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Sjögren's syndrome

Summary

Sjögren's syndrome (SjS) is an autoimmune disease characterized by the triad of sicca symptoms, fatigue and pain. This diagnosis is usually made in women at the average age of 60 years. Diagnosis is made when sicca symptoms persist for more than three months, after the exclusion of possible differential diagnoses, and using the ACR/EULAR 2016 classification criteria for SjS. Many organs can be affected in the course of this disease. Xerosis cutis and pruritus are the most common skin manifestations, followed by leukocytoclastic vasculitis and subacute cutaneous lupus erythematosus. In addition, SjS patients often have myoarthralgia and neuropsychiatric symptoms. In the long term, attention must be paid to the increased risk of cardiovascular disease and lymphoma. Due to the multiorgan involvement in SjS patients, interdisciplinary care is required.

Introduction

Sjögren's syndrome (SjS) is a connective tissue disease. It is defined by the clinical triad of sicca symptoms, fatigue, and pain.

Sjögren's syndrome (SjS) is a chronic autoimmune connective tissue disease. The clinical symptom triad includes sicca symptoms, fatigue, and pain [1]. Patients may also display additional organ manifestations.

History

In 1892, Mikulicz was the first scientist to report on a patient with sicca symptoms and bilateral swelling of the parotid glands [2]. Gougerot introduced the term "sicca syndrome" in 1925. Eight years later, Henrik Sjögren first reported on a systemic disease he called "keratoconjunctivitis sicca". He described this as a combination of dry eyes and mouth associated with rheumatoid arthritis (RA).

Etiology and pathogenesis

Etiology and pathogenesis are not fully understood, but it is assumed that various factors such as genetics, environmental factors, hormones, and immune dysregulation play a role in the pathogenesis of this disease.

SjS is often called "autoimmune epithelitis" [3] since epithelial cells play a key role in this disease – as both targets and initiators of the autoimmune process [4]. The epithelial cells produce pro-inflammatory cytokines, which in turn leads to impaired function of the salivary glands [5].

Etiology and pathogenesis are not fully understood [6], but a multifactorial process is assumed to be the most likely explanation (Figure 1).

Genetic predisposition is a prerequisite (HLA-DRB1*03: 01, DQA1*05: 01, DQB1*02: 01 [7, 8], X chromosomes), but epigenetic modifications [6] are also required for the development of this autoimmune disease. An increased risk for connective tissue diseases (such as systemic lupus erythematosus [SLE], systemic scleroderma [SS]) or other autoimmune diseases has been demonstrated in families of SjS patients [9]. Other factors such as immune dysregulation, hormones, and environmental influences (among other factors, stress [10], infections [11], drugs

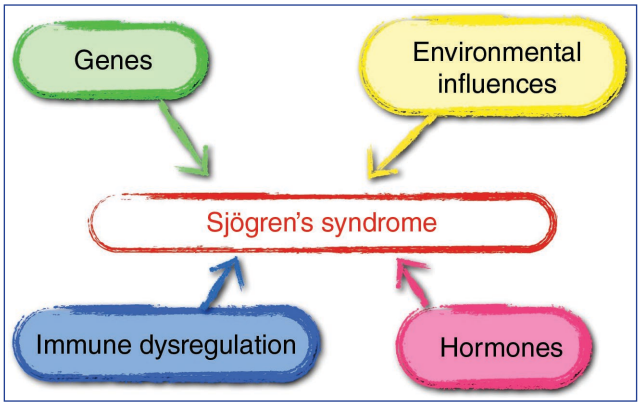

Figure 1 Pathogenesis of Sjögren's syndrome (adapted from [133]).

[12], vaccines [13], or silicone breast implants [14] are currently being discussed) then lead to misdirected activation of the innate and adaptive immune system. This activates the type 1 and type 2 interferon signaling cascades that stimulate proliferation of B cells.

Viral infections, in particular [11], mainly the Epstein-Barr virus [15] are suspected candidates for inducing SjS. Interestingly, an increased incidence of SjS as compared to earlier years was reported in Brazil during the COVID-19 pandemic [16].

Epidemiology

SjS is one of the most common rheumatological diseases.

SjS is one of the most common rheumatological diseases. Its prevalence is estimated to be about 0.5 % and its incidence about 4/1000 people per year [17]. It has an unusual age at diagnosis of around 60 years (between the 5th and the 7th decade of life) [18]. In cases where SjS is diagnosed in younger patients (less than 35 years of age), presentation is frequently associated with fever, lymphadenopathy, and high disease activity [19]. In clinical studies, disease activity is measured by the ESSDAI (European League against Rheuma Sjögren's syndrom disease activity index).

SjS is most commonly diagnosed in women between the 5th and 7th decade of life.

SjS is diagnosed eight times more frequently in women than in men [18]. Some studies have investigated differences between male and female SjS patients [20], showing that male SjS patients have more severe courses and higher mortality rates [21–23].

There are rare cases of juvenile SjS, usually appearing around ten years of age. This is characterized by recurrent parotid gland inflammation (about 67 % of patients) and arthralgia. Laboratory findings (rheumatic factor, ANA, Ro/SS-A antibodies) may be normal in patients with juvenile SjS [24, 25].

Sicca symptoms and systemic activity (ESSDAI) vary based on ethnicity. African Americans show higher disease activity scores, followed by European, Asian, and Hispanic patients [26]. In addition, SjS is frequently diagnosed at an earlier age in African Americans and Africans than in Europeans [27, 28]. Higher systemic activity has been reported for patients from more Southern latitudes (below the 50th parallel north in Europe, below the equator in America, and below the 30th parallel north in Asia) as compared with patients from more northern latitudes [26]. Possible causes are currently being discussed, including genetic factors, lifestyle (microbiome), and environmental influences such as metals in the earth, air pollution, or viral infection [26].

Diagnosis and classification

SjS is diagnosed based on the patient's subjective sicca symptoms if these cannot be explained by other differential diagnoses, after excluding certain diseases and using the objective classification criteria.

