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Review

Monogenic Lupus Is a Construct: Insights into the Current Nomenclature and Classification

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Abstract: Monogenic lupus is a rare inherited entity, which has been increasingly recognized over the past decade. Monogenic lupus demonstrates heterogeneity in etiopathogenesis, phenotypes, and outcome compared to sporadic systemic lupus erythematous (SLE). Its distinctive features include early-onset disease, atypical manifestations of underlying diseases such as immunodeficiency, immune dysregulation, and refractory disease course. The term "monogenic lupus" has been used internationally to collectively describe a group of patients presenting with SLE or SLE-like symptoms with a proven underlying pathogenic variant. It has been considered a form of SLE irrespective of the differences observed. To date, there is no standardized definition or criteria to identify monogenic lupus. Therefore, this review highlights the differences between monogenic lupus and sporadic SLE to discuss the challenges related to the current nomenclature and unmet needs in the diagnosis of monogenic lupus. A considerable number of underlying pathogenic variants have recently been uncovered, leading to various pathways' involvement with significant overlap. This allows us to propose a new definition for monogenic lupus which can be considered as a construct rather than a disease or syndrome.

Keywords: Monogenic lupus, Systemic lupus erythematosus, Early onset lupus, Type I interferon

1. Introduction

Systemic lupus erythematosus (SLE) is a complex multisystem autoimmune disease characterized by loss of self-tolerance, excessive autoantibody formation, and immune complex deposition. Several mechanisms are involved, including defective

regulatory T cells, defective lymphocyte homeostasis, and defects in the clearance of apoptotic cells and immune complexes. Therefore, T and B-lymphocytes, myeloid cells, and interferon-alpha (IFN-α) play key roles in SLE pathogenesis in addition to numerous cells and cytokines interplay [1–4]. Despite remarkable advances in the etiopathogenesis of SLE, the exact etiology is still unknown. However, it is widely accepted that SLE is a polygenic multifactorial disease with multiple genetic–epigenetic interactions including environmental and hormonal factors [5–9]. To date, there are no diagnostic criteria yet. However, several validated classification criteria for adult- and childhood-onset SLE are available and are widely used worldwide [10–12]. There is a distinctive group of patients whose lupus features are linked to a single genetic variant as an association or causation [13,14]. Accordingly, they are labeled as patients with monogenic lupus. Thus, the term "SLE" needs to be used carefully for those patients. This review highlights the differences between monogenic lupus and sporadic SLE and discusses the challenges related to the current nomenclature and unmet needs in the diagnosis of monogenic lupus. Furthermore, in this review, we propose a new definition for monogenic lupus and for it to be considered as a construct rather than a disease or syndrome.

2. Current Challenges

Recently, monogenic lupus is becoming increasingly recognized worldwide. However, the precise prevalence is unknown as the available data is limited to case reports and small cohorts. It is a rare-inherited entity with great heterogeneity in etiopathogenesis, phenotypic features, and disease course and outcome [15,16]. The term "monogenic lupus" has been used internationally to collectively describe a group of patients presenting with lupus or lupus-like features with proven underlying pathogenic variants. These variants are sorted into four major pathogenic pathways: complement protein defects (e.g., C1q and C4 deficiency), endonuclease gene defects (e.g., DNase 1L3, DNase II), proteins directly involved in the IFN type I pathway (e.g., TREX1, ISG15), and self-intolerance related to B and T lymphocyte dysregulation (PRKCD) [13,14,16]. The consequence of these pathways leads

to robust production of IFN type I, which is the driving force in the pathogenesis of monogenic lupus by participating in inflammatory reactions, tissue damage, plasmacytoid dendritic cell maturation, and activation of autoreactive T and B cells [17].

Table 1 shows a list of gene variants that have been seen in the cohort of monogenic lupus. These variants are involved in the main pathogenic pathways of monogenic lupus. One of the current challenges for understanding monogenic lupus is a lack of the proper definition and nomenclature as monogenic lupus differs greatly from other lupus categories regarding genetic and immunologic findings [15–21].

