A proposed clinical tool to identify high-risk patients for monogenic lupus: a pilot study

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Abstract

Objective

To develop an easy-to-use and efficient clinical score to identify monogenic lupus based on clinical presentations and to stratify patients who may benefit from confirmatory molecular genetic testing.

Methods

A comprehensive literature review identified 55 distinct items across 12 clinical and laboratory domains, narrowed down to the top ten by a panel of 12 expert paediatric rheumatologists with 80% consensus. The proposed score was tested in a pilot study on 10 patients with monogenic lupus and 30 control subjects with various autoimmune and autoinflammatory diseases. All patients, both with monogenic lupus and the control group, were then scored, and a receiver operating characteristic curve was employed to determine the threshold that distinguishes monogenic lupus from non-monogenic lupus.

Results

The clinical score comprised 10 items. Among all patients, the most frequent items were antinuclear antibody positivity and consanguinity, followed by early disease onset (<5 years), with no significant differences between monogenic lupus patients and the controls. However, the monogenic lupus patients exhibited significantly higher rates of family history of lupus, failure to thrive, cutaneous lesions, brain imaging changes, a low C1q level, and recurrent infections. Also, they achieved the highest scores compared to the controls. A score of more than three was found to be highly predictive for diagnosing monogenic lupus, with a sensitivity of 90% and a specificity of 90%.

Conclusion

Our clinical score appears to be a valuable tool for the early identification of patients with monogenic lupus who may require further molecular genetic testing for confirmation.

Key words

monogenic lupus, childhood-onset systemic lupus erythematosus, clinical score, genetic testing, DNase1L3, C1q

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Introduction

Systemic lupus erythematosus (SLE) is a complex systemic inflammatory disease with a wide range of clinical and laboratory features (1). The precise aetiology and pathophysiology of SLE are not fully understood. The genetic contribution to lupus is evident through observed twin concordance and heightened risk among siblings, emphasising the significant role of genetic factors in the development of this autoimmune disorder. Furthermore, new insights from the innate immune response studies have underlined the key role of the complement and type I interferon (IFN) systems in the pathogenesis of SLE (1-3). Monogenic lupus is a rare form of lupus that emerges in individuals with specific single gene variants in the coding region of proteins which contribute to inflammation and loss of tolerance. Numerous genes associated with monogenic lupus have been identified, with a majority of these gene defects being linked to complement deficiencies, specifically, C1q, C2, and C4, or type I interferonopathies, such as *DNase1L3* (4-9). To date, the prevalence of monogenic lupus has not been systematically assessed using large cohorts; additionally, the lack of extensive sequencing in a large number of childhood-onset SLE patients introduces a potential ascertainment bias, limiting the comprehensive assessment of genetic rates and emphasising the need for broader genomic investigations in this population, which is therefore still unknown (10). Typically, patients with monogenic lupus experience severe early-onset disease, often with mucocutaneous manifestations and guarded therapeutic responses. It is noteworthy that many affected patients with monogenic lupus have a strong family history of lupus (11,12). The clinical manifestations of monogenic lupus vary depending on the genetic variants involved, including systemic multi-organ complications, and patients often share clinical and immunological features with patients with immunedysregulation disorders and interferonopathies. However, these clinical features are not specific to monogenic lupus, which can lead to misdiagnosis and delayed appropriate management (13). The study aims to develop an easily applicable and time-efficient clinical tool for identifying monogenic lupus based on clinical presentations. Moreover, we attempted to identify the best cut-off point for the developed tool. Given the limited accessibility and cost of genetic testing, the ultimate goal of this tool is to identify individuals who would benefit from confirmation molecular genetic testing and to facilitate the timely initiation of proper therapeutic interventions.

Materials and methods

Our study encompassed two distinct workflows. The first flow focused on the development of the tool, entailing a thorough process that included: 1. compiling an item list; 2. assembling an expert consensus panel; and 3. refining the tool through a rigorous selection process, ultimately narrowing it down to ten items. The subsequent phase involved the establishment of a cut-off or threshold value, followed by a comprehensive assessment of the diagnostic performance of this tool (14).

Creating a list of features of monogenic lupus

The steering committee (SMA, HS) created a list of all clinical and laboratory features that have been reported in patients with monogenic lupus. A comprehensive review of the English literature was conducted using the PubMed platform (Supplementary file). The resultant dataset was extracted from a carefully chosen selection of 33 articles, and it comprised a total of 55 distinct items organised within 12 clinical and laboratory domains. This systematic categorisation approach was employed to ensure a structured and coherent representation of the diverse facets of monogenic lupus, as supported by the genetic testing-backed literature (Table I).