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Subjective criteria for sicca symptoms

Patients must have had sicca symptoms for at least three months before the SjS classification criteria can be applied. The following questions need to be clarified when talking with the patient:

Patients must have had sicca symptoms for at least three months before the SjS classification criteria can be applied.

- Have you had a sensation of dry eyes every day for more than three months?
- Do you often have the sensation of sand/grit in your eye?
- Do you use artificial tears more than three times per day?
- Have you had a sensation of a dry mouth every day for more than three months?
- Do you frequently need to drink something to help you swallow dry food?

If one of these questions is answered in the affirmative, the patient has subjective sicca symptoms.

Differential diagnoses of xerostomia and xerophthalmia

Sicca symptoms should not be explainable by other possible causes. Differential diagnoses for xerostomia [29] and xerophthalmia [30] are listed in Table 1.

Exclusion diagnoses

The following diseases must be excluded before SjS can be diagnosed [31]: History of radiation therapy in the head and neck area, active hepatitis C infection (positive HCV-PCR), AIDS, sarcoidosis, amyloidosis, graft-versus-host disease (GvHD), IgG4-associated disease. Pre-existing lymphoma is no longer considered an exclusion diagnosis. Patients with sicca symptoms who are taking an anticholinergic should discontinue this and be re-evaluated after an appropriate interval (> 5 half-lives).

The following diseases must be excluded before SjS can be diagnosed [31]: History of radiation therapy in the head and neck area, active hepatitis C infection (positive HCV-PCR), AIDS, sarcoidosis, amyloidosis, graft-versus-host disease (GvHD), IgG4-associated disease.

Classification criteria 2016

There are different classification criteria for SjS [31–33]. The current classification criteria for primary SjS (pSjS) were published in 2016 by ACR/EULAR (American College of Rheumatology/European League against Rheumatism) [31]. Table 2 lists the classification criteria. The primary aim of the ACR/EULAR criteria is to define inclusion criteria for clinical studies. pSjS is diagnosed in patients with a total score of ≥ 4. Sensitivity (96 %) and specificity (95 %) are high, however a total score of ≥ 4 is sometimes not reached in early stages of the disease. For example: Xerophthalmia may have been present for five months and differential diagnoses excluded, but objective tests may only detect Ro/SS-A antibodies (3 points). If there is still a justified suspicion of SjS, repeating the objective tests listed in the classification criteria after a few months may therefore make sense. Among the objective criteria, Ro/SS-A antibodies and histological investigation of the salivary glands (focus score [FS] ≥ 1) are mandatory criteria. SjS can only be diagnosed if at least one of these criteria is fulfilled.

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Table 1 Differential diagnoses of xerostomia and xerophthalmia.

	Xerostomia	Xerophthalmia
General	Age, pollinosis, malignancy	
Metabolic causes	Diabetes mellitus	
	Vitamin deficiency (B1, B2, B6, B12), anemia, hypercalcemia Hyperthyreosis and hypothyreosis, dialysis, chronic renal failure	Vitamin A deficiency, hypoandrogenemia
Environmental influences	Radiotherapy, chemical and thermic burns, scarring, nicotine abuse/cigarette smoke	
	Sialadenitis/sialolithiasis	Wind, low air humidity, computer work, contact lenses
Hereditary causes	Hereditary gelsolin amyloidosis	Congenital alacrimy, familial dysautonomy
Neuropsychiatric causes	Anxiety disorder, depression, schizophrenia, Parkinson's disease, Alzheimer's disease	
Inflammatory diseases	Primary biliary cholangitis, amyloidosis, sarcoidosis, GvHD, mucosal pemphigoid, IgG4 associated disease	
	Lichen planus	Rosacea, chronic blepharitis
Infections	HIV, HCV	
	Varicella, hand-foot-mouth disease, herpes stomatitis	Trachoma, post-zoster neuropathy, adenoviruses
Drugs	Antihistamines, anticholinergics, diuretics, tricyclic antidepressants	
	Bronchodilators, psychotropic drugs (anxiolytics, neuroleptics), antihypertensives, opioids, interferon-alpha, triptans, appetite suppressants	Retinoids, topical medications with preservatives

Eyes

Staining the cornea with lissamine green or fluoresceine shows degenerated and/or dead cells on the corneal surface. The Schirmer test measures the amount of lacrimal fluid with filter paper.

Mouth

The unstimulated whole saliva (UWS) flow rate is the amount of saliva produced within five to 15 minutes while the patient is sitting quietly without speaking or chewing [34].

Laboratory investigations

The only laboratory value valid for a SjS diagnosis according to the classification criteria is the SS-A/Ro antibody. SS-A/Ro antibodies are antinuclear antibodies (ANA) against Ro52 and/or Ro60. Detection of SS-B/La antibodies in the absence of SS-A/Ro antibodies is no longer relevant for diagnosing SjS according to the classification criteria.

Table 2 2016 ACR/EULAR classification criteria for primary Sjögren's syndrome (adapted from [31]). After controlling the inclusion criteria (dry eyes and/or mouth for at least 3 months without other explanation) and exclusion criteria, the classification criteria can be used. The diagnosis of SjS is confirmed when ≥ 4 points of the classification criteria are reached.

Inclusion criteria	(1) Have you had a sensation of dry eyes every day for more than three months? (2) Do you often have the sensation of sand/grit in your eye? (3) Do you use artificial tears more than three times per day? (4) Have you had a sensation of a dry mouth every day for more than three months? (5) Do you frequently need to drink something to help you swallow dry food? ≥ 1 positive response to 1 question
Subjective sicca symptoms NOT explained by other differential diagnoses (Table 1)?	
Exclusion criteria	(1) History of radiotherapy in the head and neck area (2) active hepatitis-C infection (HCV-PCR positive) (3) AIDS (4) Sarcoidosis (5) Amyloidosis (6) Graft versus Host Disease/IgG4-associated disease No exclusion criteria
Classification criteria	(1) Histology of the labial salivary gland: focal lymphocytic sialadenitis & focus score ≥ 1 **(3 points)** (2) Detection of SS-A/Ro antibodies **(3 points)** (3) Pathological findings in lissamine green or fluorescein staining (Eye staining score ≥ 5 or van Bijsterveld score ≥ 4) in at least one eye **(1 point)** (4) Pathological Schirmer test: ≤ 5 mm after 5 min in at least one eye **(1 point)** (5) Unstimulated whole saliva flow rate = UWS ≤ 0,1 ml/min **(1 point)** Total points ≥ 4 → Sjögren's Syndrome diagnosed

