

Early Neuropsychiatric and Cutaneous Manifestations as Sentinel Signs of Systemic Disease

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ABSTRACT

Systemic diseases may present with cutaneous, neurological, or psychiatric manifestations before the classical diagnostic phenotype becomes fully established, creating a clinically relevant prediagnostic window. This study analyzed the main neuropsychiatric and cutaneous manifestations associated with systemic lupus erythematosus, Sjögren syndrome, Behçet disease, sarcoidosis, antiphospholipid syndrome, and systemic vasculitis, with emphasis on their temporal relationship with definitive diagnosis and their potential value as early warning signs. An integrative literature review based on the scientific method was conducted using evidence

obtained from PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The analysis considered the type of systemic disease, cutaneous findings, neurological or psychiatric manifestations, predominant pathophysiological mechanisms, and timing in relation to diagnosis. The reviewed evidence showed that systemic lupus erythematosus presented the broadest clinical heterogeneity, while neurological manifestations in Sjögren syndrome may precede classical glandular symptoms. Recurrent mucosal ulceration was particularly relevant in Behçet disease, granulomatous skin lesions provided diagnostic support in sarcoidosis, and vascular skin abnormalities were associated with neurological ischemic events in antiphospholipid syndrome and systemic vasculitis. The most recurrent mechanisms included autoimmune-inflammatory, vascular-thrombotic, vasculitic, and granulomatous pathways. Clinically relevant combinations included purpura with peripheral neuropathy, livedoid skin changes with cerebrovascular events, recurrent mucosal ulceration with neurological inflammation, photosensitive lesions with neuropsychiatric abnormalities, and granulomatous skin disease with neurological involvement. These findings indicate that isolated manifestations have limited specificity, whereas coherent multisystem patterns may increase suspicion of an underlying systemic disorder. Integrating dermatological and neuropsychiatric findings into multidisciplinary clinical assessment may contribute to earlier diagnostic recognition and reduce delays before significant organ involvement develops.

KEYWORDS

systemic diseases, neuropsychiatric manifestations, cutaneous manifestations, early diagnosis, sentinel signs, systemic lupus erythematosus, Sjögren syndrome, Behçet disease, sarcoidosis, antiphospholipid syndrome, systemic vasculitis, peripheral neuropathy, autoimmune diseases, vascular manifestations

INTRODUCTION

Systemic diseases frequently challenge conventional diagnostic models because their earliest manifestations may arise outside the organ system that ultimately defines the disorder. Autoimmune, inflammatory, thrombotic, and granulomatous conditions can evolve through an extended prediagnostic phase in which patients experience apparently isolated dermatological, neurological, cognitive, behavioral, or psychiatric abnormalities before the development of a recognizable systemic phenotype. In this context, the skin and nervous system represent two particularly relevant clinical interfaces. Both are highly responsive to immunological, vascular, metabolic, and inflammatory disturbances and may therefore reveal pathological processes before conventional laboratory abnormalities or major-organ involvement becomes sufficiently evident to establish a definitive diagnosis. Recognizing these manifestations as potential sentinel signs rather than unrelated complaints may consequently shorten diagnostic pathways and allow earlier identification of systemic disease [1], [2].

The diagnostic relevance of this problem is considerable because many systemic disorders are heterogeneous by nature. Systemic lupus erythematosus (SLE), Sjögren syndrome, Behçet disease, sarcoidosis, antiphospholipid syndrome (APS), and systemic vasculitides can affect multiple organs with markedly different combinations of symptoms among patients [1], [8], [10], [14], [17], [20]. Their clinical expression does not necessarily follow a predictable chronological sequence. In some individuals, classical systemic manifestations appear early; in others, subtle neurological symptoms, psychiatric disturbances, mucocutaneous abnormalities, vascular skin lesions, or peripheral neuropathic complaints may dominate the initial presentation. Such variability creates an important diagnostic gap between the biological onset of disease and the moment at which sufficient clinical evidence accumulates to support formal recognition of the underlying systemic disorder.

Cutaneous manifestations are particularly important within this diagnostic interval because the skin provides a directly observable representation of inflammatory and vascular processes occurring throughout the body. Erythematous eruptions, photosensitivity, purpura, livedo, ulcers, nodules, mucosal lesions, vasculitic lesions, alopecia, and other dermatological findings may represent more than local disease. Depending on their morphology, distribution, persistence, recurrence, and associated systemic manifestations, these abnormalities may provide evidence of immune-complex deposition, small-vessel inflammation, thrombosis, granulomatous inflammation, or autoantibody-mediated

disease [2], [11], [16], [18], [19]. The clinical value of these findings is therefore not limited to dermatological diagnosis; in selected patients, they may constitute an accessible marker of a pathological process that has not yet been recognized as systemic.

SLE provides one of the clearest examples of this relationship. It is a chronic autoimmune condition capable of producing mucocutaneous, musculoskeletal, hematological, renal, cardiovascular, pulmonary, and neuropsychiatric involvement [1]. Cutaneous lupus encompasses several phenotypes, including acute, subacute, and chronic forms, which may occur independently or in association with systemic disease [2]. Importantly, patients initially presenting with disease apparently limited to the skin do not constitute a homogeneous prognostic group. A systematic review of longitudinal studies demonstrated that progression from cutaneous lupus erythematosus to systemic lupus can occur over time, with reported rates varying considerably according to study population, diagnostic criteria, disease subtype, and duration of follow-up [3]. Positive antinuclear antibodies, hematological abnormalities, and the accumulation of additional classification features have been identified among factors associated with subsequent systemic disease [3]. These observations illustrate the potential importance of viewing selected dermatological manifestations longitudinally rather than as isolated events.

The nervous system provides another major source of early diagnostic information. Neuropsychiatric manifestations associated with systemic disease include a broad spectrum ranging from headache, neuropathic symptoms, seizures, cerebrovascular events, and movement abnormalities to cognitive dysfunction, mood disorders, psychosis, confusional states, and other behavioral changes. Their interpretation is difficult because many of these symptoms are nonspecific and common in the general population. Nevertheless, when they appear in an appropriate clinical context or coexist with inflammatory, vascular, immunological, or dermatological abnormalities, they may represent manifestations of a systemic pathological process rather than an independent neurological or psychiatric disorder [5], [6].

Neuropsychiatric systemic lupus erythematosus exemplifies the complexity of this relationship. Neurological and psychiatric involvement in SLE is clinically heterogeneous, and proposed mechanisms include autoantibody-mediated neuronal injury, inflammatory pathways, disruption of the blood-brain barrier, cytokine-mediated effects, and thrombotic or ischemic mechanisms [5], [6]. Patients may develop cognitive impairment, seizures, cerebrovascular disease, headache syndromes, mood disturbances, psychotic manifestations, or peripheral nervous system abnormalities. Because several of these manifestations are not specific to lupus, determining their attribution to systemic autoimmunity requires integration of clinical history, disease activity, laboratory findings, neuroimaging, vascular risk factors, medication exposure, and alternative diagnoses [5], [6]. The diagnostic problem becomes particularly important when neurological or psychiatric abnormalities occur before SLE has been formally recognized.

A similar temporal challenge exists in Sjögren syndrome. Although traditionally associated with ocular and oral dryness, Sjögren syndrome is a systemic autoimmune disease capable of involving the peripheral and central nervous systems and producing a wide range of extraglandular manifestations [13]–[15]. Neurological manifestations may include peripheral neuropathies, sensory abnormalities, autonomic dysfunction, cranial neuropathies, cognitive symptoms, central nervous system involvement, and other neurological syndromes, while psychiatric symptoms may coexist or complicate clinical assessment [14], [15]. Importantly, neurological manifestations can emerge before classical sicca symptoms become sufficiently prominent to suggest Sjögren syndrome, creating the possibility that a patient may initially be evaluated within neurology or psychiatry rather than rheumatology [14], [15]. Cutaneous manifestations, including vasculitic lesions and other inflammatory abnormalities, may further provide evidence of systemic involvement [13], [16].

Behçet disease offers another model in which mucocutaneous and neurological findings must be interpreted as interconnected components of multisystem inflammation. Recurrent oral and genital ulceration and other skin manifestations may precede or accompany ocular, vascular, gastrointestinal, articular, and neurological disease. Neuro-Behçet disease represents one of its most clinically significant complications and may involve parenchymal inflammatory syndromes or vascular manifestations such as cerebral venous thrombosis [8], [9]. International recommendations emphasize that the neurological manifestations of Behçet disease require careful differentiation from infectious, demyelinating, vascular, and other inflammatory neurological disorders [8]. Recognition of recurrent mucocutaneous lesions in a patient presenting with unexplained neurological symptoms may therefore substantially alter the diagnostic hypothesis and direct appropriate systemic evaluation.

Sarcoidosis further illustrates the importance of combining dermatological and neurological information. As a granulomatous multisystem disorder, sarcoidosis can involve the lungs, lymphatic system, skin, eyes, nervous system, and other organs. Cutaneous sarcoidosis is notable for its morphological diversity, while neurosarcoidosis can affect the meninges, cranial nerves, brain parenchyma, spinal cord, hypothalamic-pituitary structures, and peripheral nervous system [10]–[12]. Because neurological involvement can mimic infectious, neoplastic, demyelinating, and other inflammatory diseases, diagnosis frequently depends on recognizing evidence of systemic granulomatous disease outside the nervous system [10], [12]. In this context, accessible cutaneous lesions can have particular diagnostic value because they may offer a clinically visible indication of systemic inflammation and, where appropriate, a potential site for histopathological confirmation.

Vascular manifestations establish another important link between the skin and nervous system. APS is primarily characterized by a thrombotic predisposition associated with antiphospholipid antibodies, but its clinical phenotype extends beyond classical large-vessel thrombosis. Neurological manifestations include ischemic stroke, transient ischemic events, cerebral venous thrombosis, seizures, headache, and cognitive dysfunction, among other reported neurological associations [17]. Simultaneously, cutaneous abnormalities such as livedo and thrombotic or ischemic skin lesions may provide visible evidence of an underlying vascular process [18]. The coexistence of neurological and cutaneous vascular manifestations may therefore be diagnostically informative, particularly in younger patients or in individuals without conventional explanations for recurrent vascular events.

The systemic vasculitides reinforce this principle through direct inflammatory injury to blood vessels. ANCA-associated vasculitis encompasses granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis, all of which may produce dermatological and neurological manifestations [19], [20]. Cutaneous involvement includes petechiae, palpable purpura, ulcerative lesions, livedoid changes, nodules, and other abnormalities reflecting vascular inflammation or ischemia [19]. In a large international cohort, cutaneous manifestations were documented across the major forms of ANCA-associated vasculitis, and certain skin findings were associated with severe systemic manifestations, supporting the diagnostic and potentially prognostic importance of dermatological assessment [19]. Neurological involvement, particularly peripheral neuropathy, mononeuritis multiplex, and central nervous system complications in selected forms of vasculitis, may likewise represent a major source of morbidity and occasionally an early reason for medical consultation [20].

Despite these established associations, an important conceptual limitation persists in clinical practice: manifestations are frequently analyzed according to specialty rather than according to the systemic mechanisms connecting them. A patient with recurrent rash may initially be evaluated exclusively for dermatological disease, whereas a patient with cognitive changes, neuropathy, headache, or psychiatric manifestations may follow an entirely separate neurological or psychiatric diagnostic pathway. When these manifestations occur at different moments, are individually mild, or are separated by months or years, their systemic relationship may remain unrecognized. This fragmentation is particularly relevant in diseases characterized by relapsing-remitting activity, fluctuating autoantibody profiles, incomplete classification criteria during early disease, or manifestations that precede the development of definitive organ involvement.

