



Review

Schnitzler syndrome, an autoimmune–autoinflammatory syndrome: Report of two new cases and review of the literature

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ABSTRACT

Schnitzler syndrome is a rare disorder characterized clinically by chronic urticarial rash accompanied by fever, arthralgia or arthritis, bone pain and lymphadenopathy and biochemically by monoclonal gammopathy and elevation of inflammatory indices. The disorder is very likely under-recognized and its origin remains obscure although it may be included among the immune mediated inflammatory diseases with features of autoinflammation and autoimmunity.

We describe here two patients affected by Schnitzler syndrome, both refractory to corticosteroids and immunosuppressive therapy, successfully treated with the interleukin-1 receptor antagonist Anakinra. Unfortunately after two weeks, one patient experienced an important local adverse reaction to the biological drug. We decided to discontinue Anakinra with flare of the disease after 24 h. We therefore switched to Rituximab obtaining a complete remission in two months.

We searched MEDLINE in order to analyze the frequency of the disease, its pathogenesis and outcome. The electronic search was conducted using the following key words “Schnitzler syndrome” and “Treatment of Schnitzler syndrome”. All the selected papers, except the clinical reviews, described at least one case of Schnitzler syndrome. The review of the literature highlighted that Schnitzler syndrome remains an enigmatic disorder hard to categorize and to treat.

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1. Introduction

Schnitzler syndrome is a rare disabling disorder first described in 1972 [1] and characterized by the simultaneous occurrence of chronic urticaria and monoclonal gammopathy, accompanied to varying degrees by intermittent unexplained fever, arthralgias/arthritis, bone pain, bone densification, lymphadenopathy, hepato- or splenomegaly, leukocytosis, and increased erythrocyte sedimentation rate (ESR)

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and C-reactive protein (CRP). Due to the wide spectrum of signs and symptoms, patients are cared for by different specialists and sometimes it can take years before the correct diagnosis is determined. Moreover the increased risk of lymphoproliferative disorders and the rare association with amyloidosis type A need to be carefully considered [2,3].

To date approximately a hundred cases have been reported [2,4,5]. The pathophysiology of Schnitzler syndrome is largely unclear: both autoimmune [6,7] and autoinflammation mechanisms may be present in the disease [8–10]. In addition, Schnitzler syndrome remains a therapeutic challenge. Indeed, despite the administration of numerous immunosuppressive and immunomodulant regimens including methotrexate [11], cyclophosphamide [12], cyclosporine [13], thalidomide [14], interferon [15] and psoralen plus ultraviolet A [16,17], high doses of steroids are still the major option to control the disease.

Recently biological therapies such as TNF α blockade [18,19], Anakinra [5,20] and Rituximab [21,22] have been used to treat Schnitzler syndrome with conflicting results.

We describe here the cases of two patients with a good response to biological therapies and discuss the reasons why the disease may be considered both autoinflammatory and autoimmune in origin.

2. Case reports

2.1. Patient 1

DP, a 43 year old Caucasian male, was diagnosed to have Schnitzler syndrome in 2007 at the age of 41. Recurrent fever, chronic urticaria, lymph nodes enlargement, poly-arthralgias and bone pain were the leading symptoms from December 2005. The patient was initially treated with low doses of corticosteroids without remission of symptoms. Laboratory testing revealed a raised CRP (49 mg/L) and ESR (66 mm/h), serum electrophoresis showed a monoclonal gammopathy IgM k band of 2 g/l together with leukocytosis and increased LDH. On April 2006 a bone marrow biopsy was performed and a diagnosis of non Hodgkin lymphoplasmocytic mantellar lymphoma was performed. High doses of corticosteroids and leukeran (six cycles in total) were started with remission of fever and partial control of arthralgias and bone pain. On February 2007 a relapse of cutaneous lesions occurred and a skin biopsy was performed. Immunofluorescence revealed a dense perivascular and interstitial infiltrate almost exclusively of neutrophils and with leukocytoclasia but without vasculitis. The histopathologic findings were those of neutrophilic dermatosis. Conventional X-ray showed bone densification of the proximal part of the tibia and humeri with hyperfixation on bone technetium scanning. The patient was recognized as affected by

Schnitzler syndrome and treated with Methotrexate for 3 months at a dosage of 15 mg/week without any effect on skin lesions, arthralgias and bone pain and with relapse of fever. The patient was treated with ibuprofen and corticosteroids for 6 months with partial remission at the beginning of the therapy. Laboratory testing still revealed high levels of CRP (36 mg/L) and ESR (51 mm/h) and the persistence of a monoclonal IgM-K light chain band of 2 g/L.