Establishing an expert consensus panel

Based on their publications and clinical experience, 16 paediatric rheumatologists with competence in monogenic lupus have been identified. As a result, they were invited to serve on the ex-

pert consensus panel. Twelve of them agreed and verbally consented to participate in the tool's design.

Selection of the tool items

The expert panelists engaged in a two-round process to narrow down the items to the top ten, reaching an 80% agreement among them. In the first round, each panelist independently scored every item's clinical significance and relevance, considering both clinical and laboratory aspects. To accomplish this, we employed a rating system where items were assigned scores ranging from one to four: rare = one, sometimes = two, often = three, always = four. Items rated as one and two were discarded, while those rated three or four were retained. Consequently, the initial list of items was reduced to 30. In the second round of evaluation, the initial set of 30 items underwent scrutiny. Each panelist participated independently, providing their expert opinion by ranking the items and voting for their chosen top ten. Through this process, items that garnered agreement from >80% of the expert panelists were accepted. These collectively approved items constitute the final set of the top 10 items (Table II). This clinical tool has a maximum score of 10, with each item assigned equal weight, receiving one point if present.

Calculation of the cut-off value and evaluated the reproducibility and reliability

A pilot evaluation was conducted to assess the validity of the proposed clinical score. Ten patients with monogenic lupus with confirmed genetic variants and 30 control subjects were scored. We obtained the patient's data from our paediatric rheumatology database at King Faisal Specialist Hospital and Research Center (KFSHRC), Riyadh. A control group consisting of patients with systemic autoinflammatory diseases (SAIDs) confirmed by genetic testing (none of which are categorised as interferonopathies) (15), sporadic SLE based on the criteria of SLICC (16), and juvenile dermatomyositis (JDM) based on the Bohan and Peter criteria (none of SLE and JDM patients have been genetically sequenced) (17).

Table I. Monogenic lupus features grouped in domains and items extracted from a systematic review.

Domains	Items
Demographic	Early disease onset (less than 5 years) Consanguinity (1st or 2nd degree relatives). Family history of lupus
Constitutional	Fever (recurrent/chronic) Lymphadenopathy- Failure to thrive Recurrent infections
Mucocutaneous	Photosensitivity, malar rash, maculopapular rash Alopecia (scarring, non-scarring) Oral ulcers Urticaria Nail dystrophy Other lesions (Chilblain lesions, livedo reticularis, petechial rash, acral ulcers/ vasculitis lesions, Raynaud's phenomenon, purpura, bullous lesions)
Musculoskeletal	Arthralgia, arthritis, synovitis Myalgia, myositis Contracture/Deformity
Renal	Haematuria Proteinuria Hypertension Biopsy proven lupus nephritis Biopsy proven another nephritis Thrombotic microangiopathy
Neurologic	Headache, psychosis, behavioural changes, cognitive impairment Global developmental delay Seizures Cranial nerve palsy Upper/ lower motor neuron lesions Ataxia Spasticity Other imaging changes (Basal ganglia calcifications, stroke, white matter changes, intracranial haemorrhage, volume loss, transverse myelitis, high intracranial pressure)
Cardiopulmonary	Serositis Interstitial lung disease, pneumonitis, bronchitis, bronchiectasis Pulmonary haemorrhage
Gastrointestinal	Transaminitis Abdominal pain, vomiting, diarrhoea Pancreatitis Gastrointestinal tract bleeding Hepatosplenomegaly
Ocular	Retinopathy Scleritis, uveitis
Haematological	AIHA (positive Coombs) Pancytopenia, leukopenia, thrombocytopenia Thrombosis Macrophage activation syndrome
Autoimmune	ANA ds-DNA Ro, La, Smith, RNP Antiphospholipid antibody ANCA
Immunologic	Low (C3, C4) Low CH50 Low C1q Elevated inflammatory markers Hypergammaglobinaemia Hypogammaglobinaemia

AIHA: autoimmune haemolytic anaemia, ANA: antinuclear antibody, ds-DNA: double-stranded DNA, RNP: ribonucleoprotein ANCA: antineutrophil cytoplasmic antibody.

For the control group, we employed systematic sampling from the database; the first patient from each set was chosen randomly, and subsequent patients were selected at intervals of three.
All patients including monogenic lupus and controls, were then assessed using the clinical tool.