The concept of a **sentinel clinical manifestation** is therefore useful for understanding the prediagnostic phase of systemic disease. In this framework, a sentinel manifestation is not necessarily pathognomonic, nor does its presence independently establish a diagnosis. Instead, it represents a clinical event that acquires diagnostic significance when interpreted alongside other findings, temporal patterns, risk factors, laboratory abnormalities, histopathology, imaging, or subsequent disease evolution. Such a framework avoids overdiagnosis while emphasizing the importance of pattern recognition. Photosensitive eruptions, recurrent oral or genital ulceration, palpable purpura, livedo, unexplained neuropathy, cognitive deterioration, seizures, atypical cerebrovascular events, psychiatric changes, or combinations of these abnormalities may warrant broader systemic assessment when their characteristics cannot be adequately explained by a localized disorder [2], [8], [14], [17]–[20].

Another clinically important issue is that the diagnostic value of cutaneous and neuropsychiatric manifestations may increase substantially when they occur together. Individually, headache, anxiety, depressive symptoms, rash, pruritus, or nonspecific sensory symptoms have limited specificity. However, combinations such as recurrent mucosal ulceration with inflammatory neurological disease, livedoid skin changes with unexplained cerebral ischemia, purpura

with peripheral neuropathy, photosensitive cutaneous lupus with cognitive or neurological abnormalities, or granulomatous skin lesions with cranial neuropathy create a substantially different diagnostic context. The simultaneous consideration of these signs may increase clinical suspicion for a systemic inflammatory, autoimmune, granulomatous, or thrombotic process and encourage earlier multidisciplinary investigation.

Previous literature has extensively characterized individual diseases and their organ-specific manifestations. Reviews of SLE have described both mucocutaneous and neuropsychiatric involvement [1], [2], [5], [6]; studies of Sjögren syndrome have emphasized neurological, psychiatric, and cutaneous manifestations [13]–[16]; consensus recommendations have defined the diagnostic approach to neuro-Behçet disease [8]; and reviews of sarcoidosis, APS, and systemic vasculitis have documented clinically relevant neurological and dermatological phenotypes [10]–[12], [17]–[20]. Nevertheless, these conditions are often examined independently, and less emphasis has been placed on a transversal clinical question: **which neuropsychiatric and cutaneous findings can function as early warning signals of systemic disease before the underlying diagnosis has been established?**

Addressing this question is relevant for several reasons. First, diagnostic delay in systemic inflammatory and autoimmune disease can permit progressive organ injury before disease-modifying treatment is initiated. Second, early symptoms may be attributed to common primary psychiatric, neurological, or dermatological conditions, especially when systemic laboratory findings are absent or incomplete. Third, fragmentation between specialties can delay recognition of meaningful combinations of manifestations. Finally, improved characterization of prediagnostic clinical patterns may facilitate more rational decisions regarding when serological testing, neuroimaging, vascular assessment, histopathological examination, or rheumatological evaluation is justified.

Accordingly, the present study examines neuropsychiatric and cutaneous manifestations associated with systemic diseases from a temporal and integrative perspective, emphasizing findings that may occur before definitive systemic diagnosis. A structured integrative review and comparative clinical synthesis were adopted to examine evidence concerning SLE, Sjögren syndrome, Behçet disease, sarcoidosis, APS, and systemic vasculitides. Particular attention was directed toward the type of manifestation, the biological mechanism that could explain the association, the temporal relationship between symptom appearance and systemic diagnosis, and the potential clinical value of combining dermatological and neuropsychiatric information. Evidence from reviews, cohort studies, consensus recommendations, and clinically relevant observational investigations was considered in order to construct a cross-disease framework rather than an organ-specific description.

The central research question was: **Which neuropsychiatric and cutaneous manifestations of systemic diseases can appear before formal diagnosis and function as clinically meaningful warning signals for earlier recognition?** A secondary question was whether combinations of manifestations involving both the nervous system and skin provide greater diagnostic information than isolated findings considered independently. Based on existing evidence, the working hypothesis proposes that selected cutaneous and neuropsychiatric manifestations precede definitive diagnosis in a clinically relevant subset of systemic diseases and that their combined evaluation can identify recognizable patterns associated with autoimmune, inflammatory, granulomatous, vasculitic, or thrombotic mechanisms [3], [8], [10], [14], [17], [19].

The design of the study is aligned with this hypothesis by organizing the available evidence according to clinical presentation, underlying systemic disorder, temporal sequence, and potential diagnostic relevance. Rather than considering skin, neurological, and psychiatric findings as independent complications occurring after diagnosis, the analysis focuses specifically on their possible role during the prediagnostic interval. This approach permits comparison across diseases with distinct pathophysiological mechanisms while identifying recurring clinical patterns such as immune-mediated inflammation, vascular injury, thrombosis, granulomatous infiltration, and autoantibody-associated tissue dysfunction. Such integration may provide a more clinically useful representation of how systemic diseases first become visible in routine practice.

Ultimately, early recognition does not depend on assigning high specificity to every isolated symptom but on identifying meaningful constellations of findings and placing them within the appropriate temporal and biological context. The skin may reveal inflammation or vascular injury that is otherwise clinically silent, whereas neurological and psychiatric manifestations may indicate systemic involvement before conventional disease-defining features have

fully developed. Understanding how these signs converge offers an opportunity to move from reactive diagnosis—established only after overt multisystem disease—to earlier pattern-based recognition. Therefore, investigating neuropsychiatric and cutaneous manifestations as potential sentinel signals may contribute to reducing diagnostic delay, guiding multidisciplinary evaluation, and improving the timely recognition of systemic diseases before irreversible organ damage develops.

DEVELOPMENT

Systemic diseases frequently evolve through heterogeneous clinical trajectories in which the first manifestations may occur in organs that are not traditionally considered the primary site of disease. This phenomenon is particularly relevant in autoimmune, inflammatory, granulomatous, thrombotic, and vasculitic disorders, where the skin and nervous system may become clinically involved before the systemic nature of the underlying process is formally recognized. From a diagnostic perspective, these early manifestations represent a major challenge because many of them are individually nonspecific. However, when their morphology, temporal pattern, recurrence, associated symptoms, and biological plausibility are evaluated together, they may provide clinically meaningful evidence of an evolving multisystem disorder.

The central premise of this study is that neuropsychiatric and cutaneous manifestations should not be viewed exclusively as complications of already diagnosed systemic disease. In a substantial proportion of patients, these findings can constitute the earliest observable expression of systemic immune dysregulation, vascular injury, inflammation, thrombosis, or granulomatous infiltration. This distinction is clinically important because diagnostic models traditionally rely on the accumulation of sufficient criteria to classify a disease, whereas patients frequently experience symptoms before such criteria are fully met. Consequently, a gap may emerge between the biological onset of disease and its formal clinical diagnosis.

The skin as an early marker of systemic disease

The skin is uniquely positioned as a diagnostic organ because it allows direct visual examination of inflammatory and vascular processes that may be occurring simultaneously in internal tissues. Cutaneous signs may therefore function as externally visible markers of systemic pathophysiology. Depending on the underlying mechanism, the skin may show erythema, photosensitivity, purpura, livedo, ulcers, papules, nodules, alopecia, mucosal lesions, vasculitic eruptions, or granulomatous changes. These findings can reflect immune-complex deposition, vascular inflammation, microthrombosis, autoantibody-mediated injury, inflammatory cell infiltration, or altered tissue repair [2], [11], [16], [18], [19].

The diagnostic value of cutaneous manifestations depends not only on their presence but also on their clinical context. A nonspecific rash may have limited value when considered in isolation; however, recurrent photosensitive eruptions in association with arthralgia, cytopenias, cognitive changes, or serological abnormalities may substantially increase suspicion for systemic autoimmune disease. Similarly, livedoid changes associated with neurological ischemic events may suggest an underlying thrombotic disorder, while palpable purpura associated with neuropathic symptoms may raise concern for systemic vasculitis.

Among systemic diseases, systemic lupus erythematosus provides a particularly important model of the relationship between cutaneous findings and later systemic disease. Cutaneous lupus erythematosus includes acute, subacute, and chronic phenotypes, each of which may occur in patients with or without systemic involvement [2]. The clinical spectrum includes malar eruption, photosensitive lesions, discoid plaques, subacute annular or papulosquamous lesions, alopecia, oral ulcers, and vascular abnormalities. These manifestations may precede the diagnosis of systemic lupus, remain limited to the skin, or evolve into more widespread disease over time.

The systematic review by Curtiss, Walker, and Chong demonstrated that progression from cutaneous lupus erythematosus to systemic lupus occurs in a clinically relevant subset of patients, although the reported frequency varies according to the population studied, follow-up period, classification criteria, and cutaneous subtype [3]. This progression supports the concept that cutaneous lupus can represent an early stage in the systemic autoimmune continuum rather than an entirely independent process in every case. Additional clinical and serological features, including antinuclear antibody positivity and hematological abnormalities, may help identify patients with greater probability of systemic evolution [3].

These findings have direct implications for clinical reasoning. A patient with apparently isolated cutaneous lupus should not necessarily be regarded as having a purely dermatological disease without longitudinal assessment. Instead, the presence of compatible systemic symptoms, hematological abnormalities, neurological complaints, renal findings, or persistent autoantibody positivity may indicate the need for more extensive evaluation. The skin can therefore serve as the initial clinical entry point into a diagnostic process that ultimately identifies multisystem disease.

Neuropsychiatric manifestations as sentinel clinical events

The neurological and psychiatric manifestations of systemic disease are especially difficult to interpret because they frequently overlap with common primary neurological and mental health conditions. Headache, anxiety, depression, fatigue, cognitive complaints, paresthesia, sleep disturbances, seizures, or dizziness can occur in many clinical settings. Nevertheless, these manifestations may also result from immune-mediated inflammation, vascular injury, autoantibody activity, cytokine dysfunction, thrombosis, blood-brain barrier disruption, or direct infiltration of neural tissue [5], [6], [10], [14], [17], [20].

The concept of a neuropsychiatric sentinel event is therefore based on clinical context rather than specificity alone. A psychiatric or neurological symptom becomes more diagnostically meaningful when it is atypical for the patient's age, follows an unusual course, is associated with other systemic abnormalities, lacks a conventional explanation, or occurs together with dermatological signs. For instance, unexplained psychosis in a young patient with photosensitive rash and hematological abnormalities carries a substantially different diagnostic meaning than isolated psychosis. Similarly, multifocal neuropathy occurring together with palpable purpura may indicate systemic vascular inflammation rather than a primary neuropathic disorder.

In systemic lupus erythematosus, neuropsychiatric manifestations encompass both central and peripheral nervous system disorders. They may include seizures, cerebrovascular events, cognitive dysfunction, mood disorders, psychosis, confusional states, headache syndromes, movement disorders, cranial neuropathies, and peripheral neuropathies [5], [6]. The mechanisms responsible for these manifestations are diverse. Proposed pathways include inflammatory cytokine activation, autoantibody-mediated neuronal damage, immune-complex injury, endothelial dysfunction, thrombosis, disruption of the blood-brain barrier, and accelerated vascular disease [6].

This heterogeneity creates major challenges in attribution. Not every neurological or psychiatric manifestation in a patient with lupus is directly caused by lupus, and differential diagnosis must include infection, metabolic disorders, medication effects, primary psychiatric disease, structural neurological conditions, and traditional vascular risk factors. However, this complexity does not diminish the potential importance of early neuropsychiatric manifestations. On the contrary, it emphasizes the need for systematic integration of clinical, immunological, dermatological, radiological, and neurological information.

