did not fulfill these criteria. Among the 5 patients with a monoclonal IgG, 3 did not meet Strasbourg criteria, one was classified as a probable Schnitzler syndrome, and only one had a definite diagnosis. These results are summarized in Table 3.

Control population

There were 22 females and 16 males. One control patient met the Lipsker criteria for the diagnosis of Schnitzler syndrome and was classified as probable Schnitzler syndrome according to the Strasbourg criteria. All the others fulfill neither the Lipsker criteria nor the Strasbourg criteria for the diagnosis of Schnitzler syndrome.

The patient who met the diagnostic criteria was part of the 'CAPS group'. He had Muckle-Wells syndrome diagnosed at the age of 5 years, although no *NLRP3* mutation was evidenced. He had an urticarial eruption, recurrent fever, sensorineural deafness, papilledema, joint pain, enlarged lymph nodes, splenomegaly, elevated ESR, and leukocytosis. Twelve years after the onset of the disease, a monoclonal IgGk component was detected with no evidence of multiple myeloma at bone marrow biopsy and at CT scan evaluation. Interestingly, 9 years later, the monoclonal gammopathy was not detected anymore, while the patient was treated with prednisone and colchicine.

These results are summarized in Table 3.

Table 3 Evaluation of the performance of the Lipsker and the Strasbourg diagnostic criteria in patients with Schnitzler syndrome and in controls

Criteria system	Schnitzler syndrome (n = 42)		Controls (n = 38)		AOOSD (n = 12)		CAPS (n = 7)		CSU (n = 10)		WD (n = 9)	
	LC	SC D/P	LC	SC D/P	LC	SC D/P	LC	SC D/P	LC	SC D/P	LC	SC D/P
Diagnosis +	42	34/5	1	0/1	0	0/0	1	0/1	0	0/0	0	0/0
Diagnosis –	0	3	37	37	12	12	6	6	10	10	9	9

AOOSD, Adult-onset Still's disease; CAPS, Cryopyrin-associated periodic syndrome; CSU, chronic spontaneous urticaria; D, definite; LC, Lipsker criteria; P, probable; SC, Strasbourg criteria; WD, Waldenström disease.

Table 4 Sensitivity, specificity, and positive and negative predictive values of the Lipsker and the Strasbourg criteria of Schnitzler syndrome

Criteria	Sensitivity		Specificity		Positive predictive value		Negative predictive value	
	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
Lipsker criteria	1	[0.84–1]	0.97	[0.83–0.99]	0.98	[0.88–1]	1	[0.91–1]
Strasbourg criteria 'definite diagnosis'	0.81	[0.66–0.89]	1	[0.82–1]	1	[0.90–1]	0.83	[0.68–1]
Strasbourg criteria 'probable diagnosis'	0.93	[0.79–0.97]	0.97	[0.83–0.99]	0.97	[0.87–0.99]	0.92	[0.80–0.99]

CI, confidence interval.

Sensitivity and specificity of the Lipsker and Strasbourg criteria for the diagnosis of Schnitzler syndrome

Sensitivity and specificity of the Lipsker criteria was 100% and 97%, respectively. For the Strasbourg criteria, sensitivities for definite diagnosis and probable diagnosis were 81% and 93%, respectively. Corresponding specificities were 100% and 97%.

When we compared the Lipsker and the Strasbourg criteria, only the sensitivities of the Lipsker and the Strasbourg criteria with 'definite diagnosis' were significantly different ($P = 0.008$). These results are summarized in Table 4.

Positive and negative predictive values of the Lipsker and Strasbourg criteria for Schnitzler syndrome

Positive and negative predictive values of the Lipsker criteria were 98% and 100%, respectively. For the Strasbourg criteria, positive predictive values for definite diagnosis and probable diagnosis were 100% and 97.5%, respectively. Respective negative predictive values were 83% and 92.5%.

When we compared the two systems, the negative predictive values of the Lipsker and the Strasbourg criteria 'definite diagnosis' were statistically significantly different ($P = 0.002$).

These results are summarized in Table 4.

Discussion

This study shows that the diagnostic criteria currently in use to diagnose Schnitzler syndrome are reliable. It is the first time that diagnostic criteria are evaluated in this very rare disorder. To do so, we performed a multicentric study to test

the performance of both the Lipsker and the Strasbourg diagnostic criteria of Schnitzler syndrome in real-life conditions, to assess their limits and their accuracy and to validate them in comparison with a relevant control group. Both sets of criteria performed very well in terms of sensitivity, specificity, and positive and negative predictive values.