Histology

Salivary gland biopsy remains a rarely used diagnostic instrument [35]. The specimen can be taken from the lower lip [36]. In salivary gland histology, the focus score is the gold standard for quantifying lymphocytic infiltration. (Grade 0: no lymphocytes/4 mm^2, grade 1: minor lymphocyte infiltration, grade 2: moderate infiltration but less than one focus, grade 3: one focus, grade 4: more than one focus; a focus is an accumulation of ≥ 50 lymphocytes/4 mm^2 salivary gland tissue) [37]. Specificity is high, but sensitivity is low [38]. Tissue samples can be particularly helpful in the early stages of the disease when other criteria are still negative and differential diagnoses must be excluded. Histology is only recommended if Ro/SS-A antibodies cannot be detected [39, 40].

Diagnostic imaging

Diagnostic imaging methods (such as ultrasound, scintigraphy, sialography) are not currently recommended in the classification criteria, but in everyday clinical

practice, ultrasound of the salivary gland is a simple, reliable, and helpful diagnostic procedure [39, 40].

Additional laboratory parameters

Additional laboratory parameters for diagnosing SjS or monitoring disease activity are currently being developed but are not yet validated [41]. In future diagnostics, it may be possible to detect some biomarkers in saliva (profilin and CA-I or IL-4, IL-5 and mi-RNA) or in tears (cathepsin S). Myxovirus resistance protein A (MxA) in correlation with interferon type-1 activity may reflect disease activity [41].

pSjS and secondary SjS (sSjS)

The term sSjS is used when the SjS occurs together with other autoimmune diseases. However, the distinction between pSjS and sSjS varies in the scientific literature [42, 43]. Initially, SjS was called "secondary" when it occurred in conjunction with rheumatoid arthritis (RA) [44]. SjS is diagnosed in up to 30 % of RA patients [45]. Interestingly, patients with combined RA and sSjS have more severe, destructive arthritis compared to patients with RA alone [46, 47]. The term "sSjS" is mostly used for SjS in association with RA, systemic lupus erythematosus (SLE), or systemic sclerosis (SS). Associated SjS is diagnosed in up to 20 % of patients with SLE or SS [45]. There are also many similarities between LE and SjS (etiology, pathogenesis, epidemiology, treatment) [48]. The greatest difficulty concerning clinical presentation of SjS arises because of the frequent overlapping manifestations with SLE, SS, or overlap syndromes. Clear differentiation (SLE versus SjS versus SS) is often impossible.

The term secondary SjS (sSjS) is used when SjS occurs in association with other autoimmune diseases. However, the distinction between pSjS and sSjS varies in the scientific literature.

If SjS and SS occur in association with primary biliary cholangitis, this is called Reynolds syndrome [49]. The term sSjS is sometimes also used if SjS occurs in association with autoimmune diseases that are not connective tissue diseases (such as primary biliary cholangitis, or Hashimoto thyreoiditis) [50]. Depending on how pSjS and sSjS are differentiated, the ratio of pSjS to sSjS varies between 1/3 [51] and 3/1 [50]. Note that the term "secondary" in this context does not signify any temporal sequence in the occurrence of the autoimmune diseases.

Clinical presentation

Sicca symptoms

Sicca symptoms impair quality of life in SjS patients [52]. Subjective symptoms frequently show little correlation with the objective measurements of gland functionality [53]. An association between the severity of xerophthalmia (in particular inflammatory keratolysis and scleritis) and mortality in SjS patients has been reported [54]. Quality of life is impaired by keratoconjunctivitis sicca since this is associated with foreign body sensation, burning, and increased sensitivity to light. In the long term, ocular involvement in SjS may lead to blindness [55]. SjS patients therefore need to be closely monitored by an ophthalmologist. Xerostomia is characterized by difficulty chewing and masticating, especially for dry foods, and also difficulty is speaking. Xerostomia is also associated with an increased risk of caries, early loss of teeth, and increased fungal infections with *candida albicans*.

Sicca symptoms impair quality of life in SjS patients.

The prevalence of vaginal dryness in SjS patients is comparable with that found in women of the same age in the general population [56, 57]. However, 61–68 % of SjS patients report dyspareunia [56, 58]. This is significantly more common than in studies on dyspareunia in women of the same age in the general population (8 %) [59]. One possible cause for the more frequent occurrence in SjS patient may be an altered composition of the vaginal secretions [57]. Sicca symptoms can also affect other mucous membranes, leading to symptoms like heartburn, sore throat, chronic cough (tracheobronchitis sicca), and recurrent urinary tract infections in SjS patients.

Swelling of the parotid gland

About one-third of patients have recurrent parotitis [60, 61]. Parotitis is usually found in juvenile SjS. In adult patients, possible differential diagnoses such as non-Hodgkin lymphoma need to be considered (Table 3).

Table 3 Treatment of Sjögren's syndrome (adapted from [1]).

Clinical Manifestation		Treatment
Sicca symptoms	Xerophthalmia	1) ED (≥ 2 x per day) and eye gels/ointments 2) Topical GC/NSAID 3) CyA AT 4) Serum tear drops 4) Pilocarpine or silicone plugs in the tear duct, scleral lenses
	Xerostomia	1) Topical fluorides/sugar-free chewing gum/boiled sweets/artificial aliva (mouth sprays, gels, or rinsing solutions) 2) Pilocarpine
	Xerosis cutis	1) Moisturizers 2) Topical GC
	Mucous membranes	1) Rhinitis sicca: Nose oil 2) Tracheobronchitis sicca: Pilocarpine, bromhexine, inhalation with sodium chloride 3) Dyspareunia: estrogen-containing suppositories
	Immunosuppressants and rituximab are generally not recommended due to their potential side effects.	
Parotitis	Acute	NOTE: Exclude infection! 1) Symptomatic treatment 2) GC 3) RTX/BLM
	Chronic	NOTE: Exclude lymphoma or other causes! ± surgery
Joints	Arthralgia	1) NSAID 2) HCQ
	Arthritis	1) NSAID + HCQ 2) HCQ + GC 3) SsI 4) RTX or ABA

Continued

Table 3 Continued.