In January 2008 Anakinra was started at the dosage of 100 mg/day with a rapid and complete resolution of symptoms (Fig. 1) and normalization of laboratory findings, including the disappearance of the monoclonal gammopathy. The treatment was discontinued for one week on three occasions because of odontostomatological treatment and the patient experienced a flare with large urticarial lesions, bone pain, arthralgias and high temperature. The patient is still in complete remission after 2 and half years of treatment.

2.2. Patient 2

SM, a 35 year old Caucasian female, was diagnosed to be affected by Schnitzler syndrome in 2008 when she was 33. Recurrent episodes of fever, pruritic urticaria, malaise, night sweats, poly-arthralgias and bone pain were the leading symptoms from 2005. High CRP levels and leukocytosis had been present even longer. There was no evidence of a lymphoma or a monoclonal gammopathy. The patient was initially treated with antihistamines and low doses of corticosteroids without remission of symptoms. Since 2007 corticosteroids and Cyclosporin at 200 mg/day was started with the resolution of fever but not of cutaneous lesions. In April 2008 a relapse occurred; the hands, the wrists, the knees and feet were severely affected with signs of arthritis, the urticaria showed no remission with pruriginous wheals persisting for few days. Laboratory tests revealed high CRP (9.8 mg/L), ESR (55 mm/h) and for the first time, serum electrophoresis showed a monoclonal gammopathy IgG k band of 3 g/L. Tests revealed negative FR, anti-CPP antibodies, ANA, ENA, anti-DNA, Lupus anticoagulant, anti-cardiolipin and anti- β 2glycoprotein I antibodies and normal complement C3 and C4 levels; cryoglobulins were absent.

The patient was treated with Anakinra with a complete resolution of cutaneous and articular symptoms. Unfortunately after the fourth injection the patient experienced a severe local reaction at the inoculus site with the appearance of a diffuse urticarial rash and pruritus. Anakinra was stopped and corticosteroid treatment was started with a partial resolution of the skin lesions, but with a flare of the disease including fever and arthralgias. Anakinra was restarted after one month and the severe local skin reaction reappeared within few hours after the first injection. Two months later the patient was put on Rituximab at the dosage of 1 g two weeks apart, with complete

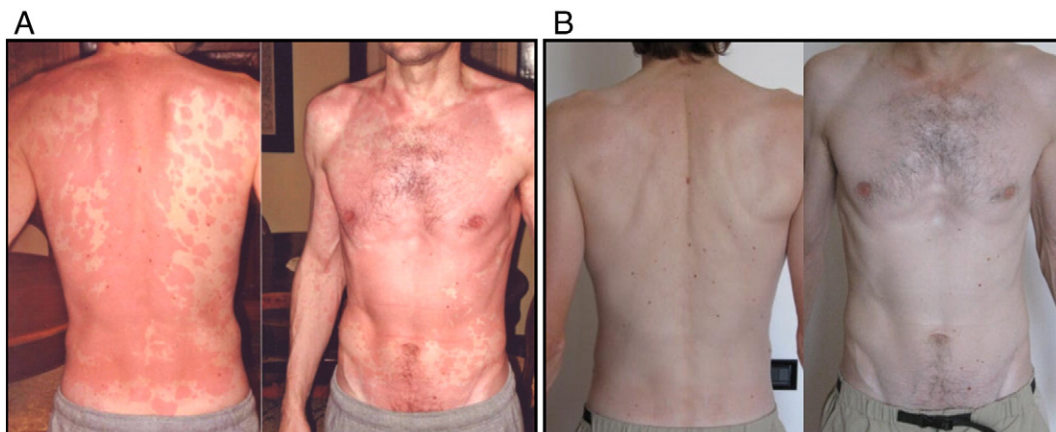


Fig. 1. Urticarial eruptions on the trunk before (A) and after (B) Anakinra treatment in patient 1.

remission of the disease within the following 2 months. Two months after the treatment with anti-CD20 antibodies, laboratory tests showed normalization of CRP and ESR while serum electrophoresis showed a reduction of the monoclonal gammopathy to 0.5 g/l. The patient is still in clinical and biochemical remission.

