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Clinicoradiologic Criteria for the Diagnosis of Stroke-like Episodes in MELAS

Vadim Khasminsky, MD,* Eitan Auriel, MD,* Judith Luckman, MD, Ruth Eliahou, MD, Edna Inbar, MD, Keshet Pardo, MD, Yuval Landau, MD, Rani Barnea, MD, Maor Mermelstein, MD, Shahar Shelly, MD, Jonathan Naftali, MD, and Shlomi Peretz, MD

Correspondence
Dr. Peretz
shlomip@shamir.gov.il

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Abstract

Background and Objectives

Stroke-like episodes (SLEs) in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome are often misdiagnosed as acute ischemic stroke (AIS). We aimed to determine unique clinical and neuroimaging features for SLEs and formulate diagnostic criteria.

Methods

We retrospectively identified patients with MELAS admitted for SLEs between January 2012 and December 2021. Clinical features and imaging findings were compared with a cohort of patients who presented with AIS and similar lesion topography. A set of criteria was formulated and then tested by a blinded rater to evaluate diagnostic performance.

Results

Eleven MELAS patients with 17 SLE and 21 AISs were included. Patients with SLEs were younger (median 45 [37–60] vs 77 [68–82] years, $p < 0.01$) and had a lower body mass index (18 ± 2.6 vs 29 ± 4, $p < 0.01$), more commonly reported hearing loss (91% vs 5%, $p < 0.01$), and more commonly presented with headache and/or seizures (41% vs 0%, $p < 0.01$). The earliest neuroimaging test performed at presentation was uniformly a noncontrast CT. Two main patterns of lesion topography with a stereotypical spatiotemporal evolution were identified—an anterior pattern (7/21, 41%) starting at the temporal operculum and spreading to the peripheral frontal cortex and a posterior pattern (10/21, 59%) starting at the cuneus/precuneus and spreading to the lateral occipital and parietal cortex. Other distinguishing features for SLEs vs AIS were cerebellar atrophy (91% vs 19%, $p < 0.01$), previous cortical lesions with typical SLE distribution (46% vs 9%, $p = 0.03$), acute lesion tissue hyperemia and venous engorgement on CT angiography (CTA) (45% vs 0%, $p < 0.01$), and no large vessel occlusion on CTA (0% vs 100%, $p < 0.01$). Based on these clinicoradiologic features, a set of diagnostic criteria were constructed for possible SLE (sensitivity 100%, specificity 81%, AUC 0.905) and probable SLE (sensitivity 88%, specificity 95%, AUC 0.917).

Discussion

Clinicoradiologic criteria based on simple anamnesis and a CT scan at presentation can accurately diagnose SLE and lead to early administration of appropriate therapy.

Classification of Evidence

This study provides Class III evidence that an algorithm using clinical and imaging features can differentiate stroke-like episodes due to MELAS from acute ischemic strokes.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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*These authors contributed equally to this work and co-first authors.

From the Departments of Imaging (V.K., J.L., R.E., E.I.) and Neurology (E.A., K.P., R.B., M.M., J.N., S.P.), Rabin Medical Center, Petach Tikva, Israel; Sackler Faculty of Medicine (V.K., E.A., J.L., R.E., E.I., Y.L., R.B., S.P.), Tel Aviv University; Metabolic Diseases Clinic (Y.L.), Schneider Children's Medical Center, Petach Tikva; Department of Neurology (S.S.), Rambam Health Care Campus, Haifa, Israel; and Department of Neurology (S.S.), Mayo Clinic, Rochester, MN.

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Glossary

AIS = acute ischemic stroke; **CTA** = CT angiography; **MCA** = middle cerebral artery; **MELAS** = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; **MRS** = MR spectroscopy; **NCCT** = non-contrast CT; **PCA** = posterior cerebral artery; **RMC** = Rabin Medical Center; **SLE** = stroke-like episode.