Clinical Manifestation		Treatment
Skin	Sunscreen!	
	Cutaneous LE	1) Topical GC or HCQ +/- GC 2) other antimalarials +/- GC 3) Retinoids, SsI
	Cutaneous vasculitis	1) GC 2) Oral SsI or RTX 3) CyC ± Pex
Fatigue		1) Exercise, endurance training 2) HCQ
Raynaud symptoms		Keeping warm, paraffin hand baths, Ca antagonists, AT-II receptor blockers, phosphodiesterase inhibitors Statins ± aspirin
Kidney	Tubular	1) symptomatic (Bicarbonate or electrolyte supplementation) 2) GC 3) SsI
	Glomerulonephritis	1) GC 2) RTX or CyC 3) Pex
Lung	Bronchitis	Inhalation treatment (ß2 mimetics, steroids)
	ILD	1) GC 2) SsI 3) CyC or RTX 4) Nintedanib
PNS	Mononeuritis multiplex	1) GC 2) oral SsI or RTX 3) CyC ± Pex
	Axonal PN	1) Symptomatic 2) IVIG 3) Pulses MP 4) CyC
	Ganglionopathy/CIDP	1) IVIG 2) Pulses MP 3) CyC
CNS	CNS vasculitis/NMOSD	1) GC 2) CyC 3) RTX ± Pex, eculimumab
	Lymphocytic meningitis	1) Symptomatic 2) GC 3) CyC 4) RTX ± Pex, eculimumab
	Symptoms resembling multiple sclerosis	Treatment for multiple sclerosis
Hematological Manifestation	Neutropenia < 500	1) consider G-CSF 2) GC

Continued

Table 3 Continued.

Clinical Manifestation		Treatment
	Thrombocytopenia < 20,000	GC
	Hemolytic anemia	1) GC + IVIG 2) RTX 3) Pex or CyC
	NOTE: if blood count values show persistent deviation from the normal range, lymphoma or other causes must be excluded.	
B cell lymphoma		Depending on the type of lymphoma (surgery, radiotherapy, chemotherapy, RTX, R-CHOP)

Abbr.: ABA, Abatacept; BLM, belimumab; CIDP, chronic-inflammatory demyelinizing polyneuropathy; CNS, central nervous system; CyA, ciclosporin; CyC, cyclophosphamide pulsed therapy; ED, eye drops; GC, glucocorticoids; HCQ, hydroxychloroquine; ILD, interstitial lung disease; IVIG, intravenous immunoglobulins; LE, lupus erythematosus; NMOSD, Neuromyelitis optica spectrum diseases; NSAID, non-steroidal anti-inflammatory drugs; PEX, plasma exchange; PNS, peripheral nervous system; RTX, rituximab; SjS, Sjögren's syndrome; SsI, steroid-sparing immunosuppressants (MTX, methotrexate; AZA, azathioprine; MMF, mycophenolate mofetil).

Skin

Skin manifestations occur in 14–16 % of SjS patients.

Skin manifestations occur in 14–16 % [62, 63] of SjS patients; however "dry skin" was not included in these studies [62, 63].

Xerosis cutis and pruritus

Dry skin and pruritus are common cutaneous symptoms of SjS.

Dry skin and pruritus are common cutaneous symptoms of SjS. Xerosis cutis occurs with a prevalence of up to 68.4 % in patients with SjS [64, 65]. For a long time, dysfunction of the sweat glands was assumed to be the underlying cause, but this has not been confirmed [66]. The current assumption is that a defective skin barrier causes this problem [66]. The prevalence of pruritus in SjS is estimated at about 53 % [65], compared to 25.5 % in the general population [67]. The pathophysiology of SjS-associated pruritus in currently still unknown [65]. In SjS, pruritus does not correlate with the severity of xerosis cutis. Its intensity in SjS appears to be higher than in other connective tissue diseases [65].

Vasculitis

Vasculitis is the second most common skin manifestation.

Vasculitis is the second most common skin manifestation. Depending on the study, vasculitis has been reported in up to 30 % of SjS patients [63, 64, 68]. Patients present with palpable purpura, but in some cases also non-palpable purpura (Figure 2a) as well as urticarial eruptions (Figure 2b) on the lower legs. Histology will usually confirm leukocytoclastic vasculitis. Medium-sized vessels are only rarely affected [63, 69]. Vasculitis in SjS patients appears to be associated with severe disease [63] and an increased risk of lymphoma [70].