Table 1. List of genes involved in the main pathogenic pathways of monogenic lupus.

Gene	Mode of Inheritance	Phenotype
Complement protein defects		
C1q	AR	Recurrent infection. FTT, mucocutaneous lesions, alopecia, discoid rash, nail dystrophy. Arthritis.GN, lung infiltrates. CNS involvement with basal ganglia calcification, spastic diplegia. Pancreatic pseudocyst. Hypothyroidism.
C3	AR	Cutaneous vasculitis, recurrent infection. Progressive GN with renal impairment. lung infiltration. arthritis,
C4	AR	FTT, hemolytic anemia. Cutaneous vasculitis, arthritis, Bronchiectasis. Mitral regurgitation, dilated ascending aorta.
Endonuclease gene defects		
DNASE1L3	AR	Mucocutaneous lesions, urticarial rash, arthritis, GN, lung infiltration.
DNase II	AR	Deforming arthropathy, recurrent infection. GN with renal impairment. White matter changes
Proteins directly involved in IFN type I		
ISG15	AR	Malar rash, oral ulcer, recurrent skin ulceration, periorbital swelling, epilepsy, basal ganglia calcification, cognitive, behavioral impairment. MSMD, AGS
TREX1	AD/AR	Malar rash, Chilblain lupus oral ulcer, arthritis, CNS involvement
STAT1		Deforming arthropathy, CNS: white matter changes, optic atrophy.
ACP5	AR	Hematologic, GN, Spondyloenchondrodysplasia
Self-tolerance		
PRKCD	AR	Mucocutaneous lesions, pancytopenia, arthritis, CNS involvement.
B and T lymphocyte and phagocyte dysregulation		
PIK3CD	AR	Mucocutaneous lesions, lung infiltration, bronchiectasis, arthritis.
PNP	AR	Recurrent infection. FTT, short stature, arthritis, mucocutaneous lesions, alopecia, GN, lung infiltrates, dysarthria, ataxia.
CYBB	X-linked	FTT, recurrent infection, GN, cutaneous vasculitis.
Other defects		
IL2RB	AR	Oral ulceration, hemolytic anemia, thrombocythemia.
PETN	AR	Mucocutaneous lesions, thrombocythemia, GN.

3. Nomenclature: Introducing New Concept

Monogenic lupus is considered a part of the lupus cluster that represents an umbrella for phenotypically heterogeneous entities with variations in onset and severity of etiopathogenesis, including SLE, discoid lupus, drug-induced lupus, and neonatal lupus. Taking into consideration that the precise etiology of SLE is still not fully defined, and on the contrary, the etiopathogenesis of monogenic lupus may be related to the genetic variant. Therefore, monogenic lupus cannot be considered a subset of SLE. In our opinion, the following terms are incorrectly used to describe monogenic lupus in the literature: early-onset of SLE, a monogenic form of SLE, SLE-like phenotype, lupus-like disease, lupus-like syndrome, familial SLE, and Mendelian lupus [6,15,16,19]. However, it is not simple to describe it because monogenic lupus is not a disease or syndrome with a well-defined clinical phenotype. In reality, it has multiple clinical phenotypes and multiple pathogenic mechanisms associated with expanding genetic variants. Most of the reported cases of monogenic lupus are associated with genetic variants related to inborn errors of immunity. However, several monogenic predisposing conditions of inborn errors of metabolism that may induce the manifestations of monogenic lupus have been described in various articles [14,16,22–25]. Additionally, a wide spectrum of clinical and laboratory features of monogenic lupus may overlap with other monogenic disorders [26,27]. Figure 1 demonstrates the heterogeneity and overlapping manifestations of monogenic lupus.