Statistical considerations
Data was entered into a datasheet using the Statistical Package for Social Sciences (SPSS). This program was used for data cleaning, management, and analysis. Descriptive statistics were carried out by reporting the number and percent for categorical variables, whereas the mean and standard deviation were reported for continuous variables. The association between the groups and different characteristics was assessed using the chi-square test or independent t-test, as appropriate. Finally, the performance of the developed tool was assessed using the Receiver Operating Curve (ROC) based on the number of scored items from the developed score, where the cut-off value was calculated through the Area Under the Curve (AUC) by Youden's index. A p-value <0.05 was considered to indicate statistical significance.

Ethical considerations
This study adheres to the ethical principles outlined in the Declaration of Helsinki (2000), the guidelines of the Research Advisory Council (RAC) of the KFSHRC, and the laws of Saudi Arabia This work was part of a previously approved study under the study approval RAC#2221105. All clinical and laboratory assessments were the result of routine medical care. Informed consent for genetic testing as part of patient care was obtained from the parents at the time of blood extraction. All collected data was analysed under confidentiality practices, and no personal identity was required.

Results

The clinical tool in this pilot study consisted of ten distinct items, and all items were scored as present (1) or absent (0), with a maximum score of 10 and a minimum score of 0.0. Patients with monogenic lupus exhibited a median age of 11.5 years (IQR 8.0–13) and a disease onset age of 1.4 years (IQR 0.5–4.0), whereas controls had a median age of 11 years (IQR 10–13) and a disease onset age of 5.0 years (IQR 2.0–9.0). Five patients with monogenic lupus had C1q deficiency, three were biallelic for pathogenic variants in *DNase1L3*, and one each with *DNase II* and *PRKCD*. In the control populations, three patients with familial Mediterranean fever, three patients with mevalonate kinase deficiency, one each with Majeed's syndrome, cryopyrin-associated periodic syndrome, tumor necrosis factor receptor-associated periodic syndrome, and haploinsufficiency A20. Males predominated in patients with monogenic lupus (60%) and SAIDs (80%), whereas in sporadic SLE and JDM patients, a female predominance was observed at the same frequency of 90%. The most commonly observed features were the presence of antinuclear antibodies (ANA); according to our laboratory reference, an ANA titre of 1:80 is considered positive; and a history of

Table II. Top ten items with the highest rankings constituting the proposed clinical score.*

Early disease onset <5 years.
Consanguinity (1st or 2nd degree relatives).
Family history of lupus.
Elevated antinuclear antibody.
Pancytopenia.
Failure to thrive.
Cutaneous lesions (Chilblain lesions, livedo reticularis, petechial rash, acral ulcers/vasculitis lesions, Raynaud's phenomenon, purpura, bullous lesions).
Imaging changes (Basal ganglia calcifications, stroke, white matter changes, intracranial haemorrhage, volume loss, transverse myelitis, high intracranial pressure).
Low C1q.
Recurrent infections.

*Each item is assigned a weight of one point.

Table III. Prevalence of the proposed clinical score items in monogenic lupus patients and controls.

Clinical score items	Monogenic lupus	Sporadic SLE	JDM	SAIDs
Early onset <5 years	8/10	0/10	4/10	10/10
Consanguinity (1st or 2nd degree relatives).	9/10	4/10	6/10	6/10
Family history of lupus	8/10	3/10	1/10	0/10
Elevated antinuclear antibody	10/10	10/10	9/10	2/10
Pancytopenia	4/10	5/10	0/10	0/10
Failure to thrive	6/10	1/10	2/10	1/10
Cutaneous lesions*	5/10	1/10	1/10	1/10
Brain imaging**	5/10	0/10	0/10	1/10
Low C1q	6/10	0/10	0/10	0/10
Recurrent infections	5/10	2/10	1/10	0/10

SLE: systemic lupus erythematosus; JDM: juvenile dermatomyositis; SAIDs: systemic autoinflammatory disorders.
* Chilblain lesions, livedo reticularis, petechial rash, acral ulcers/vasculitis lesions, Raynaud's phenomenon, purpura, bullous lesions.
** Basal ganglia calcifications, stroke, white matter changes, intracranial haemorrhage, volume loss, transverse myelitis, high intracranial pressure.

Table IV. Scores obtained in the pilot study.

	Number	Mean ± SD
Monogenic lupus	10	6.6 ± 2.4
Sporadic SLE	10	2.6 ± 0.7
JDM	10	2.4 ± 1.6
SAIDs	10	2.1 ± 0.9

SLE: systemic lupus erythematosus; JDM: juvenile dermatomyositis; SAIDs: systemic autoinflammatory disorders.