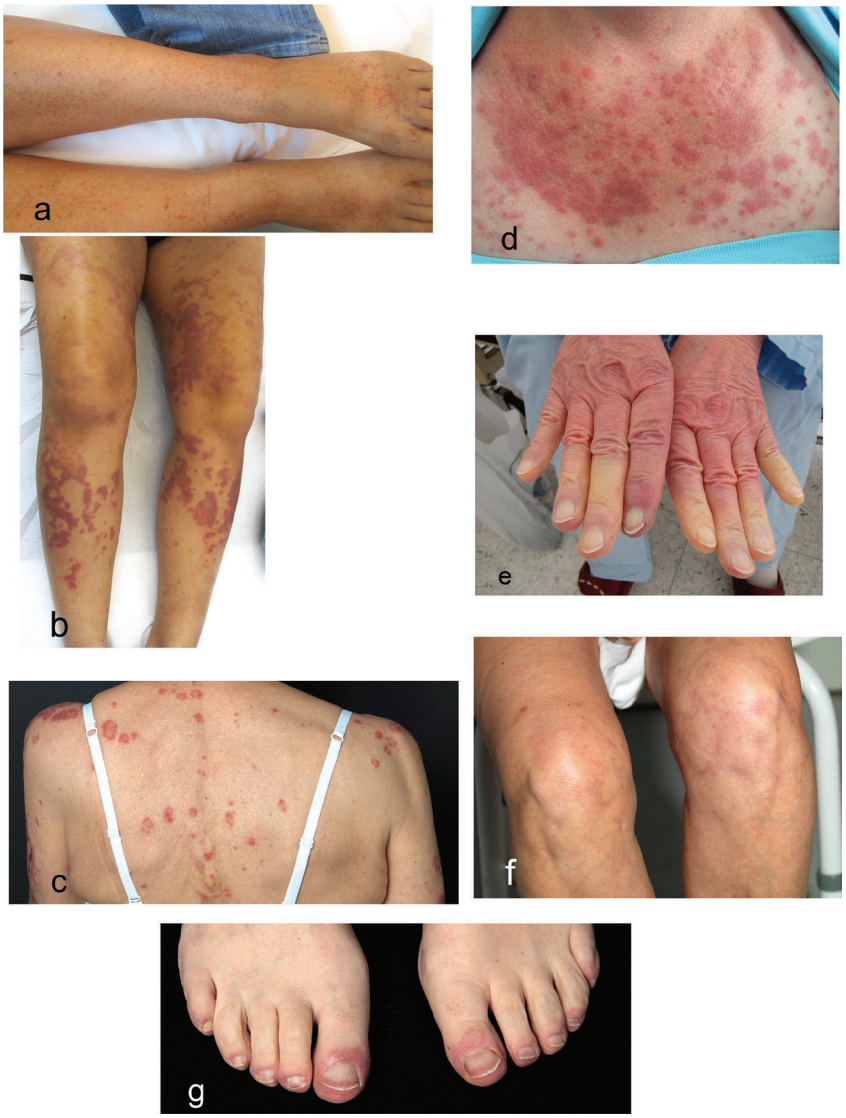

Figure 2 Dermatological clinical pictures in the context of Sjögren's syndrome. purpura as a clinical manifestation of leukocytoclastic vasculitis (a). Urticarial vasculitis (b). Subacute cutaneous lupus erythematosus (c). Lupus erythematosus tumidus (d). Raynaud phenomenon (e). Livedo racemosa (f). Chilblain lupus erythematosus (g).

Lupus erythematosus

Subacute cutaneous LE is the most common LE-specific skin manifestation in the context of SjS.

Subacute cutaneous LE (Figure 2c) is the most common LE-specific skin manifestation in SjS. Out of 185 SjS patients treated at our hospital between January 2000 and December 2016, about 10 % had subacute cutaneous LE (unpublished data on our files). Conversely, SjS was found in 14 % of patients with subacute cutaneous LE [71]. According to a Japanese study, in Asian patients annular erythema is the equivalent of subacute cutaneous LE in patients of European descent [72]. Annular erythema of SjS is reported almost exclusively in Asian patients [73]. Only one study [74] reported this annular erythema in 9 % of non-Asian SjS patients.

Its clinical presentation with urticarial plaques, however, is comparable with LE tumidus (Figure 2d). Histology shows perivascular and periadnexial lymphocytic infiltration with dermal mucin deposits. Healing is achieved with hydroxychloroquine. In summary, it is still unclear if annular erythema of SjS is truly a separate entity or if it represents a manifestation of tumid LE/subacute cutaneous LE in the context of SjS [72, 75].

Other

Raynaud's phenomenon occurs in 16–35 % of SjS patients.

Raynaud's phenomenon (Figure 2e) occurs in 16–35 % [19, 64] of SjS patients. The clinical symptoms of Raynaud's phenomenon in SjS are usually milder than in other connective tissue diseases. In severe cases of Raynaud's syndrome in SjS, clinicians need to consider concomitant or developing SS. Other skin conditions associated with SjS include chronic urticaria [76], frontal fibrosing alopecia [77], vitiligo [78], and lichen planus [79].

In retrospective studies and case series, the following additional skin manifestations in SjS have been published [80–83]: Erythema-multiforme-like eruptions, Sweet syndrome, erythema nodosum, cutaneous nodular amyloidosis, lymphomatoid papulosis, and cutaneous T-cell lymphoma. Livedo patterns [81] have been reported in some cases, yet without coagulation diagnostics. There is a general association between antiphospholipid syndrome and connective tissue disease [84–86], thus coagulation diagnostics (antiphospholipid antibodies and lupus anticoagulant) need to be initiated in SjS patients with corresponding skin manifestations (livedo racemosa, Raynaud's symptoms, purpura) (Figure 2f). Chilblains have also been observed in SjS patients [83], and it is debatable whether some of these patients may have had Chilblain LE (Figure 2g), and if patients with erythema multiforme-like eruptions may have had subacute cutaneous LE as also named Rowell syndrome. The abovementioned dermatological diagnoses in the literature were usually made by clinical means and were not confirmed by tissue sampling.

Other organs

Serositis

In SjS, as compared with SLE [87], serositis is very rare. Asymptomatic pericarditis is common (33 %), but symptomatic pericarditis is only observed in 1 % of SjS patients [88]. Pleuritis has only been described in individual SjS patients [89].

Liver

Increased levels of liver enzymes are found in about one-third of SjS patients. Infectious causes need to be excluded first.

In a retrospective study, increased levels of liver enzymes were detected in one-third of SjS patients [90]. When liver enzymes are elevated in SjS patients, infectious causes need to be excluded first [91]. The prevalence of autoimmune hepatitis in SjS is estimated at 1–4 %, and that of primary biliary cholangitis at 4–9 % [91].

Lungs

Interstitial lung disease and its sequelae are frequent causes of death in SjS patients; therefore, early diagnosis and treatment are essential.

The lungs are affected in up to 20 % of SjS, mostly presenting as a dry cough [92]. Recurrent respiratory infections are observed in 10–35 % of SjS patients. Interstitial lung disease and its sequelae are frequent causes of death in SjS patients; therefore, early diagnosis and treatment are essential. Conventional X-ray investigations are insufficient for early diagnosis. Initially, and also later for monitoring

purposes, high-resolution computed tomography (HR-CT) as well as pulmonary function testing including measuring of diffusion capacity are recommended. Interstitial lung disease frequently presents as lymphocytic interstitial lung disease, characterized by cystic changes of the lung parenchyma and ground-glass opacities [93].