Systemic lupus erythematosus: convergence of cutaneous and neuropsychiatric manifestations

SLE represents one of the most relevant systemic diseases for investigating the interaction between skin manifestations and neuropsychiatric symptoms. The disease is characterized by loss of immune tolerance, autoantibody formation, immune-complex deposition, complement activation, and inflammatory damage across multiple organs [1]. Its clinical heterogeneity means that no single pattern defines all patients.

Cutaneous manifestations may develop early, while neuropsychiatric abnormalities may emerge either before, during, or after the diagnosis of systemic disease. This temporal variability is clinically important. A patient initially treated for recurrent photosensitive lesions may later develop cognitive dysfunction, mood symptoms, seizures, or cerebrovascular events. Conversely, another patient may first present to neurology or psychiatry and only subsequently develop characteristic dermatological or systemic abnormalities.

The coexistence of both types of manifestation may significantly increase diagnostic suspicion. Cutaneous lupus provides visible evidence of autoimmune activity, while neurological or psychiatric symptoms may suggest systemic extension or vascular involvement. According to Meier et al., neuropsychiatric manifestations remain an important source of morbidity in lupus and can involve several clinical domains, including mood, cognition, cerebrovascular function, and seizure activity [5]. Jeltsch-David and Muller further highlighted the complex interaction between autoantibodies, vascular mechanisms, inflammatory mediators, and blood-brain barrier dysfunction in the pathogenesis of neuropsychiatric lupus [6].

This combined framework supports a key argument of the present study: diagnostic value increases when manifestations are interpreted as part of a multisystem pattern rather than as independent events.

Sjögren syndrome: neurological manifestations may precede classical sicca symptoms

Sjögren syndrome is traditionally recognized through dryness of the eyes and mouth caused by autoimmune involvement of exocrine glands. However, this representation does not adequately reflect the systemic nature of the disease. Patients may develop neurological, cutaneous, pulmonary, renal, hematological, vascular, musculoskeletal, and constitutional manifestations [13]–[16].

Neurological involvement is particularly important because it may precede the development or recognition of classic sicca symptoms. Peripheral nervous system manifestations include sensory neuropathy, painful small-fiber neuropathy, sensory neuronopathy, mononeuropathy, cranial neuropathy, and autonomic dysfunction. Central nervous system involvement may include cognitive disturbances, myelopathy, inflammatory lesions, and other less frequent presentations [14], [15].

This temporal relationship is diagnostically significant. When neurological symptoms appear before dryness becomes clinically prominent, patients may undergo extensive neurological investigations without consideration of Sjögren

syndrome. Teixeira et al. emphasized that neurological manifestations may represent an important component of the disease and, in some patients, may precede the diagnosis [15]. More recent literature also recognizes psychiatric and cognitive manifestations as clinically relevant features that can complicate presentation and delay recognition [14].

Cutaneous involvement further broadens the clinical spectrum. Patients may develop xerosis, vasculitic lesions, purpura, urticaria-like eruptions, Raynaud phenomenon, and other cutaneous abnormalities [13], [16]. Vasculitic skin disease is particularly important because it may indicate systemic immune-complex activity and may coexist with peripheral neuropathy. Thus, the combination of purpura and neurological deficits in a patient with previously unexplained systemic symptoms should prompt consideration of an autoimmune process such as Sjögren syndrome.

Behçet disease: mucocutaneous disease as a clue to neurological inflammation

Behçet disease is a systemic inflammatory disorder characterized by recurrent oral ulceration, genital ulcers, ocular inflammation, skin lesions, vascular disease, and variable involvement of the gastrointestinal and nervous systems. Its diagnosis is primarily clinical because no single laboratory biomarker is sufficiently specific to confirm the disease.

Mucocutaneous manifestations often constitute the earliest and most persistent component of Behçet disease. Recurrent oral aphthae are especially common and may precede more severe systemic manifestations by years. Genital ulceration, acneiform lesions, erythema nodosum-like lesions, and other cutaneous abnormalities may subsequently appear [7].

Neurological involvement, known as neuro-Behçet disease, represents one of the most serious forms of systemic involvement. It can be divided broadly into parenchymal and non-parenchymal patterns. Parenchymal disease often affects the brainstem, cerebral hemispheres, spinal cord, or basal ganglia, whereas non-parenchymal involvement may include cerebral venous thrombosis and other vascular manifestations [8], [9].

The diagnostic importance of mucocutaneous history becomes particularly evident when a patient presents with neurological disease before Behçet disease has been formally recognized. A history of recurrent painful oral or genital ulcers may initially appear unrelated to neurological symptoms. However, once both features are integrated, the probability of a systemic inflammatory disorder becomes more apparent. International recommendations for neuro-Behçet disease emphasize the importance of combining neurological findings with systemic and mucocutaneous evidence because neurological manifestations can mimic multiple infectious, vascular, inflammatory, and demyelinating disorders [8].

The temporal sequence of these manifestations makes Behçet disease an illustrative example of why detailed clinical history is essential. The earliest clues to systemic disease may not be found in current laboratory results but in recurrent mucocutaneous episodes occurring months or years before neurological deterioration.

Sarcoidosis: visible granulomatous disease and occult neurological involvement

Sarcoidosis is a multisystem granulomatous disorder characterized by noncaseating granuloma formation in affected tissues. Although pulmonary and lymphatic involvement are most common, the disease may also affect the skin, eyes, nervous system, heart, liver, and other organs.

Cutaneous sarcoidosis is clinically diverse and may present as papules, plaques, nodules, lupus pernio, scar infiltration, or other lesions [11]. Because these manifestations are directly accessible to physical examination and biopsy, they can play an important diagnostic role. In a patient with unexplained systemic or neurological findings, recognition of a compatible cutaneous lesion may provide the clue required to pursue granulomatous disease.

Neurosarcoidosis can affect almost any component of the nervous system. Cranial neuropathies, meningeal disease, hypothalamic-pituitary involvement, myelopathy, seizures, cognitive abnormalities, peripheral neuropathies, and intracranial mass-like lesions have all been described [10], [12]. The disease can mimic multiple alternative diagnoses, including infection, malignancy, demyelinating disorders, and other inflammatory diseases.

Bradshaw et al. emphasized that diagnosis requires integration of neurological findings with evidence of systemic sarcoidosis whenever possible [10]. This is particularly relevant when cutaneous lesions coexist because biopsy of accessible skin abnormalities may help establish granulomatous pathology without requiring invasive neurological procedures. Thus, dermatological findings may facilitate recognition of a systemic disease whose most clinically concerning manifestation is neurological.

Sarcoidosis therefore provides a powerful example of diagnostic complementarity between skin and nervous system findings. A neurological syndrome alone may have a broad differential diagnosis, and a cutaneous lesion alone may seem benign. Their coexistence, however, can substantially narrow diagnostic possibilities.

Antiphospholipid syndrome: the vascular link between skin and nervous system

Antiphospholipid syndrome is an autoimmune thrombotic disorder characterized by arterial, venous, or microvascular thrombosis and/or pregnancy morbidity in association with persistent antiphospholipid antibodies. Although the classical diagnostic framework emphasizes thrombosis and obstetric complications, APS can produce a much broader range of neurological and cutaneous manifestations.

Neurological manifestations frequently result from thrombotic mechanisms. Ischemic stroke and transient ischemic attacks are among the best-established complications, but cerebral venous thrombosis, seizures, migraine-like

headache, movement disorders, cognitive abnormalities, and other neurological manifestations have also been reported [17].

Cutaneous manifestations may include livedo reticularis or livedo racemosa, ulcers, superficial thrombophlebitis, ischemic lesions, digital necrosis, and other findings related to impaired vascular perfusion or thrombosis [18]. These abnormalities are important because they may provide visible evidence of systemic vascular dysfunction before a major thrombotic event occurs.

The relationship between skin and nervous system manifestations is especially relevant in young adults with cerebrovascular events that cannot be explained by traditional cardiovascular risk factors. The coexistence of livedoid skin changes, recurrent thrombosis, thrombocytopenia, pregnancy morbidity, or autoimmune features should prompt consideration of APS.

This pattern demonstrates another major principle of the study: the same systemic mechanism may produce clinically different manifestations in multiple organs. In APS, vascular obstruction can become visible on the skin while simultaneously causing cerebral ischemia. Recognizing this shared mechanism can transform apparently unrelated findings into a coherent diagnostic pattern.

Systemic vasculitis: vascular inflammation expressed in skin and peripheral nerves

Systemic vasculitides represent a heterogeneous group of diseases characterized by inflammation and damage of blood vessel walls. Their clinical manifestations depend on vessel size, anatomical distribution, immune mechanism, and affected organs. Because both the skin and peripheral nervous system contain extensive vascular networks, they are frequently involved.

Cutaneous manifestations of systemic vasculitis include palpable purpura, petechiae, ulcers, livedo, nodules, infarcts, digital ischemia, and necrosis. In ANCA-associated vasculitis, dermatological involvement may occur across granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis [19].

Micheletti et al. demonstrated that cutaneous findings are frequent in ANCA-associated vasculitis and may correlate with systemic disease patterns [19]. Although these lesions are not always disease-specific, they can provide an early clue to vascular inflammation, particularly when accompanied by renal, respiratory, constitutional, or neurological abnormalities.

Neurological involvement is also clinically significant. Peripheral neuropathy and mononeuritis multiplex are characteristic manifestations of several systemic vasculitides and result from ischemic injury caused by inflammation of the vasa nervorum [20]. Patients may develop asymmetric pain, sensory loss, weakness, or multifocal nerve deficits. Because these symptoms may initially appear localized, diagnosis can be delayed unless systemic features are actively sought.

The combination of palpable purpura and painful asymmetric neuropathy is particularly important because it suggests a shared vascular inflammatory mechanism. This association exemplifies the diagnostic benefit of integrating findings from different organ systems rather than evaluating them separately.

Pathophysiological mechanisms connecting skin and nervous system manifestations

The coexistence of neuropsychiatric and cutaneous abnormalities across different systemic diseases is not coincidental. Several biological mechanisms can simultaneously affect the skin and nervous system.

One major mechanism is autoantibody-mediated injury. In autoimmune disease, antibodies directed against cellular, endothelial, phospholipid, or neural targets may contribute to tissue dysfunction. SLE and APS provide prominent examples in which autoantibodies participate in vascular, inflammatory, or neuronal injury [6], [17].

A second mechanism involves immune-complex deposition. Circulating immune complexes can activate complement and promote vascular inflammation. When small vessels are affected, manifestations may appear in the skin as purpura or vasculitic lesions and in peripheral nerves as ischemic neuropathy.

A third mechanism is endothelial dysfunction and thrombosis. This mechanism is particularly relevant in APS but can also occur in lupus and other inflammatory diseases. Vascular injury may produce livedoid skin changes, digital ischemia, cerebral infarction, or other neurological complications.

A fourth mechanism is granulomatous inflammation, exemplified by sarcoidosis. Granulomas may infiltrate skin, meninges, cranial nerves, neural tissue, or endocrine structures, producing diverse manifestations depending on location [10]–[12].

A fifth mechanism involves systemic cytokine activation. Proinflammatory cytokines can alter endothelial function, neural signaling, immune cell recruitment, and central nervous system function. These pathways may contribute to fatigue, mood changes, cognitive dysfunction, and inflammatory skin manifestations.

Understanding these mechanisms is clinically relevant because it provides biological coherence to multisystem findings. A dermatological lesion and a neurological symptom should not be considered connected solely because they occur in the same patient; their relationship becomes meaningful when a plausible shared mechanism exists.