Table V. Coordinates for different cut-offs (Receiver Operating Curve).

Test result variable(s): total. Positive if greater than or equal to[a]	Sensitivity	Specificity
-1.00	1.000	1.000
0.50	1.000	0.967
1.50	1.000	0.800
2.50	1.000	0.433
3.50	0.900	0.100
4.50	0.700	0.067
5.5	0.700	0.000
6.50	0.600	0.000
7.50	0.300	0.000
9.00	0.200	0.000
11.00	0.000	0.000

The test result variable(s): the total has at least one tie between the positive actual state group and the negative actual state group.
[a]The smallest cut-off value is the minimum observed test value minus 1, and the largest cut-off value is the maximum observed test value plus 1. All the other cut-off values are the averages of two consecutive ordered observed test values.

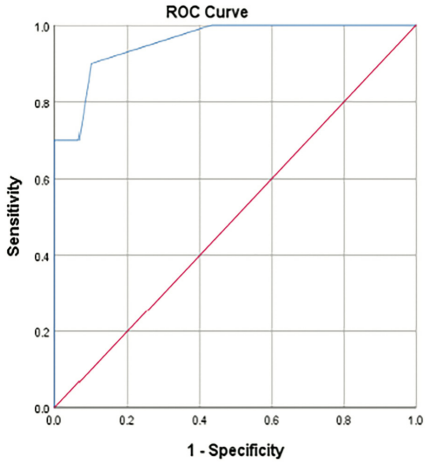

Fig. 1. Receiver operating curve for different cut-offs. Diagonal segments are produced by ties. Area under the curve = 95.7.

consanguinity, which was closely followed by early disease onset. Notably, there were no significant differences in these aspects between patients diagnosed with monogenic lupus and those belonging to the control group. In the ANA positivity category, all patients were positive except nine, and notably, eight of these individuals were SAIDs patients. In terms of consanguinity, it was observed in 90% of patients with monogenic lupus, compared to 40% in those with sporadic SLE, while patients with JDM and SAIDs showed a same frequency of 60%. Eight (80%) patients with monogenic lupus had a family history of lupus; interestingly, six of them had affected siblings, whereas three with sporadic SLE had a family history, and one patient had an affected first cousin. As for early disease onset, it was more frequent among patients with SAIDs and monogenic lupus, with a median age of disease onset of one (IQR 0.5–3.0) and 1.5 (IQR 0.5–4.0) years, respectively. Nevertheless, patients with monogenic lupus exhibited markedly higher frequencies in other items. These encompassed a more prevalent family history of lupus, failure to thrive, cutaneous lesions, brain imaging abnormalities, a lower C1q level, and a history of recurrent infections, as summarised in Table III. In addition to a greater infection rate, monogenic lupus patients had more severe and opportunistic infections. Failure to thrive was noted in six (60%) patients with monogenic lupus compared to four (13.3%) patients in the controls. Cutaneous lesions included urticarial rash, acral vasculopathy, diffuse maculopapular rash, diffuse nodular rash, and panniculitis. Five patients with monogenic lupus had neurological symptoms, and, brain imaging revealed abnormalities, including basal ganglia calcifications, stroke, white matter changes, and volume loss. Only six patients with monogenic lupus had low C1q levels. Patients with monogenic lupus were more susceptible to recurrent severe infections than controls. Consequently, these factors contributed to the monogenic lupus patients achieving the highest scores with a mean of 6.6 ± 2.2 compared to the controls, as seen in Table IV.

The performance of the developed score was assessed using the ROC, where the AUC was calculated. There was a statistically significant difference between the scores of the monogenic lupus and controls. Three (30%) of the ten patients with monogenic lupus, however, scored less than five. Interestingly, those patients had *DNase1L3*. We noted that a minimal score of 3.5, as a cut-off, was best predictor for the diagnosis of monogenic lupus, with a sensitivity of 90% and a specificity of 90% when used as the only variable predictor. Table V presents the ROC coordinates, and Figure I illustrates the ROC for various cut-offs. However, because early disease onset, consanguinity, and ANA positivity were commonly observed in patients with monogenic lupus and controls, these three items may not be sufficient to determine monogenic lupus; however, based on the analysis, the presence of additional three items or more enabled the score to stratify the monogenic lupus patients since it was high in only them but not in the controls.