3. Review of the literature

We searched the MEDLINE database (National Library of Medicine, Bethesda, MD) and selected articles published between 1972 and December 2010 with the headings “Schnitzler syndrome” and “Treatment of Schnitzler syndrome”. All the 99 selected papers, except the clinical reviews, described at least one case of Schnitzler syndrome. The literature reported many additional articles mainly in the English and French literature, but also cases from Bulgaria, Czech Republic, Turkey and the Netherlands.

The review of the literature highlights that Schnitzler syndrome crosses the field of several medical specialties and remains an enigmatic disorder hard to diagnose and to treat.

4. Definition and clinical features

The diagnosis of Schnitzler syndrome requires the simultaneous presence of chronic urticaria and monoclonal gammopathy IgM or less frequently IgG, that are the major diagnostic criteria, accompanied by at least 2 of the minor criteria (Table 1), represented by intermittent/recurrent fever, arthralgias or arthritis, bone pain, lymphadenopathy or hepato-splenomegaly, elevated ESR or leukocytosis, abnormal findings on bone morphological investigations [2].

Women are more frequently affected than man (1.6:1) [2]. Most patients documented to date are of western European origin and probably the low number of cases diagnosed outside Europe may be due to a lack of familiarity with the disease [4,23,24].

The disease usually starts around the fourth decade [2] with urticarial skin lesions and characteristically with mild pruritus. However in the majority of the cases an intensified itching has been reported during the course of the disease. The skin lesions have a predilection for the trunk and last for about 12–36 h, on a daily basis. Fever bouts are observed in about 88% of patients and is frequently associated with flares of urticaria, fatigue and weakness [2]; weight loss is frequent. The intervals between individual fever bouts may present a high variability ranging between once a day and twice a year [25].

The onset of arthralgias, especially of the large joints, as well as of bone pain, mostly of the tibia and the pelvic bone, occurs in more than 70% of cases few months after the onset of skin lesions [2].

Lymphadenopathy in the axillary and inguinal regions is commonly present. The lymph nodes can be persistently enlarged up to 3 cm so that a biopsy is frequently mandatory to exclude the presence of lymphoma. Hepatomegaly is also a common feature and splenomegaly is found in 12% of patients [2].

Table 1

Diagnostic criteria for Schnitzler's syndrome: the two major criteria and at least 2 of the minor criteria are necessary for the diagnosis.

Major criteria	Minor criteria
-Chronic urticarial rash	-Intermittent fever
-Monoclonal IgM (or IgG: variant type)	-Arthralgias or arthritis
	-Bone pain
	-Lymphadenopathy
	-Hepato- and/or spleno-megaly
	-Elevated ESR and/or leukocytosis
	-Bone abnormalities (on radiological imaging or histological investigation)

A monoclonal IgM or alternatively IgG component must be present to meet the diagnostic criteria. In most of the cases light chains are of the κ -type. The monoclonal component can either remain stable or show a progressive increase of about 0.5 to 1 g/L/year [25]. However the monoclonal component may still be undetectable at the time of disease presentation. A monoclonal component greater than 10 g/L may be an indication of haematological disorder [26].

Signs of systemic inflammation may also be found: elevated ESR, elevated concentrations of acute phase proteins, leukocytosis and sometimes anemia of chronic diseases. Characteristically ESR and CRP levels are continuously increased throughout the course of the disease, peaking during exacerbations.

Since there is no specific serological markers of the disease, the diagnosis can be made after the exclusion of other autoimmune, autoinflammatory disorders such as adult-onset Still's disease, SLE, acquired C1 inhibitory deficiency, hereditary auto-inflammatory syndromes, of haematological disorders, of infectious diseases, chronic idiopathic urticaria, hyper-IgD syndrome and hypocomplementemic urticarial vasculitis [2,25,27–29].