Psychiatric manifestations and the risk of diagnostic attribution errors

Psychiatric symptoms represent one of the most difficult components of systemic disease diagnosis because they are frequently attributed to primary psychiatric conditions, psychological stress, chronic illness, or medication exposure. Mood disturbances, anxiety, psychosis, sleep abnormalities, cognitive complaints, and behavioral changes may occur during systemic autoimmune and inflammatory disease [5], [6], [14].

The diagnostic challenge is bidirectional. On one hand, excessive attribution of psychiatric symptoms to systemic disease may lead to unnecessary investigation or immunosuppressive treatment. On the other hand, assuming that psychiatric manifestations are always primary may delay recognition of underlying neurological or systemic pathology. Clinical evaluation should therefore consider several warning features: abrupt psychiatric onset, atypical age of presentation, cognitive decline, associated neurological deficits, seizures, systemic inflammatory symptoms, unexplained fever, vascular skin lesions, recurrent mucosal disease, autoimmune serology, or concurrent multiorgan abnormalities.

In SLE, neuropsychiatric manifestations can include psychosis and mood disorders, but their attribution requires careful exclusion of alternative causes [5], [6]. In Sjögren syndrome, cognitive and psychiatric symptoms may coexist with neurological disease and systemic autoimmunity [14]. Similar principles apply to other systemic disorders.

The broader implication is that psychiatric assessment should sometimes include systemic clinical reasoning, especially when the presentation includes atypical neurological or dermatological features.

Temporal sequence and the prediagnostic window

One of the most important dimensions in this study is chronology. The appearance of manifestations before formal diagnosis creates a prediagnostic window during which disease is biologically active but incompletely recognized.

This interval may be brief or may extend over several years. In some patients, recurrent cutaneous disease is followed later by systemic autoimmunity. In others, neurological or psychiatric symptoms appear before the classic systemic phenotype. Longitudinal progression from cutaneous lupus to systemic lupus provides a clear example of this phenomenon [3]. Neurological manifestations occurring before recognized Sjögren syndrome represent another [14], [15].

The clinical importance of this window lies in the opportunity for earlier detection. However, early detection should not be confused with premature diagnosis. The objective is not to classify every nonspecific symptom as systemic disease, but to identify patterns that justify longitudinal observation or targeted investigation.

Several characteristics may increase the significance of an early manifestation:

- recurrence without a clear external trigger;
- association with symptoms from another organ system;
- atypical severity or age at presentation;
- persistent inflammatory or immunological abnormalities;
- histopathological evidence of vasculitis, autoimmunity, or granulomatous inflammation;
- unusual thrombotic events;
- progressive neurological deficits;
- simultaneous cutaneous and neurological findings.

These characteristics can help differentiate ordinary isolated symptoms from possible manifestations of an evolving systemic disorder.

Diagnostic fragmentation and the importance of multidisciplinary assessment

One factor contributing to delayed diagnosis is the organizational separation between medical specialties. Patients with skin lesions may be evaluated by dermatology, whereas neurological symptoms lead to neurology and psychiatric symptoms to mental health services. If information is not integrated across specialties, the systemic pattern may remain invisible.

This fragmentation is especially problematic when symptoms occur at different times. A dermatologist may not know that a patient experienced unexplained neuropathy two years earlier, while a neurologist may not recognize the significance of recurrent photosensitive eruptions documented elsewhere. A systemic diagnosis may only become apparent when major organ involvement develops.

A multidisciplinary approach can reduce this problem. Dermatology can characterize lesion morphology and obtain histopathological samples. Neurology can define central or peripheral nervous system involvement. Psychiatry can assess behavioral and cognitive manifestations while identifying atypical features. Rheumatology can integrate autoimmunity and systemic inflammation. Internal medicine can coordinate multiorgan assessment, while radiology and pathology provide structural and tissue-level evidence.

This approach is particularly relevant for SLE, Sjögren syndrome, Behçet disease, sarcoidosis, APS, and systemic vasculitis because all can cross conventional specialty boundaries [1], [8], [10], [14], [17], [20].

Pattern recognition instead of isolated symptom interpretation

The available evidence supports a transition from symptom-centered interpretation toward pattern-based clinical reasoning. A single manifestation often lacks sufficient diagnostic specificity, but combinations of manifestations may provide substantially more information.

Examples of clinically relevant patterns include photosensitive rash associated with cognitive or seizure manifestations; palpable purpura accompanied by painful asymmetric neuropathy; recurrent oral or genital ulceration followed by inflammatory neurological disease; livedoid skin abnormalities associated with cerebrovascular events; and granulomatous skin lesions occurring together with cranial nerve dysfunction.

These patterns are important because they connect clinical observation with pathophysiological mechanisms. The diagnostic reasoning does not rely solely on coexistence but on whether a common systemic process can reasonably explain both manifestations.

This strategy may be particularly useful during the early disease phase when formal classification criteria are not yet completely satisfied. Classification criteria are essential for research and standardized diagnosis, but they should not replace clinical judgment during the prediagnostic period.

Clinical implications of recognizing sentinel manifestations

Earlier recognition of systemic disease has several potential advantages. First, it may facilitate appropriate diagnostic testing before severe organ involvement develops. Second, it may enable earlier referral to the relevant specialty. Third, it may reduce repeated consultations for apparently unrelated complaints. Fourth, it may prevent attribution of neurological or psychiatric manifestations to primary disorders when a systemic cause is present.

However, the concept of sentinel manifestations also carries a risk of overinterpretation. Many skin lesions and psychiatric symptoms are common and benign. Therefore, the identification of a possible systemic signal must be based on context, recurrence, associated findings, and objective evidence.

The clinical objective is consequently not indiscriminate screening but targeted suspicion. A patient with one transient nonspecific rash does not require extensive systemic evaluation solely on that basis. By contrast, recurrent vasculitic skin lesions associated with neuropathy, constitutional symptoms, inflammatory markers, or renal abnormalities represent a substantially different clinical situation.

Integrative interpretation of the evidence

Across the diseases examined, several recurring patterns become apparent. First, the skin frequently provides an early and visible manifestation of systemic immune or vascular activity. Second, neuropsychiatric abnormalities may precede recognition of the underlying systemic disorder, particularly when their presentation is atypical. Third, combinations of cutaneous and neurological findings often provide greater diagnostic value than either manifestation alone. Fourth, different systemic diseases may produce similar clinical manifestations through distinct biological mechanisms, making mechanistic interpretation essential.

SLE illustrates the autoimmune and immune-complex model [1]–[6]. Sjögren syndrome emphasizes that neurological disease can precede the classical glandular phenotype [13]–[16]. Behçet disease demonstrates the importance of recurrent mucocutaneous history in patients with inflammatory neurological syndromes [7]–[9]. Sarcoidosis reveals how accessible skin lesions can support the diagnosis of otherwise difficult neurological granulomatous disease [10]–[12]. APS highlights the shared thrombotic mechanism linking livedoid skin abnormalities to cerebrovascular disease [17], [18]. Systemic vasculitis demonstrates how vascular inflammation can simultaneously produce palpable purpura and ischemic neuropathy [19], [20].

Taken together, these observations support the interpretation that neuropsychiatric and cutaneous manifestations may represent clinically meaningful signals during the prediagnostic phase of systemic disease. Their greatest value does not lie in functioning as independent diagnostic criteria but in increasing clinical suspicion when they appear in characteristic combinations, follow recurrent or progressive courses, or are associated with objective evidence of inflammation, thrombosis, autoimmunity, or granulomatous disease.

The evidence therefore supports a diagnostic framework based on temporal sequence, multisystem pattern recognition, and biological plausibility. Within this framework, the clinician is encouraged to ask not only what diagnosis explains an individual rash, neuropathy, cognitive symptom, or psychiatric event, but whether multiple manifestations could represent different expressions of a single systemic pathological process. This shift in clinical reasoning may be particularly valuable in reducing diagnostic delay and identifying systemic disease before major irreversible organ damage becomes established.

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

General Objective

To **analyze** the neuropsychiatric and cutaneous manifestations associated with systemic diseases that may precede definitive diagnosis, integrating clinical, pathophysiological, and temporal evidence in order to identify early warning patterns that may facilitate timely recognition and multidisciplinary assessment.

Specific Objectives

Cognitive Domain

1. To **identify** the main neuropsychiatric and cutaneous manifestations reported in systemic diseases such as systemic lupus erythematosus, Sjögren syndrome, Behçet disease, sarcoidosis, antiphospholipid syndrome, and systemic vasculitis.
2. To **describe** the pathophysiological mechanisms that explain the relationship between systemic inflammation, autoimmunity, vascular injury, thrombosis, and the appearance of neurological, psychiatric, and dermatological manifestations.
3. To **compare** the clinical patterns and temporal sequences through which these manifestations may appear before the definitive diagnosis of systemic disease.
4. To **evaluate** the diagnostic relevance of combined cutaneous and neuropsychiatric findings as potential early warning signals.

Psychomotor Domain

5. To **classify** the manifestations identified in the literature according to affected system, underlying disease, probable pathophysiological mechanism, and temporal relationship with diagnosis.
6. To **organize** the available clinical evidence into comparative categories that facilitate recognition of recurrent patterns among different systemic diseases.
7. To **construct** an integrative clinical framework that can support the systematic assessment of patients presenting with unexplained combinations of dermatological and neuropsychiatric findings.

Affective Domain

8. To **promote** awareness of the importance of considering systemic disease when atypical or recurrent neuropsychiatric and cutaneous manifestations occur together.
9. To **value** multidisciplinary collaboration among dermatology, neurology, psychiatry, rheumatology, and internal medicine as an essential component of early diagnosis.
10. To **encourage** a comprehensive clinical approach that reduces diagnostic fragmentation and prioritizes early recognition of potentially progressive systemic disease.

OBJECT OF STUDY

The object of study is the **early neuropsychiatric and cutaneous manifestations associated with systemic diseases**, particularly those that may appear before the establishment of a definitive diagnosis.

The analysis focuses on systemic lupus erythematosus, Sjögren syndrome, Behçet disease, sarcoidosis, antiphospholipid syndrome, and systemic vasculitis. The principal phenomena examined include cognitive alterations, mood and behavioral changes, psychosis, seizures, neuropathies, cerebrovascular events, as well as photosensitive lesions, purpura, livedo, mucosal ulcers, vasculitic eruptions, and granulomatous skin lesions [2], [5], [8], [10], [14], [17], [19].

The study specifically considers the **temporal relationship between the appearance of these manifestations and the subsequent diagnosis of systemic disease**, together with the pathophysiological mechanisms that may explain their coexistence. Particular attention is given to clinical patterns in which neurological, psychiatric, and dermatological findings occur simultaneously or sequentially and may function as early warning signs.

The population of interest corresponds to patients described in the scientific literature with confirmed or subsequently diagnosed systemic autoimmune, inflammatory, granulomatous, thrombotic, or vasculitic diseases. The unit of analysis is therefore not an individual patient, but the **clinical manifestation and its diagnostic relationship with systemic disease**, as reported across observational studies, reviews, cohorts, and clinical recommendations.

METHODOLOGY

This study was conducted using the **Scientific Method applied to an integrative literature review**, since this approach allows clinical evidence from different types of publications to be systematically identified, compared, and interpreted. The methodology was designed to ensure transparency, reproducibility, and consistency between the research question, the selected evidence, and the conclusions obtained.