Kidneys

Affection of the kidneys in SjS is rare (≤ 10 %).

Affection of the kidneys in SjS is rare (≤ 10 %) [94]. The most common changes are tubulo-interstitial nephritis or membranoproliferative glomerulonephritis. In the early stages, tubulointerstitial nephritis presents with renal-tubular, metabolic acidosis. Investigation of the pH status is important for early diagnostics. Membranoproliferative glomerulonephritis is frequently caused by cryoglobulinemia. Prognosis is generally favorable. Since affection of the kidneys is often asymptomatic, regular monitoring is indicated (renal function parameters, protein-creatinine ratio, pH status [venous blood gases]) [94].

Laboratory investigations

Typical laboratory findings in SjS include ANA (79 %), Ro/SS-A antibodies (73 %), La/SS-B antibodies (45 %), rheumatoid factor RF (48 %), cryoglobulinemia (7 %), hypergammaglobulinemia, complement consumption (C3 and/or C4) [95, 96], and increased erythrocyte sedimentation rate (ESR) [50]. In some cases, patients may also display cytopenia [61]. A recent study with 10,500 patients showed that cryoglobulinemia, complement consumption, and La/SS-B antibodies were most highly correlated with systemic activity as measured by the ESSDAI [95].

Joints and muscles

Arthritis is one of the most common manifestations of SjS (15–90 %).

Arthritis is one of the most common manifestations of SjS (15–90 %) [97]. It is characterized by intermittent, symmetric, non-destructive polyarthritis. Axial involvement has been reported less frequently. If a patient presents with erosive arthritis, RA should be considered [97]. SjS patients with erosive arthritis have clinical, serological, and radiological characteristics of RA. Nevertheless, they differ from patients with "simple RA" in terms of additional organ involvement and genetic background [98].

Myalgia is common in SjS. Active myositis is rare, at 2 % [96], and is diagnosed within the context of inflammatory idiopathic myopathy or overlap syndrome.

Neuropsychiatric manifestation

Three-fourths of SjS patients show cognitive impairment, and many also have psychiatric disease (depression, anxiety disorders).

Depending on the publication, neurological symptoms occur in 18–45 % of SjS cases [99], frequently even before the diagnosis of SjS is confirmed [100]. We can differentiate between affection of the peripheral nervous system (PNS, 5.3–21 %, such as mono/polyneuropathy), the central nervous system (CNS, 2.5–60 %, such as ischemic stroke, neuromyelitis-optica spectrum diseases [NMOSD], symptoms resembling multiple sclerosis or amyotrophic lateral sclerosis) and autonomous nervous system (2–50 %, such as orthostatic hypotension, functional disorders of the bladder) [99]. Aquaporin-4 antibodies are detected in more than 80 % of SjS patients presenting with acute CNS manifestations [101]. These antibodies are typical for NMOSD. Coexistence of both diseases (SjS and NMOSD) in the same patient appears to be associated with severe neurological progression [101].

Three-fourths of SjS patients show cognitive impairment [102], and many also have psychiatric disease (such as depression or anxiety disorders [103]). After lymphoma, neuropsychiatric manifestations are the most common severe systemic manifestations of SjS [96].

Cardiovascular events

SjS is associated with an increased cardiovascular risk.

pSjS is associated with an increased risk for cerebrovascular events and myocardial infarction [68, 104]. Cardiovascular risk factors such as arterial hypertension, hypertriglyceridemia, dyslipidemia, and obesity are more common in pSjS, whereas SjS patients smoke less frequently compared to the general population [105]. Future studies are needed to determine if the risk of atherosclerosis is linked to the activity of SjS. SjS patients who have both Ro/SS-A antibodies and La/SS-B antibodies have a much higher risk of cerebrovascular events compared with the general population [104]. Antiphospholipid antibodies are also found more frequently in SjS patients than in the general population [86]; however, only about one-third of these SjS patients will develop obvious antiphospholipid syndrome [85].

Malignancy

SjS patients have a significantly increased (10–44-fold) risk for lymphoma.

SjS patients have a significantly increased (10–44-fold) risk for lymphoma [106]). Mucous-membrane-associated non-Hodgkin lymphoma [95] and other non-Hodgkin lymphomas were the most frequently observed types of lymphoma. Apart from Raynaud's symptoms, palpable purpura, and swelling of the parotid glands, the following parameters are being discussed as independent risk factors for the development of lymphoma in SjS patients: cryoglobulinemia, hypergammaglobulinemia, complement consumption in C4, FS ≥ 1 in tissue samples of the labial salivary glands, and lastly, ESSDAI at the time of diagnosis [70, 107, 108]. The higher the FS at the time of diagnosis in SjS patients, the earlier the occurrence of lymphoma is expected [107]. This appears to be caused by chronic stimulation of B cells in the exocrine glands and mucous membranes. An increased risk of malignancy (melanoma, non-Hodgkin lymphoma, breast cancer) has been reported in Ro/SS-A antibody-positive SjS patients [109]. SjS patients also have an increased risk for other malignancies apart from non-Hodgkin lymphoma [110, 111]. Other factors (sex, ethnicity, dysfunctional exocrine glands, immune dysregulation) appear to play a role in the development of malignancy. Thyroid cancer was more frequently found in women with SjS, and lung cancer more frequently in men with SjS [110].

ESSDAI/ESSPRI

Originally, scores for measuring SjS activity were focused solely on sicca symptoms [53]. Additional scores have been developed in recent years to quantify systemic activity of SjS. These are used primarily for clinical studies [112]. The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) [113] is used to assess disease activity. It comprises twelve areas: General health (fever, night sweats, weight loss), lymph nodes, involvement of glands (swelling of the salivary and/or tear glands), joints, skin, lungs, kidneys, or nerves, also hematological changes and other laboratory investigations (complement, cryoglobulins, hypergammaglobulinemia). Depending on activity, every area is allotted a score of 0–4; the scores are added and thereby provide a numerical activity score.