In the majority of cases the syndrome has a chronic benign course but evolution in lymphoproliferative disorder, such as Waldenström macroglobulinemia, lymphoplasmacytic lymphoma, multiple myeloma and marginal zone B-cell lymphoma, have been described in sporadic cases [2,30,31]. The evolution in AA amyloidosis was also described [3,32].

5. Pathogenesis

The pathophysiology of Schnitzler syndrome is largely unclear. Histological studies of skin biopsy have provided little information and have shown a dense perivascular and interstitial infiltrate containing almost exclusively neutrophils with leukocytoclasia but without vasculitis [25], as found in the first patient we have described here. In some cases among neutrophils, infiltrating eosinophils, lymphocytes and histiocytes in the superficial dermis have been described [29]. Deposits of monoclonal IgM were also shown at the dermoepidermal junction as well as on capillary walls [33] suggesting the possible induction of local inflammatory reaction [34]. Indeed IgM deposits can be seen in less than 30% of patients with Schnitzler syndrome and also occur in subjects with Waldenström macroglobulinemia without urticaria; therefore the deposits more likely represent an epiphenomenon than a causal element in the disease.

The finding of IgG3 autoantibodies towards cellular proteins and of IgG2 antibodies specific for the alpha chain of the high affinity IgE receptor (Fc ϵ RI) led to the idea that autoimmune reactions mediated by T helper lymphocytes may play a role in the pathophysiology of the disease [6]. Moreover Saurat et al. reported the detection of IgG antibodies against IL-1 α in patients affected by Schnitzler syndrome further supporting an autoimmune component in the pathogenesis of the disease [7]. It was suggested that such antibodies could increase the biological half-life of IL-1 α , increasing the systemic effects of IL-1, but data were not supported by other investigators [6,23,35–37]. IFN- α , that increases the expression of IL-1 receptor antagonist (IL-1Ra), has been found to improve the clinical manifestations of Schnitzler syndrome supporting a pathophysiological role for IL-1 [15]. In addition the good clinical response to the treatment with the IL-1Ra Anakinra further support the pivotal role played by IL-1 in the pathogenesis of the disease. Indeed IL-1 is a powerful pro-inflammatory cytokine, and dysregulation in its secretion has been observed in several inflammatory diseases such as systemic-onset juvenile idiopathic arthritis, adult Still's disease and various auto-inflammatory disorders [38,39]. Indeed Schnitzler syndrome itself is considered an auto-inflammatory disorder by some authors [9,10].

IL-1 is responsible for various clinical manifestations such as fever, chills, skin rash, urticaria and even for neutrophilia, anemia and elevation in ESR, frequently present in the disease [9,38]. IL-1 induces

the production of IL-6 by endothelial cells and indeed elevated IL-6 levels have been also demonstrated in Schnitzler syndrome [23,40]. IL-6 is the main mediator for the hepatic secretion of acute phase proteins and for elevated ESR and induces platelet mobilization from bone marrow inducing peripheral thrombocytosis [38]. As a major modulator of the acute phase response, IL-6 could be involved in the induction of the systemic features of the disease and its effects on B-cell differentiation could be responsible for the monoclonal gammopathy [7]. Recently several authors have pointed out the presence of elevated serum IL-6 levels in patients with the disease; these findings are therefore consistent with the important role played by this cytokine in Schnitzler syndrome [14,40,41].

6. Treatment

Treatment of Schnitzler syndrome has been considered difficult and unsatisfactory for a long time and both traditional immunosuppressive therapies and novel biological agents have been reported to obtain controversial results (Table 2).

Antihistamines have no efficacy in controlling the rash and pruritus, probably due to the histamine-independent etiology of the rash. The first choice treatment so far consisted of non-steroidal anti-inflammatory drugs and in particular of systemic corticosteroids [33]; such therapy seems to be successful in less than a half of the cases [25]. However since a longstanding high dose steroid regimen is needed to control the symptoms, its use is limited by the known side-effects.

Among the non-steroidal anti-inflammatory drugs, Ibuprofen seems to be the best choice to obtain an improvement of the skin lesions, fever and arthralgias, unfortunately the effect is short-lived [25].