The methodological process began with the following research question: **Which neuropsychiatric and cutaneous manifestations of systemic diseases may precede definitive diagnosis and function as early clinical warning signs?**

A structured literature search was performed in **PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar**. The search strategy combined terms related to systemic diseases with neurological, psychiatric, dermatological, and temporal manifestations. Keywords included: *systemic diseases, systemic lupus erythematosus, Sjögren syndrome, Behçet disease, sarcoidosis, antiphospholipid syndrome, systemic vasculitis, cutaneous manifestations, skin manifestations, neuropsychiatric manifestations, neurological symptoms, psychiatric symptoms, early manifestations, sentinel signs, and before diagnosis*. Boolean operators **AND** and **OR** were used to combine the terms.

The analysis prioritized publications addressing systemic lupus erythematosus, Sjögren syndrome, Behçet disease, sarcoidosis, antiphospholipid syndrome, and systemic vasculitis because these conditions demonstrate clinically relevant relationships between skin, nervous system, and systemic involvement [1], [8], [10], [14], [17], [20].

Inclusion Criteria

Studies were included when they:

- evaluated neuropsychiatric, neurological, or cutaneous manifestations of systemic disease;
- described manifestations occurring before, during the early stages of, or close to definitive diagnosis;
- provided information on clinical presentation, pathophysiology, diagnostic relevance, or disease progression;
- corresponded to systematic reviews, narrative reviews, observational studies, cohorts, clinical guidelines, or consensus recommendations;
- were published in peer-reviewed scientific journals;
- were available in English or Spanish.

Exclusion Criteria

Publications were excluded when they:

- focused exclusively on treatment without describing relevant clinical manifestations;
- addressed isolated neurological or dermatological diseases without systemic involvement;
- lacked sufficient clinical or methodological information;
- duplicated information already represented by a more complete or updated publication;
- presented manifestations unrelated to the objective of early diagnostic recognition.

Data Extraction and Analysis

For each selected publication, the following variables were extracted: **systemic disease, cutaneous manifestation, neurological or psychiatric manifestation, proposed pathophysiological mechanism, temporal relationship with diagnosis, and potential diagnostic relevance**.

The information was subsequently organized into comparative categories. Manifestations were classified according to whether they were predominantly **autoimmune-inflammatory, vascular-thrombotic, vasculitic, or granulomatous** in origin. Particular attention was given to findings reported before the establishment of a definitive systemic diagnosis. A qualitative comparative synthesis was then performed to identify recurrent clinical patterns across the selected diseases. Greater relevance was assigned to manifestations supported by several studies or by evidence demonstrating a plausible temporal and pathophysiological relationship with systemic disease [3], [5], [14], [17], [19].

Finally, the evidence was integrated to determine which combinations of cutaneous and neuropsychiatric manifestations could reasonably function as **clinical warning patterns** requiring broader systemic assessment. The methodology did not consider an isolated manifestation sufficient for diagnosis; instead, the interpretation incorporated temporal evolution, associated findings, biological plausibility, and evidence from the reviewed literature.

This methodological structure allows the review to be replicated by other researchers using the same databases, search terms, selection criteria, extraction variables, and comparative analysis strategy.

PHASES OF DEVELOPMENT

Phase 1. Identification of the Research Problem

The first phase consisted of defining the central clinical problem: neuropsychiatric and cutaneous manifestations of systemic diseases may appear before the definitive diagnosis and may initially be interpreted as isolated neurological, psychiatric, or dermatological disorders.

Based on this problem, the research question was established: **Which neuropsychiatric and cutaneous manifestations can precede the diagnosis of systemic diseases and function as early clinical warning signs?**

Phase 2. Formulation of the Hypothesis

The working hypothesis proposed that certain cutaneous and neuropsychiatric manifestations can precede the formal

diagnosis of systemic disease and that their combined interpretation may improve early clinical recognition.

This hypothesis was supported by previous evidence describing progression from cutaneous lupus to systemic lupus, neurological manifestations preceding Sjögren syndrome, and early mucocutaneous or vascular manifestations in Behçet disease, antiphospholipid syndrome, and systemic vasculitis [3], [8], [14], [17], [19].

Phase 3. Systematic Search for Scientific Evidence

A structured search was performed in **PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar** using combinations of keywords related to systemic diseases, neuropsychiatric manifestations, skin findings, early symptoms, and diagnostic timing.

Boolean operators **AND** and **OR** were used to combine search terms and improve the identification of relevant publications.

Phase 4. Selection of Studies

Retrieved publications were screened according to predefined inclusion and exclusion criteria. Priority was given to studies that described:

- early or prediagnostic manifestations;
- neurological, psychiatric, or cutaneous involvement;
- temporal relationships between symptoms and diagnosis;
- pathophysiological mechanisms;
- diagnostic relevance.

Duplicated, unrelated, or clinically insufficient publications were excluded.

Phase 5. Extraction and Organization of Information

Relevant information was extracted from each selected publication and organized according to the following variables:

- systemic disease;
- cutaneous manifestation;
- neuropsychiatric manifestation;
- underlying pathophysiological mechanism;
- timing in relation to diagnosis;
- potential clinical relevance.

This organization allowed comparisons among systemic lupus erythematosus, Sjögren syndrome, Behçet disease, sarcoidosis, antiphospholipid syndrome, and systemic vasculitis.

Phase 6. Comparative Analysis

The collected evidence was comparatively analyzed to identify recurrent clinical patterns. Manifestations were grouped according to predominant mechanisms, including:

- autoimmune-inflammatory;
- vascular-thrombotic;
- vasculitic;
- granulomatous.

Particular attention was given to combinations such as purpura with neuropathy, livedo with cerebrovascular events, recurrent mucosal ulcers with neurological inflammation, and photosensitive lesions with neuropsychiatric abnormalities [5], [8], [17], [19].

Phase 7. Interpretation of Findings

The identified patterns were interpreted according to their biological plausibility, temporal relationship with systemic diagnosis, and consistency across different studies.

A manifestation was considered potentially relevant as an early clinical signal when it was recurrent, atypical, associated with another organ system, supported by objective findings, or consistently reported in the scientific literature.

Phase 8. Integration and Clinical Synthesis

Finally, the evidence was integrated into a clinical framework focused on early recognition. Rather than considering isolated symptoms as diagnostic, the study emphasized the importance of **multisystem pattern recognition**, temporal evolution, and multidisciplinary assessment.

The final synthesis was used to determine which neuropsychiatric and cutaneous manifestations may reasonably justify broader investigation for an underlying systemic disease.

RESULTS AND DISCUSSION

Figure 1.

Distribution of the systemic diseases according to the number of relevant neuropsychiatric and cutaneous manifestations identified.

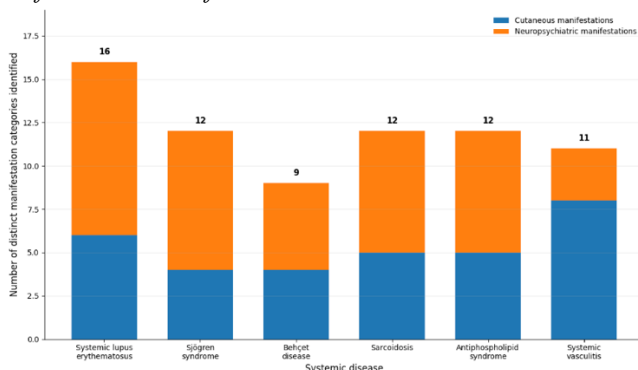


Figure 1 presents the distribution of the **distinct cutaneous and neuropsychiatric manifestation categories identified in the reviewed literature** for the six systemic diseases included in the analysis. These values represent the breadth of clinical manifestations documented within the evidence reviewed and **should not be interpreted as prevalence rates or as the number of affected patients**. This distinction is important because the purpose of the figure is to compare clinical heterogeneity across diseases rather than their epidemiological frequency.

Systemic lupus erythematosus demonstrated the greatest clinical diversity, with **16 manifestation categories**, including six predominantly cutaneous and ten neurological or psychiatric categories. This broad distribution is consistent with the multisystemic nature of SLE and its capacity to affect the skin, central nervous system, peripheral nervous system, and behavioral or cognitive domains simultaneously or sequentially [1], [2], [5], [6]. The cutaneous spectrum includes acute, subacute, and chronic forms of cutaneous lupus, mucosal abnormalities, alopecia, and vascular manifestations, whereas the neuropsychiatric spectrum includes cognitive dysfunction, mood disorders, psychosis, seizures, cerebrovascular events, confusional states, headache syndromes, movement abnormalities, and peripheral or cranial neuropathies [2], [5], [6].

The predominance of neuropsychiatric categories in SLE is particularly relevant to the objective of the study because neurological and psychiatric manifestations are not restricted to patients with advanced systemic disease. Their occurrence can sometimes coincide with the initial period of clinical recognition, while cutaneous manifestations may already have been present previously. Evidence showing progression from cutaneous lupus to systemic disease further supports the temporal importance of dermatological findings as possible early indicators in selected patients [3], [4]. Thus, the high number of categories identified for SLE reflects the considerable diversity of potential clinical pathways through which the disease may become apparent.

Sjögren syndrome accounted for **12 manifestation categories**, consisting of four cutaneous and eight neuropsychiatric categories. The neurological component was particularly prominent. Peripheral sensory neuropathies, small-fiber neuropathy, autonomic dysfunction, cranial neuropathies, cognitive alterations, and central nervous system manifestations have been reported as part of its extraglandular spectrum [14], [15]. Importantly, neurological manifestations may occur before the classical sicca phenotype becomes sufficiently evident to establish the diagnosis, making this disease especially relevant when investigating signs that may precede formal systemic recognition [14], [15].

Cutaneous abnormalities in Sjögren syndrome, although less diverse than the neurological manifestations in the present classification, included xerosis, vasculitic lesions, purpura, urticaria-like manifestations, and vascular phenomena described in the literature [13], [16]. The simultaneous presence of cutaneous vasculitis and peripheral neurological abnormalities may therefore provide a clinically important multisystem pattern rather than two unrelated findings.

Sarcoidosis also presented **12 manifestation categories**, with five cutaneous and seven neurological categories. Its distribution illustrates the ability of granulomatous inflammation to affect anatomically distant tissues. Dermatological involvement may manifest as papules, plaques, nodules, lupus pernio, or infiltration of pre-existing scars, whereas neurological involvement can include cranial neuropathies, meningeal disease, spinal cord involvement, hypothalamic-pituitary abnormalities, seizures, cognitive manifestations, and peripheral neuropathies [10]–[12].

The relevance of this distribution lies in the complementarity between visible and internal disease manifestations. Neurological sarcoidosis may have a broad differential diagnosis, but the simultaneous presence of a compatible skin lesion may provide important evidence of systemic granulomatous disease and may also offer an accessible site for histological evaluation [10], [11]. Consequently, the relatively balanced distribution observed in Figure 1 reflects the multisystem nature of sarcoidosis rather than an isolated neurological or dermatological phenotype.

Antiphospholipid syndrome similarly accumulated **12 manifestation categories**, comprising five cutaneous and seven neurological categories. In this disease, however, the connection between both groups is primarily vascular and thrombotic. Cutaneous abnormalities such as livedo, ulcerative or ischemic lesions, superficial thrombophlebitis, and digital ischemia may coexist with ischemic stroke, transient ischemic attacks, cerebral venous thrombosis, seizures, headache, movement disorders, or cognitive abnormalities [17], [18].

This pattern is relevant because the same underlying vascular mechanism may produce manifestations in the skin and central nervous system. Therefore, the coexistence of livedoid or ischemic skin abnormalities with an unexplained neurological vascular event, particularly in patients without conventional explanations for thrombosis, represents a clinically coherent pattern within the reviewed evidence [17], [18].