A chronic urticarial rash was observed in every patient with a Schnitzler syndrome. The presence of a dermal neutrophilic infiltrate on skin biopsy became a minor criterion with the Strasbourg criteria. The most typical histopathologic finding is a neutrophilic urticarial dermatosis as defined by Kieffer et al. (10). It consists of a perivascular and interstitial infiltrate of neutrophils with leukocytoclasia, but without vasculitis and without edema (Fig. 1). Only 10 of the 31 biopsied patients (32%) had this typical aspect. Furthermore, 26% of patients with Schnitzler syndrome never had a cutaneous biopsy, which is a limit to the use of the Strasbourg criteria in real life. However, as the majority of cases had been diagnosed before the publication of the Strasbourg criteria, this might change. In five of the 10 biopsied controls, a similar neutrophilic dermal infiltrate was reported, and it is indeed known that a neutrophilic urticarial dermatosis can occur in AOOSD or in cryopyrinopathies (10, 11).

A monoclonal gammopathy was observed in all of the patients with a Schnitzler syndrome and it is definitely the most discriminating finding to distinguish Schnitzler syndrome from related inflammatory diseases. Only one control patient with a Muckle-Wells syndrome had a monoclonal IgGk component, which however was not detected anymore after a few years.

The kinetics of the elevation of acute-phase reactants such as CRP (>30 mg/l) or leukocytosis ($>10\,000/\text{mm}^3$) is not

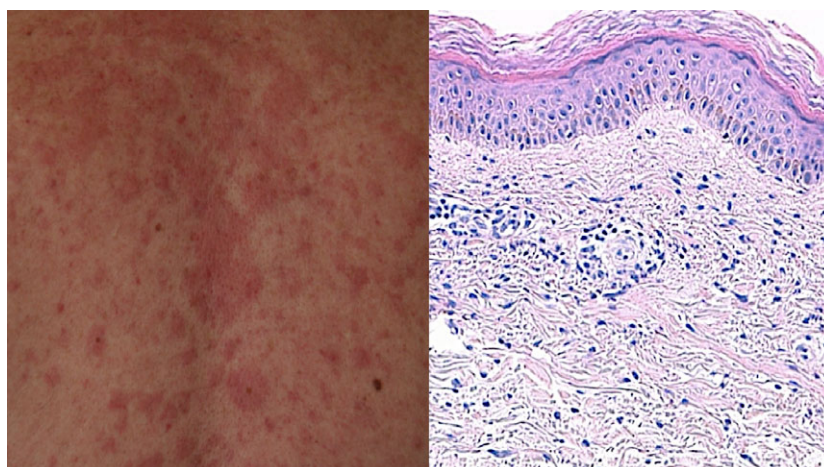


Figure 1 Clinical and histological aspects of skin lesions in Schnitzler syndrome.

precisely known in Schnitzler syndrome, notably in patients with recent-onset disease. These data need to be further investigated as these inflammatory markers are also elevated in the early stage of the two main differential diagnoses, namely AOSD and CAPS.

Recurrent fever in Schnitzler syndrome must be over 38°C and must have a pattern with fever-free intervals of at least 2 weeks. Auto-inflammatory diseases were identified as the main cause of recurrent fever (12). In this study, recurrent fever was observed in 83% of the patients with a Schnitzler syndrome and was most of the time accompanied by rash and/or bone/joint pain. Recurrent fever was also present in 47% of the control patients indicating that the control group has been correctly chosen.

Bone involvement has been already described by L. Schnitzler (13) and is common during Schnitzler syndrome. It is observed in 30 to 40% of the patients (14) and can precede the other clinical symptoms (15). In regard to the controls, bone-imaging abnormalities are one of the most specific signs of Schnitzler syndrome. In this study, bone imaging was performed in 13 controls (34%), mainly AOSD and CAPS patients (11 and 2 patients, respectively). None of them had bone abnormalities, although imaging studies could show signs of arthritis, which is rather an exceptional finding in patients with Schnitzler syndrome (0 patient in this series). Technetium bone scan seems to be the most sensitive exam to show bone lesions characterized by a focal increase in radiotracer uptake. Nevertheless, its specificity in Schnitzler syndrome has never been evaluated. In particular, it is not established if bone lesions can vary according to the treatment undertaken or the stage of the disease, especially in patients with recent-onset disease. The possible discriminating value of the dosage of VEGF and markers of bone formation as suggested by Terpos et al. (16) could not be evaluated in this study, as they were not performed in the majority of patients.