Immunosuppressants may be helpful as steroid sparing agents, although cyclophosphamide or cyclosporine induced responses only in a few patients [12,13,42]. Methotrexate has been reported to be

effective in some patients [11,35]. Neither plasma exchange nor intravenous high dose of immunoglobulins or psoralen plus ultraviolet A therapy have shown any efficacy [12,16,17,25]. Leukocyte migration inhibitors, such as colchicine and dapsone, have obtained variable results [25,43].

In recent years a few promising therapeutic options have emerged, but the number of patients treated is very small, limited to case reports. Efficacy of interferon- α [15,44] and thalidomide have been reported [14,45]. However, both interferon- α and thalidomide must be used with caution in consideration of the potential side effects. Pefloxacin may be a promising option in inducing remission of urticaria but it is less effective on arthralgias as reported in a few cases [46]. The mechanism of action may be explained by the effect of fluoroquinolones on the regulation of messenger RNA for cytokines as well as their receptors [47].

Anti-TNF α agents have been used only in very few cases with controversial results [18,19].

Anakinra, a synthetic analog of the endogenous IL-1Ra, caused complete remission within 24 h with a longstanding effect with daily injections [5,20,41,45,48,49]. However the patients who stopped the treatment temporarily, like in the case 1 above described, a flare-up of symptoms appeared within one day. However remission of symptoms is observed as soon as the drug is restarted. The only side-effect described is an erythematous painful lesion at the injection site; nobody has experienced a flare of skin signs and symptoms as our patient 2.

Rituximab is a monoclonal chimeric anti-CD20 antibody that selectively binds to CD20-positive B lymphocytes and induces lysis or apoptosis of B cells with the consequent decline in monoclonal immunoglobulins. The role of Rituximab in the treatment of Schnitzler syndrome is still undefined because of the conflicting results obtained so far as reported in the literature [21,22,49–51].

Inhibition of IL-6 signaling with the use of IL-6 antagonist Tocilizumab may represent another therapeutic option for Schnitzler syndrome in case of inefficacy or withdrawal of other therapies [52,53].

No spontaneous remission has been reported so far and also in case of good response to therapy a temporary treatment suspension is usually followed by flare of the disease [15,45]. The long-term effects of the different therapies on symptoms, laboratory and imaging findings and on the incidence of lymphoproliferative disorders are still unclear and difficult to carried out due to the rarity of the disease.

In conclusion, although the treatment of Schnitzler syndrome is not standardized, Anakinra, Rituximab and Tocilizumab may be proposed as the treatment of choice in patients with highly active disease.

7. Prognosis

Schnitzler syndrome has a favourable prognosis in term of mortality with a survival rate of 94% after 15 years which is comparable to the survival rate of the average population of the same age group in the Netherlands [2]. Although the mortality risk is not increased, patients have an increased risk of malignancy, in particular of lymphoproliferative disease such as Waldenström macroglobulinemia and IgM myeloma [2,30,54]. Development of other lymphoproliferative disorders is rare, since only one patient with Schnitzler syndrome who developed a marginal B-zone lymphoma has been described [31].

The risk of developing a lymphoproliferative disorder, as described by de Konig et al. [2], is very similar to that found by Kyle et al. in a cohort of patients with IgM MGUS quantified as 18% in 10 years [55].

Interestingly there are no reports on the development of amyloid L (AL)-type amyloidosis, even after decades of monoclonal gammopathy, but almost three cases of type amyloid A (AA) amyloidosis have been reported [2,3,32].

Table 2
Therapeutic options for the treatment of Schnitzler syndrome.