Mitochondrial stroke-like episodes (SLEs) are the hallmark of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS).[1,2] SLEs present with an acute or subacute onset of neurologic symptoms including headache, nausea and vomiting, visual disturbances, language or other cognitive impairments, and sensory-motor symptoms.[3,4] The presence of multisystem involvement, including diabetes, deafness, or cardiomyopathy, and a positive family history may suggest an underlying mitochondrial pathology and lead to the pursuit of more definitive molecular diagnosis.[4,5]

Two established sets of clinical diagnostic criteria exist for MELAS.[1,2] However, these criteria do not represent recent knowledge nor the broad range of phenotypes encountered in clinical practice. Clinical diagnosis remains elusive and extremely challenging in the acute setting. Unique neuroimaging features have been described for acute SLE but have never been formulated into formal diagnostic criteria.[6] Furthermore, they were mainly reported on MRI and MR spectroscopy (MRS) which are not routinely performed at an early stage in these patients. In clinical practice, many patients with a first SLE are misdiagnosed as acute ischemic stroke (AIS) or, less often, as viral or autoimmune encephalitis or CNS vasculitis.[7-11] This translates to significant delays in diagnosis and administration of appropriate therapy.

In this study, we explore the clinical and imaging features of SLEs in an adult cohort of patients with MELAS and compare them with AIS patients with similar lesion topography. We aim to determine unique clinical and neuroimaging features for SLEs. Based on these features, we aim to formulate clinicoradiologic criteria for the diagnosis of SLEs and test them by a blinded rater to evaluate their diagnostic performance. We hypothesize that our clinicoradiologic criteria could reliably differentiate SLEs from AISs and may assist and facilitate the early diagnosis and treatment of a SLE at presentation.

Methods

SLE Cohort Selection

The electronic medical records of the Rabin Medical Center (RMC) were queried for patients admitted between January 2012 and December 2021 whose discharge with MELAS or disorder of mitochondrial metabolism diagnosis. An additional query was performed on the study interpretation text of all CT and MRI performed with the word "MELAS" was searched to detect all patients in whom MELAS was included in the differential diagnosis based on imaging findings.

All medical records were reviewed by an experienced stroke neurologist (S.P., 8 years of posttraining experience in vascular neurology) to include only patients with a final diagnosis of MELAS (based on either clinical criteria or definitive molecular diagnosis on genetic testing) and a clear SLE with available CT or MRI during the acute phase. Episodes were determined as SLEs based on a subacute rather than acute onset of symptoms and the evolution of symptoms and imaging lesions along more than 48 hours. When a patient had more than 1 admission for neurologic symptoms, a separate SLE was defined only if recurrent symptoms were acute/subacute, dissimilar, and more than 4 weeks apart from the previous episode.

Ischemic Stroke Cohort Selection

Patients with AIS were identified using a different query. The text of neuroimaging test interpretation results from RMC, including all brain CT and MRI scans performed between January 2021 and December 2021, was queried for the words "stroke"+"PCA" or "stroke"+"temporal". These patients' images were reviewed and classified according to stroke topography (S.P.). We included only patients with AIS in posterior or temporal brain regions. The rational for this selection method was that infarcts in these locations are most likely to be confused with SLEs in clinical practice because of similar lesion topography. Matching for age and sex was not preformed.

Demographics and Clinical Data Collection

Demographics and relevant clinical data for each patient in the SLE cohort were extracted using the electronic medical records by a trained neurologist (J.N.), including age, sex, height, weight, common risk factors, early-onset diabetes, hearing loss, myopathic symptoms, gastrointestinal symptoms, time of presumed and final MELAS diagnosis, time of L-arginine treatment initiation, and time of death if deceased. For each SLE, additional data were collected including time of symptom onset, detailed list of symptoms and signs at admission, duration of episode, and time of neuroimaging acquisition. Follow-up data collected at outpatient clinic visits were also retrospectively extracted from the medical file when available. Relevant clinical data were similarly extracted for the AIS cohort.

Formulation and Evaluation of Diagnostic Criteria

The neuroimaging tests of both confirmed patients with SLE and patients with AIS including all non-contrast CT (NCCT), CT angiography (CTA), and MRI performed in the acute and subacute phases were reviewed by a board-certified neuroradiologist (V.K., 5 years of posttraining experience). He aimed to describe distinctive imaging features

and patterns of SLEs including baseline findings and spatiotemporal evolution of the acute lesion. Clinical features of patients with SLE vs AIS were compared using the *t* test for numerical variables and either χ^2 test or Fisher exact χ^2 test for categorical variables. A *p* value of <0.05 was considered significant. A set of diagnostic criteria for possible and probable SLE were constructed based on the early clinical and radiologic features that most prominently distinguished SLE from AIS.