Discussion

Monogenic lupus is a rare inherited entity that has been increasingly recognised over the past decade. Monogenic lupus demonstrates great heterogeneity in etiopathogenesis compared to sporadic SLE (9, 18, 19). Patients with monogenic lupus are often mistaken with other diagnoses as they show a wide range of non-specific clinical and laboratory features, leading to delay in diagnosis and appropriate management (5, 20). A considerable number of underlying pathogenic variants have recently been uncovered implicating various pathways' involvement with significant overlap. Thus, monogenic lupus is considered a subset of lupus in which we can identify a rare variant causing inflammation, elevated Type I IFN gene signature, and loss of tolerance, rather than a disease or syndrome. Genetic testing could confirm the diagnosis by identifying an underlying pathogenic variant and facilitating the timely initiation of precise therapeutic intervention. However, these genetic tests are expensive and not widely accessible.

In this study, we developed an easy-to-use clinical tool to identify high-risk patients for monogenic lupus. It is worth noting that the clinical tool of 10 items was chosen as a practical decision throughout the development process, based on clinical significance and relevance, considering the panelist's clinical experience. We enrolled patients with a range of clinical and laboratory features. Furthermore, in addition to patients with monogenic lupus who had underlying genetic variants, all patients with SAIDs had proven genetic variants; nevertheless, none of them were considered interferonopathies. We included

some items that were independently associated with monogenic lupus, such as elevated ANA or consanguinity, which were thought not to be specific to monogenic lupus, particularly in populations with a high rate of consanguinity. Furthermore, certain monogenic lupus patients, namely, those with complement deficiency-related monogenic lupus, may be ANA negative. Interestingly, the potential implication of nephritis had a limited impact on this newly developed tool; this could be attributed to the fact that just three patients in our monogenic lupus group had *DNase1L3* deficiency. Despite the heterogeneity of the phenotypic features of the enrolled monogenic lupus patients as well as the controls, this tool efficiently stratify monogenic lupus patients irrespective of diversity of the underlying genetic variants. Patients with monogenic lupus had the highest scores. Interestingly, the scores of patients of different diseases in the control group were comparable to each other.

Our data analysis identified an informative clinical tool threshold for monogenic lupus. This tool displayed impressive sensitivity and specificity, underscoring the value of the clinical score as a robust tool for early detection and ensuring that individuals who might benefit from confirmatory molecular genetic testing receive the attention they need. Nevertheless, it requires external validation in independent cohorts to establish its reliability.

To the best of our knowledge, our work is the first clinical tool tailored to identify patients with monogenic lupus early and aid in genetic counseling. Also, international panelists with expertise in monogenic lupus were involved in the tool's design.

There are some limitations to this study. First, despite the EULAR/ACR-2019 classification criteria being efficient in patients with monogenic lupus, there is not a true gold standard classification for monogenic lupus (21). Second, it is worth mentioning that the presence of a genetic variant may be a cause or association with the disease, and determining whether it is a disease-causing variant is considered the most crucial factor. Clearly, this concern is beyond the scope of this work and cannot answer it at this phase. Third, the data came from a single childhood lupus clinic, and all of the patients were Arab from a community with a high consanguinity rate, and the control group did not have a comparable gender distribution or disease onset. Also, lack of external validation and lack of independent control groups. Consequently, validation in populations with diverse rates of consanguinity and genetic ancestry is essential. While C1q deficiency is more prevalent in the monogenic lupus group, it is noteworthy that all tested patients with monogenic lupus demonstrated positive results for ANA. In contrast, patients with lupus caused by complement deficiency may exhibit negative results for ANA. Furthermore, this indicates that this study does not adequately reflect all known genetic causes of monogenic lupus. Furthermore, genetic testing was not conducted on sporadic SLE patients, potentially introducing bias in patient selection, with an acknowledgment of the possible influence of race. Additionally, the selection of cases and controls may impact external validity, particularly when applying the clinical score to different populations.

In summary, monogenic lupus is probably a construct that encompasses a variety of clinical and laboratory features. Confirmatory genetic testing is critical to the diagnosis. However, our study introduced an easy-to-use and time-efficient clinical score that can be used to clinically outline the most likely cases of monogenic lupus, even when genetic findings are inconclusive or in regions with restricted access to molecular genetic testing. We hope our tool will be used as a reliable efficacious source to facilitate the identification process in patients with monogenic lupus globally. This tool, however, has to be tested in a broad multi-ethnic population and assessed in correlation with genotyping from a large cohort of monogenic lupus to ascertain the properties of this clinical tool.

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