Treatment	Efficacy	References
-Antihistamines	Partial and/or temporary remission	2; 4; 12; 13; 15; 17; 25; 30; 32; 35; 36; 42; 45
-Corticosteroids	Complete remission, particular with high doses	2; 4; 12; 13; 14; 15; 16; 17; 18; 23; 25; 28; 30; 31; 32; 33; 35; 42; 45; 48; 54
-NSAIDs (Ibuprofen and Cox-inhibitors)	Partial and/or temporary remission	2; 6; 14; 23; 25; 28; 30; 32; 33; 35; 36; 40; 42; 45; 48; 54
-Cyclophosphamide	Partial remission in few cases	2; 12; 13; 30; 42; 48
-Methotrexate	Partial and/or temporary remission	2; 11; 12; 13; 30; 35; 42; 48
-Ciclosporine	Partial and/or temporary remission	2; 12; 13; 30; 42; 45; 48
-Plasma exchange	No efficacy	2; 13; 15; 36
-IVIGs	No efficacy	2; 12; 25
-Colchicine	Partial and/or temporary remission	2; 25; 43
-Dapsone	Partial and/or temporary remission	2; 25; 43
-PUVA (with or without psoralen)	No efficacy	2; 16; 17; 25
-Interferon- α	Complete or partial remission in few cases	2; 15; 44; 48
-Thalidomide	Complete remission in few cases	2; 14; 31; 45
-Pefloxacin	Remission of urticaria	2; 46; 47
-anti-TNF α agents	Rapid improvement with a flare disease in few hours	2; 18; 19
-IL-1Ra	Complete remission	2; 5; 20; 41; 45; 48; 49
-Rituximab	Contradictory outcome	2; 21; 22; 49; 50
-Tocilizumab	Potentially useful	52; 53

Indeed the Schnitzler syndrome seems to have a favorable prognosis in term of mortality but a strong impact on the quality of life because of the long time from disease onset and diagnosis and of the difficulty in finding a successful treatment.

8. Discussion

Here we describe two patients affected by Schnitzler syndrome; in both cases the correct diagnosis was made about two years after the onset of the disease and both patients had a good clinical response to Anakinra. However in the second case Anakinra had to be suspended because of severe local reaction and Rituximab was well tolerated and obtained remission of the disease.

Schnitzler syndrome remains an enigmatic disorder with an unclear pathogenesis and an obscure evolution, since clinical or laboratoristical predictors of outcome are not yet been identified [8,56].

Schnitzler syndrome has been recently considered as an autoinflammatory disorder; however several aspects remain unclear since the clinical response to a wide spectrum of anti-inflammatory and immunosuppressive regimens is transient and incomplete and since some clinical and histological features are not completely explained as an autoinflammatory disorder [2]. Indeed the patients have an urticarial rash with the histological features of neutrophilic urticaria, which is an inflammatory disorder, but cases characterized by a lymphocytic infiltrates with a lower CD4+/CD8+ ratio have also been described [57]. High blood and/or skin levels of IL-6, IL-1 and IL-18 have been described in patients affected by the disease [2,8] and the current experience suggests that complete remission can be achieved by continued treatment with the IL-1Ra Anakinra.

Tocilizumab may represent a good therapeutic option for the treatment of the disease. Moreover, the pro-inflammatory cytokines IL-1 and IL-6 are essential growth factors for B-lymphocytes and plasma cells, responsible for the paraproteinemia. For this reason Rituximab is another intriguing therapeutical option. Moreover Rituximab is used in different autoimmune diseases with good results [58–60]. The remission experienced by the second patient we have described here using Rituximab may be related to the presence of autoantibodies as already reported [6,7] and may further support the autoimmune component of the disease.

In conclusion recent advances in the understanding of the immunopathogenesis of Schnitzler syndrome point out the presence of an autoimmune and autoinflammatory component with consequent important effects on the treatment of choice.

Take-home messages

- Schnitzler syndrome is a rare disabling disorder that crosses the field of many medical specialties; its real frequency has not been established so far
- *Chronic urticaria and the presence of a monoclonal IgM or IgG are major criteria for the diagnosis*
- The etiopathogenesis is unknown, however both autoimmune and autoinflammatory features are present
- The disease is frequently refractory to anti-histamines, corticosteroids and classical immunosuppression
- Anakinra, Rituximab and Tocilizumab seem to be the treatment of choice in patients with highly active disease.