The earliest neuroimaging test that shows an acute lesion in each SLE/AIS was blindly presented for review by a second board-certified neuroradiologist (J.L., 22 years of posttraining experience) who recorded meeting of each radiologic criterium. Fulfilment of clinical criteria was recorded by a blinded neurologist (K.P., 2 years of experience in neurology) based on data extracted from the medical records. Diagnostic performance of the clinicoradiologic criteria was evaluated by receiver operating characteristic curve analysis.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the local Institutional Review Board.

Data Availability

Anonymized data will be shared by request from any qualified investigator.

Results

Baseline Characteristics and Clinical Features

Seventeen SLE were included in the SLE cohort (n = 11 MELAS patients). The median age at first SLE was 45 [37–60], and 8 (73%) were female. Diagnosis of MELAS was based on molecular testing that identified the *m.3243A>G* pathogenic variant in the mitochondrial gene *MT-TL1* in blood samples of 9 (82%) patients, ragged-red fibers on muscle biopsy in 1 patient (9%), and meeting clinical diagnostic criteria plus positive genetic testing in a first-degree relative in 1 patient (9%). One patient (10%) had already been diagnosed with MELAS when the first SLE occurred, whereas in 9 (82%), a SLE was the event that led to diagnosis. The median time interval from symptom onset at the first SLE until MELAS diagnosis was first considered was 27 [14–37] days.

The AIS cohort included 21 patients. The median age was 77 [68–82], and 4 (22%) were female. The median time from symptom onset to first neuroimaging was 0.8 [0.6–3.7] days. In 12 (57%) patients, the involved vascular territory was that of posterior cerebral artery (PCA) and in 9 (43%) a temporal branch of the middle cerebral artery (MCA).

Detailed demographics and clinical features of patients with MELAS in comparison with ischemic stroke patients are presented in Table 1. Patients with SLEs were younger that patients with AIS (45 ± 14 vs 74 ± 10, respectively, $p < 0.01$) and were mostly female (73% vs 22%, $p < 0.01$). They had remarkably higher prevalence of hearing loss (91% vs 5%, $p < 0.01$), had a lower body mass index (BMI, 18 ± 2.6 vs 29 ± 4, $p < 0.01$), and were less likely to have dyslipidemia (46% vs 100%, $p < 0.01$) or take antihypertensive medications (23% vs 71%, $p = 0.026$). Clinical presentation included headache and/or seizures in 41% of SLEs vs none in the AIS group ($p < 0.01$). The serum lactate level was significantly higher in SLEs than in AIS at presentation (42 ± 37 vs 14 ± 3, $p = 0.015$). Hemiparesis was significantly less common in SLEs than in AIS (6% vs 62%, $p < 0.01$). Of note, none of the patients with MELAS experienced a classical ischemic stroke during the study period.

Neuroimaging—Modalities

For all 17 SLE in our cohort, the earliest neuroimaging test performed at presentation was a NCCT. A proportion of the patients additionally performed CTA within 1 day of presentation (n = 11, 65%), MRI within 1 week of presentation (n = 11, 65%), and MR spectroscopy (n = 2, 12%).

The earliest neuroimaging test performed at presentation was a NCCT for all 21 patients with AIS. CTA was performed in 18 (86%) patients and MRI in 2 (9%) patients.

SLE Lesions—Spatiotemporal Pattern Analysis

Acute SLE lesions were identified as areas of parenchymal swelling with sulcal effacement that were hypodense on CT. In 11 SLEs, MRI scans were also performed within 1 week of symptom onset. The cortical lesion suspected to represent an acute SLE was uniformly hyperintense on T2/FLAIR and showed restricted diffusion on a DWI sequence with the corresponding low ADC values.

On inspection of the neuroimaging tests of patients with SLE, we identified 2 main patterns of lesion topography and spatiotemporal progression—anterior and posterior.