The *EULAR Sjögren's Syndrome-Patient Reported Index* (ESSPRI) [114] is used for quantifying symptoms reported by the patient and thus reflect her point of

view. This score comprises the patient's subjective assessment of sicca symptoms, fatigue, and pain. ESSDAI and ESSPRI complement each other but do not necessarily correlate [115].

Treatment

Since SjS can affect multiple organ systems, an interdisciplinary approach is required for individual treatment. Basically, we must differentiate between symptomatic treatment of sicca symptoms, and immunosuppressant treatment of organ involvement. Updated EULAR recommendations for treating SjS were published in 2020 [1]. These are presented in the next section (Table 3), but have also been modified according to the authors' experience and the current literature.

Since SjS can affect multiple organ systems, an interdisciplinary approach is required for individual treatment. Basically, we must differentiate between symptomatic treatment of sicca symptoms, and immunosuppressant treatment of organ involvement.

Sicca symptoms

Xerostomia

Reduced secretion of saliva results in higher incidences of caries in SjS patients. Topical fluorides, meticulous oral hygiene (dentist and patient), and refraining from smoking are recommended for prevention of caries. If the mouth is only slightly dry, non-pharmacological stimulation (such as sugar-free chewing gums or hard candies) may be prescribed. Moderate to severe xerostomia requires artificial saliva (mouth sprays, gels, or rinses) and/or pharmacological stimulation. This is achieved by muscarinic agonists (pilocarpine). Possible and also common side effects of pilocarpine include hyperhidrosis, hot flushes, headache, and nausea.

Xerophthalmia

Dry eyes are primarily treated with eye drops (at least twice a day) as well as eye gels or ointments. If eye drops are used four times a day or even more frequently, preservative-free preparations are recommended. Placing silicone plugs into the tear duct results in short-term, reversible obstruction of the tear duct and prevents rapid draining of the tear fluid. Ophthalmologists can also prescribe scleral lenses. Topical corticosteroids or topical non-steroidal anti-inflammatory drugs (NSAID) may be used for short-term treatment of severe keratoconjunctivitis sicca. If treatment is required for longer periods, ciclosporin eye drops are recommended. If patients do not respond to ciclosporin eye drops or cannot tolerate them, autologous serum eye drops may be used. Oral muscarinic agonists are considered a treatment of last resort for dry eyes.

Hydroxychloroquine is not recommended for treating xerophthalmia since studies have not shown a significant therapeutic effect as compared to placebo [116]. Steroid-sparing immunosuppressants (SsI) such as methotrexate, azathioprine, and mycophenolate mofetil are not recommended due to their potential side effects. Rituximab (anti-CD20 antibody) for treating sicca symptoms is still the subject of intense discussion since various randomized controlled trials have not consistently shown superiority to placebo. One study did observe a positive effect of rituximab on stimulated salivary secretion [117], but two others did not [118, 119]. In summary: Rituximab remains the most thoroughly studied and currently best therapeutic option for treating severe treatment-refractory sicca symptoms in SjS, particularly in view of severe long-term complications of sicca symptoms such as blindness. Any use of rituximab in SjS patients currently requires a strict indication. A recently published retrospective study found an increased

risk of severe COVID-19 infection in rheumatological patients, especially those pre-treated with rituximab [120].

Systemic symptoms

Glucocorticoids should only be administered at the minimum dose and duration required for controlling disease activity. Steroid-sparing immunosuppressants are to be preferred to save on glucocorticoid use. No specific substance from the group of SsI has proven superior to the others. Regarding the role of B cells in the pathogenesis of SjS, rituximab and belimumab (anti-BAFF antibody) represent promising therapeutic options which have proven their efficacy in treating SjS [121–123]. At this point in time, however, they are only recommended for patients with severe, refractory systemic disease. The indication for rituximab in SjS is usually in the context of vasculitis [124]. Regarding fatigue, rituximab usage remains controversial [117–119, 123, 125]. Fatigue in general is a huge diagnostic and therapeutic challenge in connective tissue disease including SjS. It may on the one hand be a symptom of related conditions (such as fibromyalgia), but on the other hand it may also be interpreted as a sign of SjS disease activity or even indicate malignancy, mostly non-Hodgkin's lymphoma. Regular physical exercise (endurance training) may prove beneficial. Hydroxychloroquine has been mentioned in reviews as a possible treatment option for fatigue, but there is currently no evidence of statistically significant improvement [126].

Future therapeutic options

The efficacy of various medications is currently being investigated in clinical studies [127]. It should be stressed that future therapeutic approaches are not limited to B cells but also target other areas of the immune response (janus kinase inhibitors, BDCA-2 antibodies, Il-12/23 antibodies). In SjS, as in other diseases, the long-term goal is to offer every patient an individualized treatment concept.

SjS and pregnancy

If maternal Ro/SS-A antibodies are passed through the placenta into the fetal circulation, autoimmune congenital heart block (CHB) in the fetus may occur as early as the 11th week of pregnancy.

If maternal Ro/SS-A antibodies are passed through the placenta into the fetal circulation, autoimmune congenital heart block (CHB) in the fetus may occur as early as the 11th week of pregnancy [128]. CHB is found in 2–5 % of fetuses from Ro/SS-A antibody-positive mothers [128]. Fetuses from mothers with SjS have an increased risk of CHB for several reasons. Most pregnancies in women with Ro/SS-A antibodies occur before full clinical manifestation of SjS, so SjS is usually neither suspected nor diagnosed in these young women before they become pregnant. These patients are therefore not treated with the appropriate medication [129]. SjS patients have high Ro/SS-A antibody titers, which is associated with an increased risk of fetal CHB [130]. In a subsequent pregnancy, the risk of fetal CHB may increase up to 18 % in Ro/SS-A antibody-positive women who have already borne an infant with CHB [131]. In Ro/SS-A antibody-positive women, weekly sonography of the fetal heart is recommended between the 16th and the 31st week of pregnancy to assess cardiac rhythm in the fetus. Such women were previously treated with glucocorticosteroids or intravenous immunoglobulins during pregnancy to prevent fetal CHB. However, this recommendation was not evidence-based [132]. A recent multicenter clinical study with hydroxychloroquine showed a reduction of CHB recurrence by more than half (from 18 % to 7.4 %) [131]. Use of hydroxychloroquine by Ro/SS-A antibody-positive women to prevent fetal CHB

may therefore be considered. Neonatal LE is rare and may present with subacute cutaneous LE, blood count anomalies (leukopenia, anemia, thrombocytopenia) and involvement of the liver [132].