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The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort

The 1996 Five-Factor Score (FFS) for systemic necrotizing vasculitides (polyarteritis nodosa [PAN], microscopic polyangiitis [MPA], and Churg-Strauss syndrome [CSS]) is used to evaluate prognosis at diagnosis. In the current study **Guillemin L, et al. (Medicine (Baltimore) 2011;90:19-27)** revisited the FFS, this time including Wegener granulomatosis (WG). They analyzed clinical, laboratory, and immunologic manifestations present at diagnosis of systemic necrotizing vasculitides for 1108 consecutive patients registered in the French Vasculitis Study Group database. All patients met the American College of Rheumatology and Chapel Hill nomenclature criteria. Univariable and multivariable analyses yielded the 2009 FFS for the 4 systemic necrotizing vasculitides. Overall mortality was 19.8% (219/1108); mortality for each of the SNV is listed in descending order: MPA (60/218, 27.5%), PAN (86/349, 24.6%), CSS (32/230, 13.9%), and WG (41/311, 13.2%) ($p < 0.001$). The following factors were significantly associated with higher 5-year mortality: age > 65 years, cardiac symptoms, gastrointestinal involvement, and renal insufficiency (stabilized peak creatinine $\geq 150 \mu\text{mol/L}$). All were disease-specific ($p < 0.001$); the presence of each was accorded +1 point. Ear, nose, and throat (ENT) symptoms, affecting patients with WG and CSS, were associated with a lower relative risk of death, and their absence was scored +1 point ($p < 0.001$). Only renal insufficiency was retained (not proteinuria or microscopic hematuria) as impinging on outcome. According to the 2009 FFS, 5-year mortality rates for scores of 0, 1, and ≥ 2 were 9%, 21% ($p < 0.005$), and 40% ($p < 0.0001$), respectively. The revised FFS for the 4 systemic necrotizing vasculitides now comprises 4 factors associated with poorer prognosis and 1 with better outcome. The retained items demonstrate that visceral involvement weighs heavily on outcome. The better WG prognosis for patients with ENT manifestations, even for patients with other visceral involvement, compared with the prognosis for those without ENT manifestations, probably reflects WG phenotype heterogeneity.

Evaluation of four novel genetic variants affecting hemoglobin A1c levels in a population-based type 2 diabetes cohort (the HUNT2 study)

Chronic hyperglycemia confers increased risk for long-term diabetes-associated complications and repeated hemoglobin A1c (HbA1c) measures are a widely used marker for glycemic control in diabetes treatment and follow-up. A recent genome-wide association study revealed four genetic loci, which were associated with HbA1c levels in adults with type 1 diabetes. In this concern, **Hertel JK, et al. (BMC Med Genet 2011;12:20)** evaluated the effect of these loci on glycemic control in type 2 diabetes. They genotyped 1,486 subjects with type 2 diabetes from a Norwegian population-based cohort (HUNT2) for single-nucleotide polymorphisms (SNPs) located near the BNC2, SORCS1, GSC and WDR72 loci. Through regression models, they examined their effects on HbA1c and non-fasting glucose levels individually and in a combined genetic score model. No significant associations with HbA1c or glucose levels were found for the SORCS1, BNC2, GSC or WDR72 variants (all P -values > 0.05). Although the observed effects were non-significant and of much smaller magnitude than previously reported in type 1 diabetes, the SORCS1 risk variant showed a direction consistent with increased HbA1c and glucose levels, with an observed effect of 0.11% ($P = 0.13$) and 0.13 mmol/l ($P = 0.43$) increase per risk allele for HbA1c and glucose, respectively. In contrast, the WDR72 risk variant showed a borderline association with reduced HbA1c levels ($\beta = -0.21$, $P = 0.06$), and direction consistent with decreased glucose levels ($\beta = -0.29$, $P = 0.29$). The allele count model gave no evidence for a relationship between increasing number of risk alleles and increasing HbA1c levels ($\beta = 0.04$, $P = 0.38$). The four recently reported SNPs affecting glycemic control in type 1 diabetes had no apparent effect on HbA1c in type 2 diabetes individually or by using a combined genetic score model. However, for the SORCS1 SNP, our findings do not rule out a possible relationship with HbA1c levels. Hence, further studies in other populations are needed to elucidate whether these novel sequence variants, especially rs1358030 near the SORCS1 locus, affect glycemic control in type 2 diabetes.