In the anterior pattern group (7 patients, 41% of SLEs), the earliest lesion was located at the region of the anterior hippocampus/temporal operculum, with the consequent spread of the process to the posterolateral temporal cortex, posterior insula, frontal operculum, and finally peripheral frontal cortex. The spatiotemporal evolution of anterior pattern SLE is artistically depicted on coronal sections in Figure 1A. Comparing anterior pattern SLE lesions with anatomically similar AIS cohort patients with MCA stroke, involvement of the anterior two-thirds of the insular cortex was detected in 4 (44%) of MCA strokes vs none of the anterior pattern SLE lesion ($p = 0.08$). Early (<3 days from symptom onset) involvement of the posterior third of the insular cortex was detected in 4 (44%) of MCA strokes vs none of the anterior pattern SLE lesions ($p = 0.08$). However, involvement of the posterior third of the insular cortex did appear later in the course of the SLE (>7 days from symptom

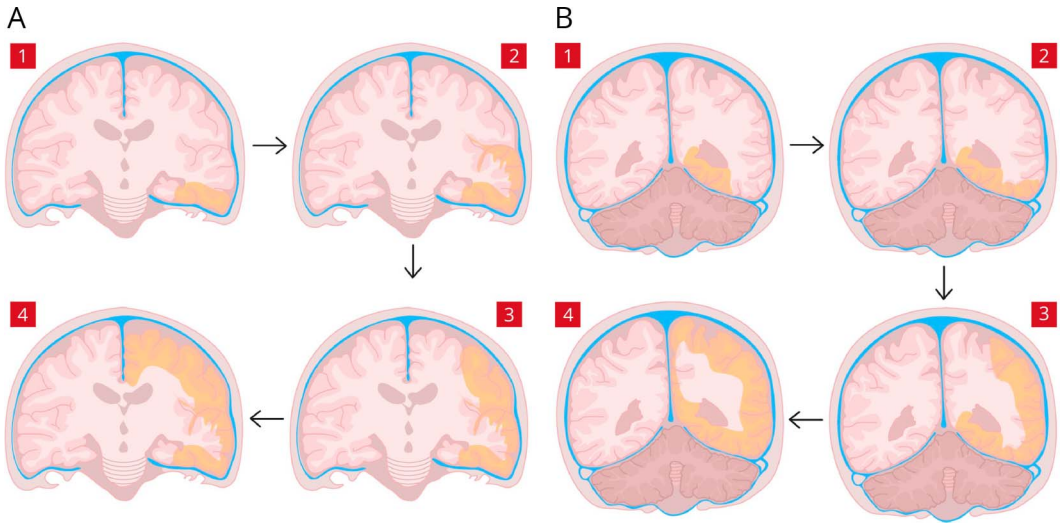
Table 1 Demographics and Clinical Characteristics of Patients With MELAS and Stroke

	MELAS (n = 11 patients, n = 17 episodes)	Stroke (n = 21 patients and strokes)	*p* Value
Age (median [IQR])	45 [37–60]	77 [68–82]	0.08
Sex—female	8 (73%)	4 (22%)	<0.01
Body mass index (mean ± SD)	18 ± 2.6	29 ± 4	<0.01
Symptoms onset to imaging (median [IQR])	4.1 [2–9]	0.8 [0.6–3.7]	<0.01
Medical background			
Ischemic heart disease	4 (46%)	7 (33%)	1
Hypertension	6 (55%)	18 (86%)	0.22
Dyslipidaemia	4 (46%)	21 (100%)	<0.01
Diabetes	9 (82%)	14 (67%)	0.25
Atrial fibrillation	0	5 (24%)	0.63
Smoking	0	7 (33%)	0.07
Chronic kidney failure	0	3 (14%)	0.28
Hearing loss	10 (91%)	1 (5%)	<0.01
Medication at first admission			
Antiaggregation	6 (55%)	10 (47%)	1
Anticoagulation	0	2 (10%)	0.5
Antihypertensive medications	2 (23%)	15 (71%)	0.03
Diabetes medications	8 (73%)	13 (62%)	0.44
Lipid lowering medications	5 (45%)	17 (81%)	0.047
Laboratory at admission			
Serum glucose (mean ± SD, mg/dL)	163 ± 78	151 ± 54	0.9
Serum lactate (mean ± SD, mg/dL)	45 ± 37	14 ± 3	0.01
Serum lactate dehydrogenase (mean ± SD, U/L)	725 ± 414	353 ± 70	<0.01
pH (mean ± SD)	7.31 ± 0.1	7.36 ± 0.04	0.03
Symptoms at admission			
Headache	4 (23%)	0	0.04
Hemianopsia or visual disturbances	8 (47%)	11 (52%)	0.74
Seizure	3 (18%)	0	0.09
Aphasia	6 (35%)	7 (33%)	0.33
Hemiparesis	1 (6%)	13 (62%)	<0.01
Confusion	5 (29%)	5 (24%)	0.71

onset) in 2 (18%) patients with wide-spread lesions of the temporal and frontal lobes.