Systemic vasculitis presented **11 categories**, with the largest cutaneous component among the conditions analyzed. Eight categories corresponded to skin manifestations, compared with three principal neurological categories. This cutaneous predominance reflects the extensive morphological expression of vascular inflammation, which may include palpable purpura, petechiae, ulcers, livedoid changes, nodules, infarction, digital ischemia, and necrotic lesions [19]. Neurological involvement in systemic vasculitis was less morphologically diverse in the classification but remained clinically significant. Peripheral neuropathy and mononeuritis multiplex are particularly important manifestations because inflammation of the *vasa nervorum* may cause ischemic nerve injury, producing pain, sensory deficits, and weakness [20]. Therefore, the numerical predominance of cutaneous categories should not be interpreted as indicating lower neurological severity. Instead, it reflects the greater visible morphological variability of skin involvement within the classification used.

Behçet disease showed the lowest overall count among the six conditions, with **nine manifestation categories**, including four mucocutaneous and five neurological categories. Nevertheless, this lower number does not indicate reduced diagnostic relevance. Recurrent oral and genital ulceration, acneiform lesions, and erythema nodosum-like abnormalities constitute highly relevant components of its systemic phenotype [7]. Neurological involvement may include parenchymal inflammatory disease affecting the brainstem or other central nervous system regions, as well as vascular complications such as cerebral venous thrombosis [8], [9].

The relationship between both groups of findings is particularly important in Behçet disease because recurrent mucocutaneous manifestations may appear well before neurological complications become clinically evident. Therefore, a detailed history of previous oral or genital ulcers may provide crucial contextual information when investigating otherwise unexplained inflammatory neurological syndromes [8], [9].

When the six diseases are evaluated together, Figure 1 demonstrates that **no condition analyzed was restricted to a single clinical domain**. Each systemic disorder showed both cutaneous and neuropsychiatric manifestations, although their relative distribution varied considerably. SLE showed the broadest overall clinical spectrum; Sjögren syndrome, sarcoidosis, and antiphospholipid syndrome demonstrated substantial neurological representation; Behçet disease showed a relatively balanced mucocutaneous-neurological pattern; and systemic vasculitis presented the greatest concentration of cutaneous categories.

These findings also demonstrate that similar manifestations can arise through different mechanisms. Neurological abnormalities associated with SLE may involve inflammatory, autoantibody-mediated, or vascular pathways [5], [6]; those associated with APS are strongly related to thrombotic mechanisms [17]; vasculitic neuropathies result predominantly from vascular inflammation and ischemia [20]; and neurological sarcoidosis results from granulomatous involvement [10]. Consequently, the clinical manifestation alone does not define the underlying systemic disease, and its interpretation requires integration with dermatological characteristics, systemic findings, temporal sequence, and pathophysiological context.

Figure 2.

Frequency of the main cutaneous manifestations reported across the systemic diseases analyzed.

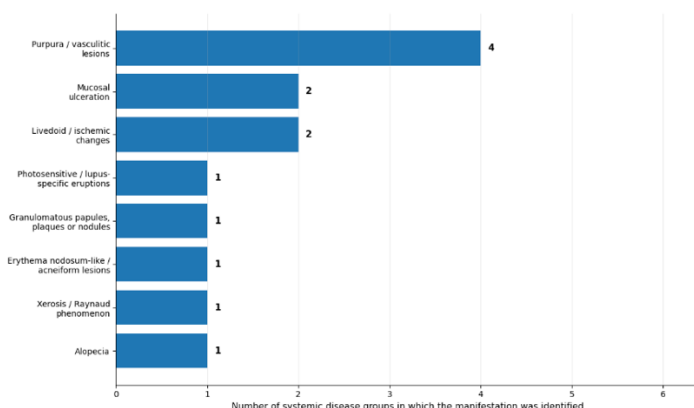


Figure 2 shows the distribution of the main **cutaneous manifestation categories identified across the six systemic disease groups included in the review**. The values correspond to the number of systemic diseases in which each dermatological pattern was documented within the analyzed evidence; therefore, they represent **cross-disease distribution rather than patient prevalence**.

The most widely represented category was **purpura and vasculitic or vascular-inflammatory skin lesions**, identified across four of the systemic disease groups analyzed. This finding reflects the importance of vascular injury as a common pathway connecting several systemic disorders. Cutaneous vasculitis may result from immune-complex deposition, inflammatory destruction of small vessels, endothelial dysfunction, or thrombotic processes and can manifest through palpable purpura, petechial lesions, ulcers, necrosis, or other ischemic changes [16], [18], [19].

Systemic vasculitis showed the clearest association with this pattern. In ANCA-associated vasculitis, cutaneous involvement can include palpable purpura, petechiae, ulcerations, nodules, livedoid abnormalities, and ischemic lesions [19]. These findings reflect direct vascular inflammation and may coexist with involvement of other organs, including peripheral nerves. Within the context of this study, their importance derives from their capacity to provide a visible indication of a systemic vascular process.

Sjögren syndrome also contributed to the vascular-inflammatory skin category. Although glandular manifestations are traditionally emphasized, cutaneous vasculitis and purpuric lesions constitute recognized extraglandular manifestations of the disease [13], [16]. Their presence becomes particularly relevant when associated with peripheral neuropathy, because both findings may reflect systemic immune-mediated vascular involvement.

Vascular skin abnormalities were also represented in antiphospholipid syndrome, although the predominant mechanism differs from classical inflammatory vasculitis. In APS, endothelial activation and thrombosis may generate livedoid abnormalities, ulcerations, digital ischemia, necrotic lesions, or other evidence of impaired cutaneous perfusion [17], [18]. This distinction demonstrates that morphologically related skin findings can arise from different pathophysiological processes and therefore require interpretation within the complete systemic context.

The second group of manifestations included **mucosal ulceration**, documented in two principal disease groups. Recurrent oral and genital ulceration is one of the characteristic clinical features of Behçet disease and may precede neurological, ocular, vascular, or other systemic manifestations [7]–[9]. In SLE, oral and other mucosal lesions may also form part of the mucocutaneous phenotype [1], [2]. Although similar in anatomical location, the morphology, recurrence, accompanying manifestations, and systemic context differ considerably between diseases.

The temporal behavior of mucosal lesions is especially relevant in Behçet disease. Recurrent ulceration may be present long before neurological involvement develops. Consequently, a previous history of recurrent oral or genital ulcers may provide relevant information when evaluating a patient who later presents with an unexplained inflammatory neurological syndrome or cerebral venous thrombosis [8], [9].

Livedoid and ischemic cutaneous changes were represented in two disease groups and were particularly associated with thrombotic and vascular mechanisms. APS represents the most characteristic example, in which livedo reticularis or livedo racemosa may accompany arterial, venous, or microvascular thrombotic disease [17], [18]. Similar ischemic or livedoid abnormalities can also occur in systemic vasculitic disorders as a consequence of vascular inflammation and impaired blood flow [19].

This category is particularly relevant to the relationship between skin and nervous system findings because cutaneous evidence of vascular compromise may coexist with neurological ischemic events. Thus, livedoid skin abnormalities accompanied by an unexplained stroke, transient ischemic attack, or other neurological vascular event represent a clinically recognizable multisystem pattern within the reviewed evidence [17], [18].

The remaining dermatological categories showed greater disease specificity. **Photosensitive and lupus-specific eruptions** were predominantly associated with systemic lupus erythematosus. Acute, subacute, and chronic cutaneous lupus encompass a broad spectrum of lesions, and their identification can provide important information regarding underlying autoimmune activity [2]. Importantly, evidence indicates that a subset of patients initially diagnosed with cutaneous lupus subsequently develops systemic disease, supporting the relevance of longitudinal surveillance [3], [4]. **Alopecia** was also primarily represented within the lupus spectrum. Although hair loss has numerous possible causes, nonscarring or scarring alopecia in an appropriate systemic and immunological context may form part of the mucocutaneous manifestations of SLE [1], [2]. Its isolated diagnostic specificity is limited, but its value increases when associated with photosensitivity, mucosal lesions, hematological abnormalities, arthralgia, or neuropsychiatric findings.

Granulomatous papules, plaques, and nodules were predominantly associated with sarcoidosis. Cutaneous sarcoidosis is morphologically diverse and may include papular, plaque-like, nodular, or lupus pernio patterns [11]. Unlike many nonspecific dermatological abnormalities, compatible granulomatous skin lesions may have substantial diagnostic value because they can provide accessible tissue for histopathological examination. This is particularly useful when systemic or neurological sarcoidosis is suspected [10]–[12].

Erythema nodosum-like and acneiform lesions were primarily represented in Behçet disease. Together with recurrent oral and genital ulceration, these findings contribute to the characteristic mucocutaneous spectrum of the disease [7]. Their presence may precede more severe manifestations and therefore becomes relevant when evaluating the longitudinal clinical history of patients who later develop neurological involvement [8], [9].

Finally, **xerosis and Raynaud-related cutaneous phenomena** were principally associated with Sjögren syndrome in the reviewed evidence. Cutaneous manifestations of Sjögren syndrome extend beyond dryness and may include vascular and inflammatory abnormalities [13], [16]. Although these findings are not sufficiently specific to establish the diagnosis independently, their coexistence with sicca symptoms, neuropathy, systemic inflammation, or immunological abnormalities may increase their clinical significance.

Figure 3.

Distribution of the principal neurological and psychiatric manifestations associated with systemic disease.

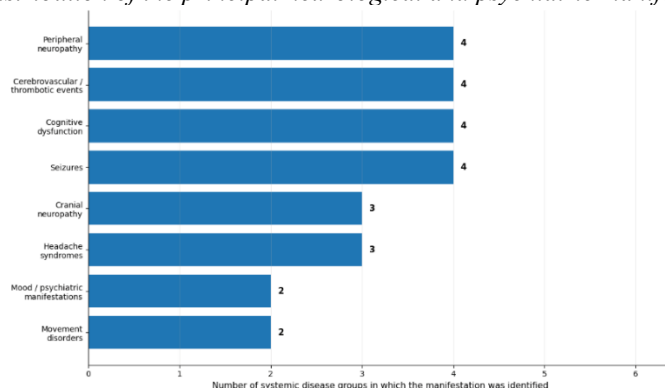


Figure 3 presents the principal neurological and psychiatric manifestations identified across the six systemic disease groups included in the analysis. The values indicate the **number of systemic disease groups in which each manifestation category was documented** and should therefore not be interpreted as prevalence estimates in individual patients.

The most widely distributed manifestations were **peripheral neuropathy, cerebrovascular or thrombotic events, cognitive dysfunction, and seizures**, each identified across four of the systemic disease groups analyzed. This distribution demonstrates that neurological involvement in systemic disease is heterogeneous and can affect peripheral nerves, cerebral circulation, higher cognitive functions, and cortical electrical activity through different pathophysiological mechanisms [5], [10], [14], [17], [20].

Peripheral neuropathy represented one of the most recurrent neurological patterns. It is particularly relevant in Sjögren syndrome, systemic vasculitis, SLE, and sarcoidosis. In Sjögren syndrome, peripheral nervous system involvement may include sensory neuropathy, small-fiber neuropathy, sensory neuronopathy, autonomic dysfunction, and cranial or multifocal neuropathies [14], [15]. Importantly, neurological abnormalities may occur before the classic sicca manifestations are sufficiently evident to establish the systemic diagnosis [14], [15].