Interdisciplinary patient management

Patients should visit an ophthalmologist and a pulmonologist once a year, and a dentist twice a year including professional teeth cleaning. Diagnostic imaging such as echocardiography, abdominal, lymph node, and parotid sonography once a year is useful. This also applies to laboratory investigations (blood count, differential blood count, renal function parameters, liver enzymes, C-reactive protein, erythrocyte sedimentation rate [ESR], complement, electrophoresis with quantitative analysis of immunoglobulins [IgG, IgA, IgM], venous blood gases [pH status], urinalysis, urine sedimentation with acanthocytes, protein/creatinine ratio in spontaneous urine).

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CME Questions/Lernerfolgskontrolle

1. Welche Faktoren spielen vermutlich eine Rolle bei der Pathogenese des SjS?

a) Infektionen
b) Rauchen
c) Medikamente
d) Hormone
e) Alle Antworten sind richtig.

2. Hinsichtlich der Epidemiologie des SjS – Welche Antwort ist richtig?

a) Das durchschnittliche Alter, in dem die Diagnose gestellt wird, liegt meist bei 20 Jahren.
b) Charakteristisch für das juvenile SjS sind rezidivierende Pleuritis und Myositis.
c) Das SjS ist häufiger bei Männern als bei Frauen.
d) Männer haben einen schwereren Verlauf der Erkrankung als Frauen.
e) Das SjS ist eine seltene rheumatologische Erkrankung.

3. Welches Kriterium wird **nicht zu den ACR/EULAR-Klassifikationskriterien 2016 gezählt?**

a) positive Ro/SS-A-Antikörper
b) positive La/SS-B-Antikörper
c) ocular staining score ≥ 5 in wenigstens einem Auge
d) Schirmer-Test ≤ 5mm/5min in wenigstens einem Auge
e) *unstimulated whole saliva flow rate* UWS ≤ 0,1 ml/min

4. Welche der unten angeführten Diagnosen muss ausgeschlossen werden, bevor die ACR/EULAR-Klassifikationskriterien von 2016 für das SjS angewendet werden können?

a) Psoriasis vulgaris
b) Basaliom
c) aktive Hepatitis-C-Infektion
d) aktinische Keratosen
e) Hidradenitis suppurativa

5. Folgende Hautmanifestation wird bei Patienten mit SjS häufig beobachtet?

a) leukozytoklastische Vaskulitis
b) Psoriasis vulgaris
c) Periorale Dermatitis
d) Herpes zoster
e) Akne vulgaris

6. Welche Therapie wird bei Xerophthalmie bei SjS nicht empfohlen?

a) befeuchtende Augentropfen
b) topische Kortikosteroide
c) TNF-alpha-Blocker
d) Ciclosporin A-Augentropfen
e) Pilocarpin-Augentropfen

7. Was trifft zu?

a) Trockene Haut und Juckreiz sind häufige kutane Symptome des SjS.
b) Migräne geht mit erhöhtem Risiko für ein Lymphom einher.
c) Bei schwerer Raynaud-Symptomatik im Rahmen eines SjS muss eine begleitende Psoriasis vulgaris in Betracht gezogen werden.
d) Fumarsäure kann als Zweitlinientherapie bei kutaner Vaskulitis eingesetzt werden.
e) Die Prävalenz des Juckreizes bei Patienten mit SjS ist niedriger im Vergleich zu der allgemeinen Bevölkerung.

8. Bezüglich klinischer Manifestationen beim SjS trifft zu?

a) Der ESSDAI ist ein Score, um die Krankheitsaktivität bei SjS zu messen.
b) Patienten mit SjS zeigen kaum neuropsychiatrische Manifestationen.
c) Eine Nierenbeteiligung beim SjS ist sehr häufig.
d) SjS-Patienten haben oft positive antimitochondriale Antikörper.
e) Die subjektiven und objektiven Symptome der Sicca-Symptomatik korrelieren miteinander.

9. Bezüglich Organmanifestationen bei SjS trifft zu?

a) Neurologische Manifestationen beim SjS sind extrem selten.
b) Das Raynaud-Phänomen tritt bei weniger als 5 % der SjS Patienten
c) Eine Autoimmunhepatitis wird bei mehr als 10 % der SjS-Patienten festgestellt.
d) Die Nierenbeteiligung beim SjS tritt sehr häufig auf.
e) SjS-Patienten haben oft Arthralgien und Myalgien.

10. Patienten mit SjS haben eine gute Prognose, ...

a) jedoch besteht ein erhöhtes Risiko für die Entwicklung eines Lymphoms.
b) eine Optimierung kardiovaskulärer Risikofaktoren ist nicht notwendig.
c) aber sie haben oft eine symptomatische Serositis.
d) allerdings besteht kein erhöhtes Risiko für einen fetalen AV-Block während der Schwangerschaft.
e) aber es besteht kein erhöhtes Risiko für die Entwicklung von Schilddrüsenkarzinomen.

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 30. September 2022. Die richtige Lösung zum Thema „Das Spektrum melanozytärer Nävi und deren klinische Bedeutung“ in Heft 4 (April 2022) ist: 1c, 2d, 3c, 4e, 5e, 6a, 7d, 8c, 9a, 10c

Bitte verwenden Sie für Ihre Einsendung das aktuelle Formblatt auf der folgenden Seite oder aber geben Sie Ihre Lösung online unter http://jddg.akademie-dda.de ein.