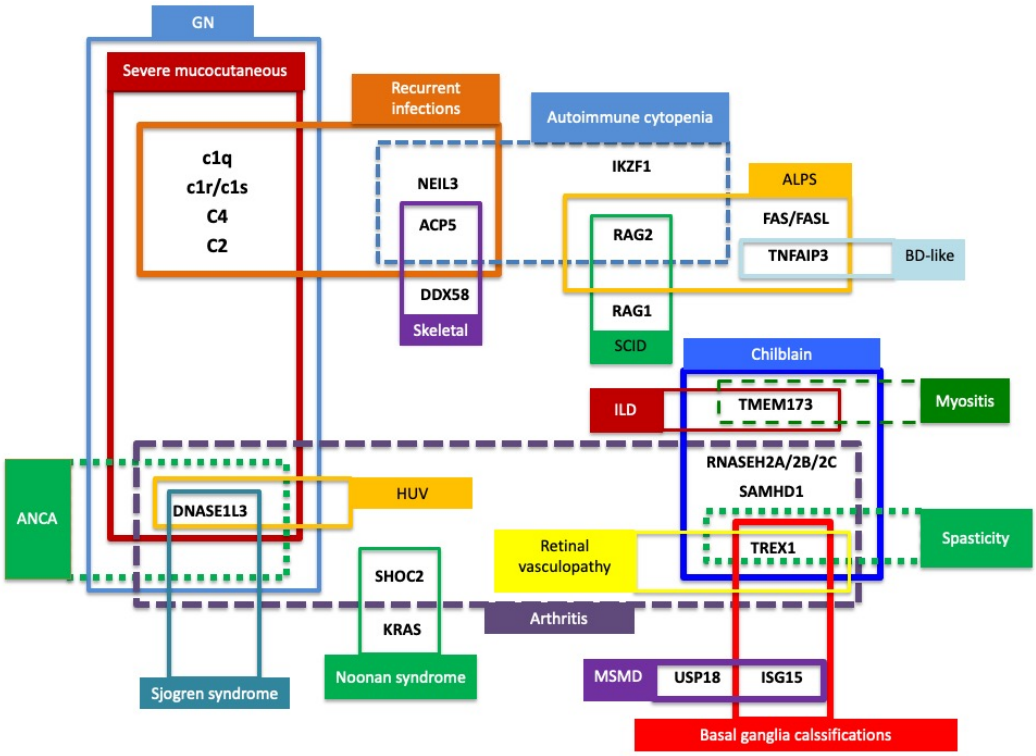

Fig.1. Heterogeneity and overlapping manifestations in monogenic lupus.

Recently, a hypothesis of "construct" has been proposed for disorders characterized by several separate pathogenic mechanisms [28]. Therefore, it may be appropriate to embrace the same proposal for monogenic lupus. Accordingly, we propose three strong components and three weak components for monogenic lupus as a construct (Table 2). The absence of two strong components strongly indicates the possibility of considering another diagnosis.

Table 2. Components of monogenic lupus as a construct.

Strong Components	Weak Components
Early disease onset (< 5 years)	Distinct phenotypic clusters
Positive family history	Variation in clinical expression
Genetic variant	Features related to immune dysregulation.

Although the available classification criteria for SLE are not diagnostic, those classification criteria have been validated for children with SLE [6,11,29]. It needs to be noted that these classification criteria are commonly used without validation as a framework for the diagnosis of monogenic lupus. Recently, we demonstrated the efficient performance of the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR-2019) criteria in comparison with Systemic Lupus International Collaborating Clinics (SLICC-2012) in classifying monogenic lupus patients, irrespective of the underlying genetic variants, which means easy and early identification of monogenic lupus [30].

4. Tentative Definition

Based on the available data, monogenic lupus can be tentatively defined as "a highly complex construct with various phenotypic features, characterized by integrating the paradoxical combination of autoimmunity and immune dysregulation due to numerous pathogenic mechanisms related to several single-gene variants". Because of genetic diversity, the presence of certain genetic variants, particularly those that are already described in other disease entities, may be allowed to use "monogenic lupus-like".