In the posterior pattern group (10 patients, 59% of SLEs), we found that the earliest lesion was in the region of the hippocampal tail and cuneus or precuneus, then occipital pole, lateral occipital cortex, and finally parietal cortex, depicted in Figure 1B. PCA infarction spared the lateral occipital and parietal cortex in 10 (84%) patients with PCA stroke, depending on the location of PCA obstruction, whereas all posterior pattern SLEs in our cohort involved these regions in the course of lesion evolution ($p < 0.01$). Involvement of the anterior medial temporal lobe including the amygdala and uncus, which is typically seen in patients with encephalitis, was not detected in any of the posterior pattern group patients. On involvement of the parietal cortex, posterior pattern lesions often attained a shape that resembled a horseshoe. Because this pattern was pathognomonic to MELAS in our

Figure 1 Artistic Depiction of the Spatiotemporal Evolution of SLE Lesions



(A) Spatiotemporal evolution of anterior pattern SLE on coronal sections at the parieto-occipital level. Presumable initial site of involvement in the medial occipital lobe (1), further spread to the occipital pole (2), lateral occipital cortex (3), and eventual extension to the parietal lobe (4). (B) Spatiotemporal evolution of posterior pattern SLE on coronal sections at the level of hippocampus and lateral sulcus. Presumable initial site of involvement in the lateroinferior temporal lobe (1) or temporal operculum (2), further expansion to frontal operculum (3), and the rest of the frontal lobe (4). SLE = stroke-like episode.

cohort, we named it "the horseshoe sign," illustrated in Figure 3. This sign was apparent in 5 (50%) patients with the posterior pattern and in none of the PCA infarctions ($p = 0.01$).

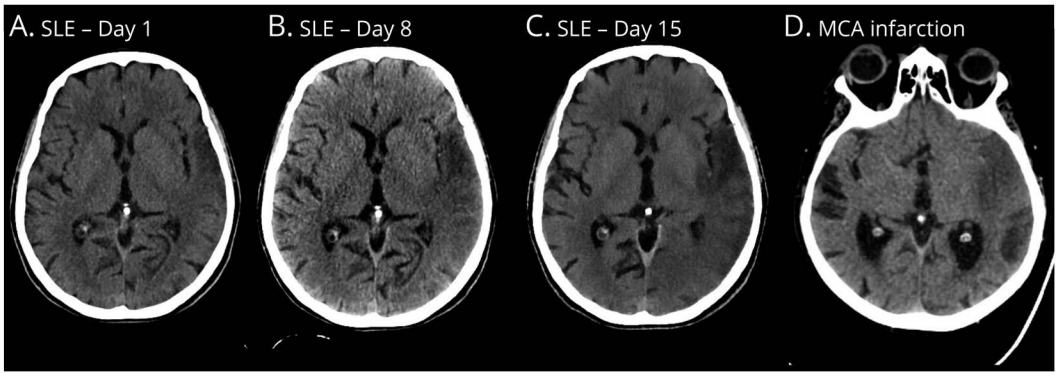
The anatomical spread of acute SLE lesions was stereotypical for each of the 2 patterns and the full extent of brain involvement became evident in the course of several days up to 2 weeks. For both anterior and posterior presentations, this pattern of spatiotemporal progression was remarkably different from that of ischemic stroke, as illustrated in Figures 2 and 3.

Other Neuroimaging Features—Stroke-like Episodes vs Acute Ischemic Stroke

At the first clinical SLE, 5 of 11 (46%) patients showed areas of encephalomalacia in a characteristic anatomical distribution indicating earlier asymptomatic SLEs compared with 2 (9%) patients with AIS who showed old infarcts in occipital/temporal distribution ($p = 0.03$).