In systemic vasculitis, peripheral neuropathy frequently results from inflammatory injury to the *vasa nervorum*, producing ischemia of peripheral nerves. Clinically, this may appear as painful asymmetric neuropathy or mononeuritis multiplex [20]. When such neurological findings coexist with palpable purpura or other vasculitic skin lesions, the combination provides a recognizable multisystem pattern involving a shared vascular-inflammatory mechanism [19], [20].

Cerebrovascular and thrombotic events were also identified in four systemic disease groups. Their presence was particularly relevant in antiphospholipid syndrome, in which arterial, venous, and microvascular thrombosis represents a central pathogenic process. Neurological manifestations may include ischemic stroke, transient ischemic attacks, cerebral venous thrombosis, and other vascular neurological abnormalities [17].

A vascular component is also observed in SLE, Behçet disease, and systemic vasculitis. In neuro-Behçet disease, cerebral venous thrombosis represents an important non-parenchymal neurological manifestation [8], [9]. In SLE, cerebrovascular events may result from several mechanisms, including accelerated vascular disease, inflammatory vascular injury, thrombosis, and the presence of antiphospholipid antibodies [5], [6]. Consequently, cerebrovascular manifestations cannot be attributed to a single mechanism across all systemic diseases.

The relevance of this category increases when neurological vascular events appear together with cutaneous evidence of vascular involvement. For example, livedoid or ischemic skin lesions combined with an unexplained cerebrovascular event create a clinical pattern compatible with an underlying systemic thrombotic process, particularly in APS [17], [18].

Cognitive dysfunction was similarly distributed across four systemic disease groups. Cognitive impairment represents a particularly complex manifestation because it may range from subtle difficulties in memory, attention, or executive functioning to more evident neurobehavioral abnormalities. In SLE, cognitive dysfunction forms part of the broad neuropsychiatric spectrum and may be associated with inflammatory, vascular, immune-mediated, or blood-brain barrier-related mechanisms [5], [6].

Cognitive abnormalities have also been described in Sjögren syndrome and APS [14], [17]. In Sjögren syndrome, their interpretation is especially relevant because neurological and neuropsychiatric manifestations may occur during the period preceding recognition of the systemic autoimmune disorder [14], [15]. In APS, cognitive changes may coexist with overt or subclinical cerebrovascular abnormalities, reinforcing the importance of considering vascular mechanisms [17].

The fourth highly represented category was **seizures**, documented across four disease groups. Seizures constitute a recognized neurological manifestation of SLE and may occur as part of neuropsychiatric lupus [5], [6]. They have also been described in neurosarcoidosis, APS, and other systemic inflammatory or vascular conditions [10], [17]. Their diagnostic significance depends heavily on the clinical context because seizures themselves are not specific for systemic disease.

However, a new-onset seizure accompanied by characteristic dermatological findings, systemic inflammatory abnormalities, recurrent thrombosis, or other neurological signs can substantially modify the diagnostic assessment. The results therefore show that seizures should be interpreted as part of a broader multisystem pattern rather than as an isolated marker.

Cranial neuropathy was identified across three systemic disease groups. It is particularly relevant in neurosarcoidosis, where cranial nerve involvement represents a recognized form of neurological disease [10], [12]. Sjögren syndrome may also involve cranial nerves as part of its peripheral neurological spectrum [14], [15]. Certain inflammatory systemic diseases can therefore first become clinically apparent through focal neurological deficits that initially resemble localized neurological disorders.

Sarcoidosis provides one of the clearest examples because neurological manifestations may occur in the context of meningeal or granulomatous inflammation. When cranial neuropathy occurs together with compatible cutaneous lesions, the combination can support investigation for systemic granulomatous disease [10]–[12].

Headache syndromes were documented across three disease groups. Headache is among the most difficult findings to interpret because of its high frequency in the general population and limited specificity. Nevertheless, it may acquire greater diagnostic relevance when associated with additional neurological, vascular, inflammatory, or dermatological abnormalities. Headache has been reported within the neuropsychiatric spectrum of SLE and among neurological manifestations associated with APS and Behçet disease [5], [8], [17].

The presence of headache alone therefore provides limited diagnostic information. In contrast, headache accompanied by cerebral venous thrombosis, recurrent mucosal ulceration, livedoid skin changes, seizures, focal deficits, or systemic inflammatory findings represents a different clinical scenario and may justify investigation of an underlying systemic disorder [8], [17].

Mood and psychiatric manifestations were identified in two of the principal disease groups represented in the analysis. These manifestations were particularly relevant in SLE and Sjögren syndrome. Neuropsychiatric SLE can

include mood disorders, psychotic manifestations, acute confusional states, and cognitive abnormalities [5], [6]. Likewise, psychiatric and cognitive manifestations have been reported within the neurological spectrum of Sjögren syndrome [14].

Psychiatric symptoms are clinically challenging because depression, anxiety, behavioral changes, and other mental health manifestations have multiple possible causes. Consequently, their systemic significance increases primarily when they demonstrate an atypical onset or coexist with objective neurological, cutaneous, inflammatory, or immunological abnormalities.

Finally, **movement disorders** were identified in two systemic disease groups. Although less broadly distributed than neuropathy or cerebrovascular manifestations, they remain relevant because systemic autoimmune or thrombotic mechanisms can involve basal ganglia and other motor circuits. Movement abnormalities have been reported within the neurological spectrum of SLE and APS [6], [17]. Their lower distribution in Figure 3 indicates greater specificity within the reviewed disease groups rather than a lack of clinical importance.

Taken together, Figure 3 shows that the neuropsychiatric spectrum of systemic disease extends well beyond psychiatric symptoms alone. The most recurrent findings involved **peripheral nerves, cerebrovascular function, cognition, and seizure activity**, demonstrating that both central and peripheral nervous systems can participate in the early clinical expression of systemic disorders.

The results also show that the same neurological manifestation may arise from substantially different mechanisms. Peripheral neuropathy may reflect immune-mediated neuronal injury, granulomatous involvement, or ischemia caused by vasculitis [10], [14], [20]. Cerebrovascular events may result from thrombosis in APS, inflammatory vascular disease, or complex autoimmune mechanisms in SLE [5], [17]. Seizures may occur in inflammatory, vascular, or granulomatous neurological disease [5], [10], [17].

Therefore, the neurological manifestation itself does not identify the systemic disease. Its diagnostic value depends on its association with **cutaneous findings, systemic symptoms, immunological abnormalities, vascular manifestations, and temporal evolution**.

Figure 4.

Comparative distribution of the predominant pathophysiological mechanisms: autoimmune-inflammatory, vascular-thrombotic, vasculitic, and granulomatous.

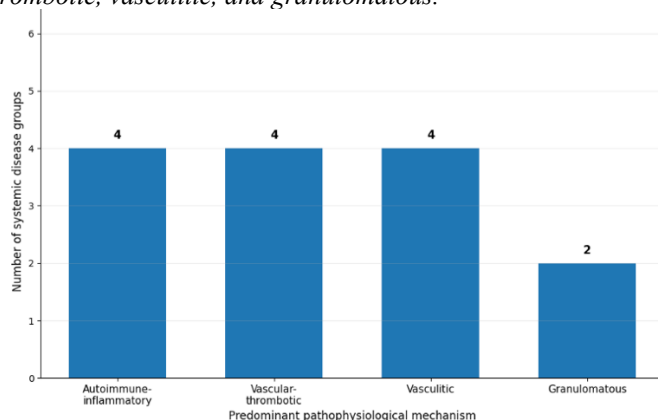


Figure 4 summarizes the principal pathophysiological mechanisms identified across the six systemic disease groups analyzed. The categories were considered **non-mutually exclusive**, since the same systemic disease may produce cutaneous and neuropsychiatric manifestations through more than one biological pathway. The values therefore represent the number of disease groups in which each mechanism had a meaningful role according to the reviewed evidence, rather than the prevalence of these mechanisms among individual patients.

The **autoimmune-inflammatory mechanism** was identified in four of the systemic disease groups. This pathway was particularly relevant in systemic lupus erythematosus, Sjögren syndrome, Behçet disease, and systemic vasculitic disorders. These diseases share abnormalities in immune regulation that can result in autoantibody production, cytokine activation, immune-complex formation, endothelial activation, or inflammatory tissue injury [1], [6], [14], [20].

In SLE, the autoimmune-inflammatory mechanism is particularly complex. Autoantibodies, immune complexes, complement activation, inflammatory mediators, and disruption of the blood-brain barrier have all been implicated in tissue injury [1], [6]. These mechanisms can simultaneously affect the skin and nervous system, providing a biological explanation for the coexistence of photosensitive cutaneous lesions, vasculitic manifestations, cognitive abnormalities, seizures, psychiatric symptoms, and peripheral neurological involvement [2], [5], [6].

Sjögren syndrome also demonstrated a strong autoimmune-inflammatory component. Although glandular dysfunction is its classical manifestation, systemic immune activity can involve peripheral nerves, central nervous system structures, and cutaneous vessels [13]–[16]. The association between vasculitic skin lesions and neuropathic manifestations illustrates how a shared immune-mediated process can become clinically evident in anatomically distinct systems.

The **vascular-thrombotic mechanism** was likewise identified in four disease groups. This category was particularly prominent in antiphospholipid syndrome but was also relevant to SLE, Behçet disease, and systemic vasculitic conditions. Neurological events resulting from vascular occlusion may include ischemic stroke, transient ischemic attacks, cerebral venous thrombosis, or other forms of cerebral ischemia, while the skin may demonstrate livedo, ischemic lesions, ulceration, or digital vascular compromise [8], [17]–[20].

APS represents the clearest example of this relationship. Persistent antiphospholipid antibodies are associated with an increased thrombotic tendency, and neurological involvement frequently results from arterial, venous, or microvascular events [17]. Simultaneously, livedoid and ischemic cutaneous abnormalities may provide visible evidence of vascular dysfunction [18]. Therefore, cutaneous and neurological findings can represent different anatomical expressions of the same thrombotic process.

A vascular component is also relevant in Behçet disease, particularly because cerebral venous thrombosis represents an established neurological manifestation [8], [9]. In SLE, vascular neurological events may result from several overlapping factors, including inflammation, endothelial dysfunction, accelerated vascular injury, and the coexistence of antiphospholipid antibodies [5], [6]. These observations demonstrate that the vascular-thrombotic mechanism is not restricted to APS.

The **vasculitic mechanism** was also represented in four systemic disease groups. Vasculitis involves inflammatory injury to blood vessel walls and can generate manifestations according to the caliber and anatomical distribution of the affected vessels. The skin is particularly susceptible because small-vessel inflammation can become clinically visible as purpura, petechiae, ulceration, livedoid abnormalities, infarction, or necrosis [19].

Neurological manifestations may appear when vascular inflammation compromises the vessels supplying peripheral nerves or central nervous system structures. In systemic vasculitis, inflammation of the *vasa nervorum* can produce ischemic nerve injury and clinical patterns such as mononeuritis multiplex or painful asymmetric neuropathy [20]. This mechanism provides a direct physiological link between cutaneous vasculitic lesions and peripheral neurological dysfunction.

Vasculitic manifestations are also recognized in Sjögren syndrome, where cutaneous purpura or inflammatory vascular lesions may coexist with peripheral neuropathy [13]–[16]. Similarly, vascular inflammatory abnormalities may occur within the broader clinical spectrum of SLE. Consequently, the repeated presence of the vasculitic mechanism across different disease groups explains why the combination of **purpura and unexplained neuropathy** emerged as one of the most recurrent multisystem patterns in the analysis.

The **granulomatous mechanism** was identified in two disease groups and showed a more restricted distribution than the other mechanisms. Sarcoidosis represented the principal disease associated with this category. Its characteristic granulomatous inflammation may involve the skin, meninges, cranial nerves, brain, spinal cord, hypothalamic-pituitary structures, or peripheral nervous system [10]–[12].