Statistical analysis showed no difference between the Lipsker and the Strasbourg criteria in terms of specificity, but the Lipsker criteria are more sensitive. The main novelty of the Strasbourg criteria was to add the presence of a dermal

neutrophilic infiltrate on skin biopsy. However, skin biopsy is not performed routinely in Schnitzler syndrome patients (only three-fourths of patients had one) and thus the added value of this criterion could not be assessed with reliability in this series of patients. This fact, and the lack of reproducibility of the skin biopsy interpretation, was found to be a problem to apply Strasbourg criteria in real-life patients.

Schnitzler syndrome is quite a rare disease; hence collecting data from 42 patients is of great interest. The large population included in this study is also likely to be representative of the general population of Schnitzler syndrome patients, as most individuals with a clinical suspicion of Schnitzler syndrome regardless of disease severity were likely to be referred to the participating centers.

However, much data were lacking, as complementary examinations were not routinely performed in all the patients. Only 21 of the 80 Schnitzler syndrome or control patients had an exploration for all the items required in the Lipsker and the Strasbourg criteria. This can be partly accounted for the fact that many of the investigations were not required for the controls, such as, for example, bone exploration for patients with WD or with CSU.

There is no gold standard to diagnose Schnitzler syndrome. Therefore, we used the 1) experience of the investigators who included the patients, all being senior physicians familiar with Schnitzler syndrome and related disorders, 2) the duration of follow-up (minimum of 5 years for each patient), and 3) the careful analysis of the patient files by two authors to validate final the diagnosis by consensus.

Moreover, in this study the diagnostic criteria were not tested for the purpose of diagnosis in suspected cases, but in patients for whom the diagnosis of Schnitzler syndrome was already established. Hence, we did not study the efficiency of those criteria in patients with recent-onset disease. To do so, prospective studies should be carried out, but they are very difficult, if not impossible, to set up in such a rare disease.

Furthermore, diagnostic criteria are not only intended to help clinicians to establish a diagnosis, but also to include phenotypically comparable patients in clinical or

physiopathological studies. Therefore, the use of the Strasbourg criteria to establish 'definite diagnosis' can lead to a selection bias, as only patients seen in expert centers with well-trained dermatopathologists and radiologist might fulfill those criteria. Careful analysis shows that it was mostly the patients with a monoclonal IgG component that did not fulfill the Strasbourg criteria. We therefore wonder whether it would not be more relevant to distinguish the patients between the type of monoclonal component IgM vs IgG than between definite and probable Schnitzler syndrome.

Continuous work is done to decipher the pathophysiology of Schnitzler syndrome and that could allow the identification of effective biological markers in the coming years, which could be incorporated in diagnostic criteria. Schnitzler syndrome is now considered as an auto-inflammatory disorder. No germline mutation has been reported, but somatic mosaicism of *NLRP3* mutations in the myeloid lineage has been reported in two patients with variant Schnitzler syndrome (17). The cytokine IL-1 plays a crucial role: hypersecretion of lipopolysaccharide-induced IL-1 secretion by peripheral blood mononuclear cells was demonstrated (18) as well as elevated serum concentration of IL-6 (19) and VEGF (16). Moreover, the lack of response to IL-1 blocking therapies should lead to reconsider the diagnosis of Schnitzler syndrome (5) and a rapid response to anakinra could also become a diagnostic criteria.

Conclusions

This is the first study to address the applicability and the value of the two different sets of diagnostic criteria of the Schnitzler syndrome in real-life patients. It is also the first time that the performance of these criteria in terms of sensitivity, specificity, and predictive values has been assessed and both sets of criteria proved quite reliable and can be used in clinical practice.

More investigations must be carried out to attest their efficiency in patients with recent-onset disease, especially the diagnostic value of a dermal neutrophilic infiltrate on skin biopsy and of bone abnormalities at the onset of Schnitzler syndrome needs to be better assessed.

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Conflicts of interest

None.

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