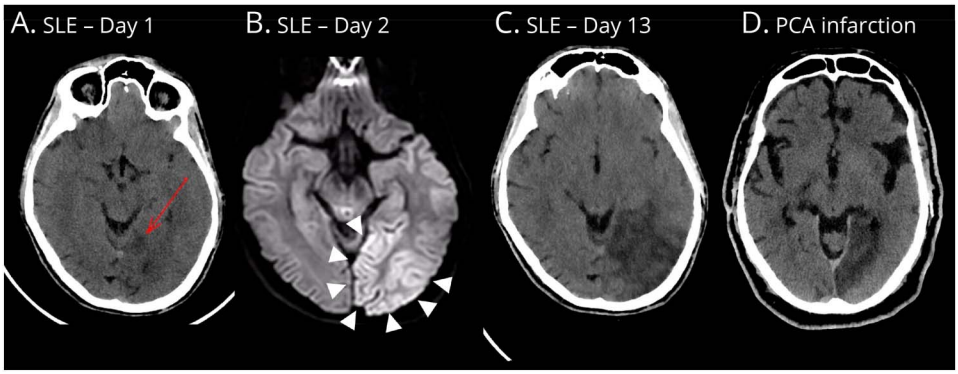
A large vessel occlusion was not detected in any of the patients with MELAS, compared with 18 of 18 (100%) patients with AIS who performed CTA ($p < 0.01$). In 5 of 11 (45%) SLEs that performed a CTA scan, signs of hyperperfusion of

Figure 2 Neuroimaging of an Anterior Pattern SLE Lesion in Comparison With MCA Branch Ischemic Stroke With Similar Topography



(A) Axial NCCT performed at admission for the first SLE in a 63-year-old woman shows a hypodense lesion in the left temporal operculum. (B and C) Axial NCCT of the same patient performed a week and 2 weeks later shows spread of the lesion to the parietal lobe and posterior third of insula but not the anterior insula in accordance with the anterior pattern of presentation. (D) Axial NCCT performed 24 hours after symptom onset in a 70-year-old patient with ischemic stroke because of occlusion of the left temporal branch of the middle cerebral artery. Note early involvement of the posterior and anterior insula. NCCT = non-contrast CT; SLE = stroke-like episode.

Figure 3 Neuroimaging of a Posterior Pattern SLE Lesion in Comparison With PCA Ischemic Stroke With Similar Topography



(A) Axial NCCT performed at admission for the first SLE in a 25-year-old man shows a small hypodense lesion in the left medial occipital lobe (red arrow). (B) Axial MRI DWI showing the same lesion on the next day. Restricted diffusion clearly involves the medial occipital cortex with more subtle involvement of the lateral occipital and parietal cortex, attaining a horseshoe shape. The "horseshoe sign" is most clearly seen in this modality (white arrowheads). (C) Axial NCCT of the same patient performed 10 days later shows a larger hypodense area involving much of the occipital lobe and spreading to the parietal lobe in accordance with the posterior type of presentation. (D) Axial NCCT performed 24 hours after symptom onset in a 76-year-old patient with ischemic stroke because of occlusion of the left posterior cerebral artery (PCA). Note sparing of the lateral occipital cortex. NCCT = non-contrast CT; SLE = stroke-like episode.

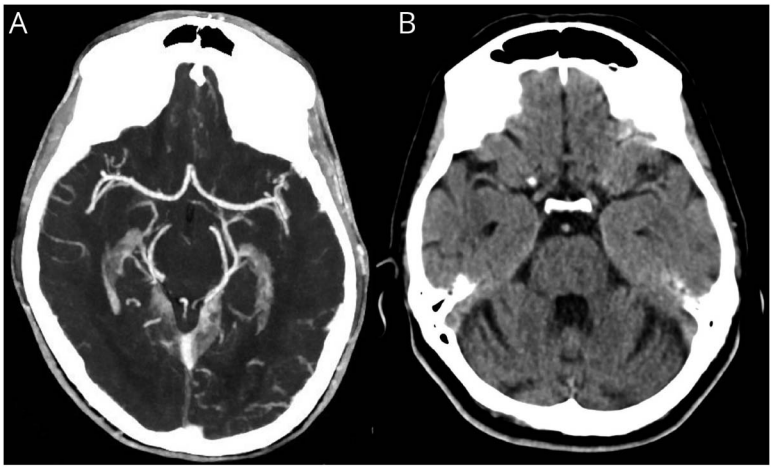
the involved brain parenchyma, namely, tissue hyperemia and venous engorgement were clearly observed (Figure 4A). These signs were also detected on early (<5 days) MRI scans but disappeared on later scans. By comparison, none of the patients with AIS showed tissue hyperemia or venous engorgement ($p < 0.01$). A lactate peak within the acute lesion was demonstrable on MR spectroscopy in 1 patient, performed on day 3 from symptom onset but not on the other, performed on day 11.