The simultaneous occurrence of cutaneous granulomatous lesions and neurological abnormalities is clinically notable because accessible skin lesions may provide evidence of the underlying systemic process. Papules, plaques, nodules, or lupus pernio can coexist with cranial neuropathy, meningeal involvement, myelopathy, or other neurological manifestations [10]–[12]. Granulomatous inflammation is also relevant within specific forms of systemic vasculitis, particularly granulomatosis with polyangiitis, explaining its representation beyond sarcoidosis [19].

Comparison of the four mechanisms demonstrates that **autoimmune-inflammatory, vascular-thrombotic, and vasculitic pathways had the widest distribution**, each appearing in four of the disease groups analyzed. Granulomatous inflammation was less widely distributed, appearing in two groups. This difference reflects the greater disease specificity of granulomatous pathology compared with the broader participation of immune and vascular mechanisms across systemic disorders.

An important finding is the considerable **pathophysiological overlap** among categories. SLE, for example, cannot be explained exclusively by autoimmunity because vascular and thrombotic mechanisms may also participate in neurological and cutaneous injury [5], [6]. Similarly, Behçet disease combines inflammatory and vascular processes [8], [9], while systemic vasculitis may incorporate both inflammatory vascular destruction and, in specific entities, granulomatous inflammation [19], [20].

This overlap explains why similar clinical manifestations may occur in different systemic diseases. Purpura can result from immune-mediated vascular inflammation, while livedoid abnormalities may reflect thrombotic or inflammatory vascular compromise. Peripheral neuropathy may result from direct immune-mediated injury, granulomatous

involvement, or ischemia secondary to vasculitis. Cerebrovascular events can similarly arise from thrombosis, vascular inflammation, or complex autoimmune mechanisms [6], [10], [17], [20].

Therefore, Figure 4 demonstrates that the association between skin and neuropsychiatric manifestations is supported by **shared biological pathways rather than simple clinical coincidence**. The predominance of autoimmune-inflammatory, vascular-thrombotic, and vasculitic mechanisms provides a pathophysiological basis for the recurrent multisystem patterns identified in the preceding figures.

These results also establish the framework for the final graphical analysis, which will examine the **temporal relationship between the appearance of cutaneous or neuropsychiatric manifestations and the definitive diagnosis of systemic disease**.

DISCUSSION

The findings of this study support the hypothesis that **cutaneous and neuropsychiatric manifestations may precede the definitive diagnosis of systemic disease and may function as clinically relevant warning signals when interpreted as part of a multisystem pattern**. Across systemic lupus erythematosus, Sjögren syndrome, Behçet disease, sarcoidosis, antiphospholipid syndrome, and systemic vasculitis, the reviewed evidence demonstrated recurrent overlap between dermatological, neurological, psychiatric, vascular, and inflammatory manifestations [1], [8], [10], [14], [17], [20].

One of the most relevant findings was the broad clinical heterogeneity observed in systemic lupus erythematosus. SLE showed the greatest diversity of both cutaneous and neuropsychiatric manifestations, which is consistent with its complex autoimmune pathophysiology and multisystem nature [1], [5], [6]. This result is particularly important because cutaneous lupus can precede systemic disease in a subgroup of patients, indicating that dermatological manifestations may represent an early stage of a broader autoimmune process rather than an isolated condition [3], [4]. Therefore, recurrent or characteristic cutaneous lupus findings associated with neurological or psychiatric abnormalities should increase clinical suspicion and justify longitudinal systemic evaluation.

The results also emphasized the importance of neurological involvement in Sjögren syndrome. Although this disease is traditionally recognized through ocular and oral dryness, peripheral neuropathy, cognitive changes, autonomic dysfunction, and other neurological manifestations may precede the classic glandular phenotype [14], [15]. This finding reinforces the possibility that patients may initially be evaluated in neurological settings before the underlying autoimmune disease is identified. In such cases, the simultaneous presence of purpura, vasculitic lesions, Raynaud phenomenon, or other cutaneous findings may provide additional evidence of systemic involvement [13], [16].

Behçet disease showed a comparatively smaller number of manifestation categories, but its temporal clinical pattern was highly relevant. Recurrent oral and genital ulceration frequently precedes neurological involvement, and therefore these mucocutaneous findings may become essential retrospective clues in patients presenting with inflammatory neurological syndromes [7]–[9]. This highlights the importance of a detailed clinical history, since early manifestations may disappear before the most severe systemic complications emerge.

Another important finding was the relationship between granulomatous skin disease and neurological involvement in sarcoidosis. Neurosarcoidosis can mimic infectious, neoplastic, demyelinating, and inflammatory disorders, making diagnosis particularly challenging [10], [12]. However, the coexistence of compatible skin lesions may increase diagnostic confidence and provide an accessible site for histopathological confirmation [11]. This illustrates how dermatological examination can contribute directly to the diagnosis of neurological systemic disease.

The vascular-thrombotic pattern observed in antiphospholipid syndrome was also clinically significant. Livedoid and ischemic skin abnormalities may coexist with cerebrovascular events, seizures, cognitive disturbances, and cerebral venous thrombosis [17], [18]. The coexistence of cutaneous vascular signs and unexplained neurological ischemia suggests that the skin may function as an external marker of systemic vascular dysfunction. This association is particularly relevant in patients with cerebrovascular events occurring at an atypical age or in the absence of conventional vascular risk factors.

Systemic vasculitis demonstrated another strong connection between skin and nervous system involvement. Purpura, ulceration, livedoid lesions, and ischemic skin changes may occur together with peripheral neuropathy or mononeuritis multiplex [19], [20]. In these disorders, both manifestations can result from vascular inflammation and ischemia, providing a clear pathophysiological explanation for their coexistence. Therefore, the combination of palpable purpura and painful asymmetric neuropathy should be considered a particularly important clinical pattern when investigating systemic inflammatory disease.

The analysis of pathophysiological mechanisms showed that autoimmune-inflammatory, vascular-thrombotic, and vasculitic pathways were the most widely distributed. This finding explains why similar clinical manifestations may appear in different systemic disorders. For example, peripheral neuropathy can arise from immune-mediated injury in Sjögren syndrome, ischemic damage in systemic vasculitis, or granulomatous involvement in sarcoidosis [10], [14], [20]. Similarly, cerebrovascular manifestations may result from thrombosis in APS, inflammatory vascular mechanisms in Behçet disease, or complex autoimmune and thrombotic processes in SLE [5], [8], [17].

These findings demonstrate that **individual symptoms have limited diagnostic specificity**. A headache, mood alteration, rash, neuropathy, or livedoid lesion does not independently establish systemic disease. Their clinical value increases when several findings converge, particularly when they share a plausible biological mechanism and appear in an unusual temporal or clinical context. Consequently, pattern recognition appears more informative than isolated symptom interpretation.

The results also support the concept of a **prediagnostic window**. During this period, patients may already exhibit manifestations of systemic disease but still fail to meet sufficient clinical or classification criteria for definitive diagnosis. Cutaneous lupus progressing to systemic lupus and neurological manifestations preceding Sjögren syndrome represent two clear examples [3], [14], [15]. Recognition of this interval may allow closer surveillance and more targeted testing before major organ involvement occurs.

However, this approach must be balanced against the risk of overdiagnosis. Many neurological, psychiatric, and dermatological manifestations are common in the general population and have multiple potential causes. Therefore, the presence of an isolated nonspecific symptom should not automatically trigger extensive systemic investigation. Greater diagnostic relevance should be assigned to recurrent, atypical, progressive, multisystem, or objectively documented manifestations.

A second important implication concerns **multidisciplinary assessment**. The diseases examined frequently cross the boundaries of dermatology, neurology, psychiatry, rheumatology, and internal medicine. Diagnostic delay may occur when manifestations are evaluated independently by different specialties without integration of the complete clinical history. The present findings suggest that communication among specialties is particularly important when cutaneous and neuropsychiatric manifestations appear sequentially or simultaneously.

The results should also be interpreted considering several limitations. The included diseases differ substantially in pathophysiology, diagnostic criteria, prevalence, and quality of available evidence. In addition, the number of manifestation categories identified in the figures reflects the breadth of findings described in the reviewed literature rather than patient-level prevalence. Therefore, direct numerical comparisons among diseases should be interpreted as descriptive rather than epidemiological.

Despite these limitations, the consistency of several patterns across independent disease groups supports the central argument of the study. Cutaneous and neuropsychiatric manifestations can provide early diagnostic information when they are interpreted together, linked to plausible biological mechanisms, and evaluated according to their temporal relationship with systemic disease. The strongest patterns identified included **purpura with neuropathy, livedoid skin changes with cerebrovascular events, recurrent mucosal ulceration with neurological inflammation, photosensitive lesions with neuropsychiatric abnormalities, and granulomatous skin disease with cranial or central neurological involvement** [5], [8], [10], [17], [19], [20].

CONCLUSION

Neuropsychiatric and cutaneous manifestations can represent important early expressions of systemic disease, particularly when they appear before the classical diagnostic phenotype becomes fully established. The evidence reviewed across systemic lupus erythematosus, Sjögren syndrome, Behçet disease, sarcoidosis, antiphospholipid syndrome, and systemic vasculitis demonstrates that the skin and nervous system may simultaneously reflect underlying autoimmune, inflammatory, thrombotic, vasculitic, or granulomatous processes [1], [10], [14], [17], [20]. The principal finding of this study is that the diagnostic value of these manifestations lies less in isolated symptoms and more in the identification of **coherent multisystem patterns**. Combinations such as purpura with peripheral neuropathy, livedoid skin changes with cerebrovascular events, recurrent mucosal ulceration with inflammatory neurological manifestations, photosensitive lesions with neuropsychiatric abnormalities, and granulomatous skin lesions with cranial or central nervous system involvement may provide clinically meaningful signals of systemic disease [5], [8], [10], [17], [19].

Systemic lupus erythematosus showed the broadest clinical heterogeneity, while Sjögren syndrome highlighted the possibility that neurological involvement may precede the recognition of classical glandular symptoms [14], [15]. Behçet disease demonstrated the importance of recurrent mucocutaneous findings as antecedents of neurological complications [8], [9]. Sarcoidosis illustrated the diagnostic complementarity between accessible skin lesions and

neurological granulomatous disease [10]–[12], whereas antiphospholipid syndrome and systemic vasculitis emphasized the close relationship between cutaneous vascular findings and neurological injury [17]–[20].

These findings support the existence of a clinically relevant **prediagnostic window** during which systemic disease may already be producing detectable manifestations without yet fulfilling all criteria required for definitive classification. Recognizing this interval may allow more timely investigation, closer surveillance, and earlier multidisciplinary referral. However, because many dermatological and neuropsychiatric symptoms are nonspecific, their interpretation must always consider recurrence, temporal evolution, associated systemic findings, biological plausibility, and objective diagnostic evidence.

The study therefore supports an integrative clinical approach involving dermatology, neurology, psychiatry, rheumatology, and internal medicine when atypical or unexplained manifestations affect more than one system. Such collaboration may reduce diagnostic fragmentation and improve recognition of systemic disease before major organ damage develops.

In conclusion, cutaneous and neuropsychiatric manifestations should not be viewed exclusively as secondary complications of established systemic disorders. In selected clinical contexts, they may function as **sentinel manifestations that precede diagnosis**. Their systematic identification and integration into multisystem clinical reasoning may contribute to earlier diagnosis, more appropriate diagnostic testing, and improved clinical decision-making in patients with evolving systemic disease.

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