5. Monogenic Versus Sporadic SLE

Both monogenic lupus and sporadic SLE are characterized by systemic inflammation with heterogeneity of clinical phenotypes. Clinical manifestations and disease progression varied between patients, ranging from mild to severe disease. Monogenic lupus remains a diagnostic challenge, particularly with its severe and ambiguous clinical presentation. Thus, it is important to keep a high index of suspicion and rule out other differential diagnoses. Despite similarities with sporadic SLE, we have observed several clinical features that are helpful to differentiate between monogenic lupus and sporadic SLE as shown in Table 3.

Table 3. Similarity and differences between monogenic lupus and systemic lupus erythematosus.

Monogenic lupus	Systemic lupus erythematosus
Mostly early childhood < 5years of age	Mostly teenager
Marginal female preponderance	Female preponderance
Multisystem interferonopathy	Multisystem autoimmune
A subset of lupus	A subset of lupus
Genetic variant (single-gene disorder)	Polygenic disorder
Inheritance pattern: autosomal recessive	Complex inheritance pattern
Positive family history of similar case	Positive family history of autoimmune disease
Distinct phenotypic clusters	Variation in clinical expression
Mucocutaneous	Musculoskeletal/ Nephritis
Autoantibodies are not impressive	Autoantibodies are impressive
Refractory to treatment	Variable response to treatment
Frequent/ recurrent infections	

These observations depend on the genetic variants that induce stimulation of type I interferon production [31]. Among the distinguished clinical findings in patients with monogenic lupus, early onset before the age of five years is found. Interestingly, several patients developed their disease in the infancy period. In addition, to the usual manifestations of renal, hematologic, and cutaneous involvement, a high number of patients with monogenic lupus, particularly those with *C1q* variants, usually present with recurrent extensive mucocutaneous and discoid lesions with scarring alopecia [18]. Additionally, several patients may present with distinct phenotypic clusters. For instance, patients with the *DNase 1L3* may suffer from recurrent urticarial vasculitis rash and pulmonary hemorrhage, while patients with *DNase II* variant experience musculoskeletal and neurological manifestations in the form of non-erosive, deforming arthropathy, and white matter changes [18,22,32]. Features of monogenic lupus have been described in patients with the *ACP5* variant. Those patients had skeletal dysplasia and intracranial calcification [33]. It is noted that several patients with monogenic lupus may exhibit overlapping features of immunodeficiency and immune dysregulation, and thus are at risk of recurrent infections. Remarkably, the presence of extractable nuclear antigens (ENA) is not impressive in patients with monogenic lupus. Those patients likely have weak ENA positivity.

6. Unmet Needs for Monogenic Lupus

Despite the remarkable progress in understanding the immunologic pathways and genetics of monogenic lupus, various clinical aspects have not yet been met. Overall, the current approach to monogenic lupus takes into account genetic variants. One of the challenges is that the discovery of genetic variants is progressively evolving, which means that monogenic lupus is an expanding construct. This presents a major task of setting diagnostic criteria for monogenic lupus. We hope that this proposal encourages the development of a clinical score to guide decision-making and makes it easier to distinguish patients with monogenic lupus from monogenic interferonopathies and other mimickers for molecular genetic testing. Nevertheless, another potential problem that needs to be considered is the distinction between a confirmatory and non-confirmatory genetic test and their interpretation. Although such a score may at times be helpful in clinical practice, we believe that the ideal setting is to design and validate evidence-based clinical classification criteria guided by genetic variants and tailored for monogenic lupus. To date, there is no standardized treatment for monogenic lupus. The available treatment is not evidence-based and is either anecdotal reports or an expert's opinion [34,35]. The current treatment approaches and new medication choices including new biologic targeting B cells, T cells, or cytokines are derived from SLE and interferonopathy trails and observational data [36,37]. Theoretically, treatment can be individualized depending on the underlying genetic defects to form the basis of decision-making for the treatment of monogenic lupus patients.

7. Conclusion

Monogenic lupus is a highly complex construct with various phenotypic features with proven underlying genetic variants. It may exhibit overlapping features with monogenic interferonopathies and immunodeficiency conditions. Thus, we need to aim to differentiate monogenic lupus from lupus erythematosus.

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