Ten (91%) patients with MELAS showed some degree of cerebellar parenchymal loss which was inappropriate for patient age. Degree of cerebellar atrophy was assessed by visual estimation of the width of cerebellar sulci and the fourth ventricle on coronal views of NCCT and noncontrast T1 images. The degree of cerebellar atrophy seemed to be dependent on the overall duration of disease (Figure 4B). By comparison, cerebellar atrophy was detected in 4 (19%) patients with AIS ($p < 0.01$). In these patients, it was mild and seemed related to normal aging. Basal ganglia calcifications, previously reported to be a frequent finding in imaging of patients with MELAS, were observed in only 2 (18%) patients in our cohort.

Construction and Validation of Clinicoradiologic Criteria

Based on the results of our clinical and radiologic analysis, we constructed a set of diagnostic criteria for SLEs that are

Figure 4 Tissue Hyperemia and Cerebellar Atrophy in the Neuroimaging of Patients With a SLE



(A) Axial slice of the CTA venous phase in maximal intensity projection performed at admission for a first SLE shows enlarged veins in the left occipital lobe compared with the normal right occipital lobe. (B) Axial NCCT slice shows widening of cerebellar sulci and the fourth ventricle in a 45-year-old female patient presenting with her first SLE. CTA = CT angiography; NCCT = non-contrast CT; SLE = stroke-like episode.

Table 2 Clinicoradiologic Criteria for the Diagnosis of SLE

Diagnosis	Criteria
Probable SLE	1) Acute or subacute onset of neurologic symptoms and/or nausea/vomiting in a patient aged <60. 2) Presence of ≥1 of the following clinical criteria: body mass index (BMI) < 20, history of sensorineural hearing loss, headache, and/or seizures at presentation. 3) An acute cortical lesion in a typical distribution for SLE: a) temporal involving at least the periopercular area and/or b) occipital involving at least the medial occipital lobe and/or c) any cortical lesion that does not follow a vascular territory. 4) Presence of ≥1 of the following neuroimaging criteria: cerebellar atrophy, presence of chronic cortical lesions with typical SLE distribution (as described in 3), hyperemia, and venous engorgement in the area of the acute lesion on CTA. 5) No large vessel occlusion.
Possible SLE	1) Acute or subacute onset of neurologic symptoms and/or nausea/vomiting in a patient aged <60. 2) Presence of ≥1 of the following clinical criteria: body mass index (BMI) < 20, history of sensorineural hearing loss, headache, and/or seizures at presentation. 3) An acute cortical lesion in a typical distribution for SLE: a) temporal involving at least the periopercular area and/or b) occipital involving the at least the medial occipital lobe and/or c) any cortical lesion that does not follow a vascular territory. 4) No large vessel occlusion.

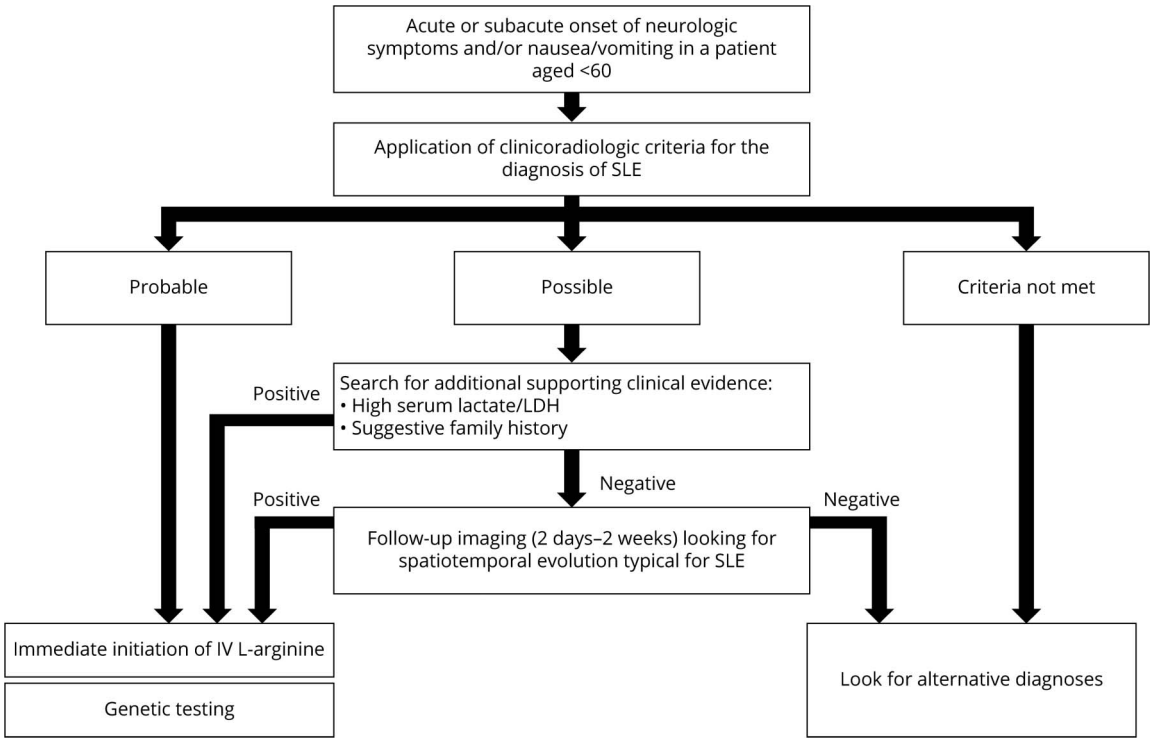
Abbreviations: CTA = CT angiography; SLE = stroke-like episode.

presented in Table 2. When applied blindly to our patient cohorts, possible SLE diagnosis criteria had sensitivity of 100%, specificity of 81%, and AUC of 0.905. Probable SLE had sensitivity of 88%, specificity of 95%, and AUC of 0.917.

Discussion

In this study, we analyzed the early neuroimaging data of patients with MELAS-associated SLE and those with similarly located acute ischemic stroke. We identified characteristic

Figure 5 Stroke-like Episode Diagnostic Algorithm



clinical features and imaging patterns and formulated a novel set of clinicoradiologic diagnostic criteria which were validated by a blinded rater.

We describe for the first time several unique imaging features of SLEs including 2 main topographic patterns with a stereotypical, predictable course of spatiotemporal progression. These 2 patterns could chronically coexist in patients with long-standing disease, indicating the accumulation of chronic lesions. However, every new attack fell into either one of these 2 patterns. We additionally describe a novel occipitoparietal "horseshoe sign" (see Figure 3B), pathognomonic for posterior pattern MELAS lesions in our cohort. Cerebellar atrophy is reported to be common in mitochondrial disease. However, the presence of cerebellar atrophy disproportionate to patient age in more than 90% of patients in our SLE cohort is striking and should be considered as highly suggestive of MELAS in the context of a young patient with acute neurologic deficit.

Previous reports on SLE neuroimaging features focused mainly on MRI and MRS.[12-15] However, many patients with a first SLE are initially misdiagnosed as AIS,[7-11] and MRI is seldom performed in the acute setting.[16] Our set of criteria does not rely on MRI but rather on a single NCCT scan performed at presentation with the optional use of additional criteria based on CTA or MRI. Subsequently, it has wide applicability in clinical practice.

All patients who presented with a first SLE in our cohort had long-standing preexisting clinical characteristics typical for MELAS including low body mass index, sensory neuronal hearing loss, a high serum lactate, and early-onset diabetes. However, in the vast majority of patients, this highly distinct clinical combination was overlooked by treating physicians until the diagnosis of MELAS was first suspected after a SLE. This highlights the significance of our new SLE-based diagnostic criteria.

The early diagnosis of MELAS has important implications for those affected and their relatives because it enables early initiation of appropriate therapy and genetic counselling. Delays in diagnosis and treatment may lead to progression of the disease, the accumulation of devastating neurologic impairment, dementia, and even death.[1,17] The acute treatment of SLEs with nitric oxide (NO) precursors and specifically with IV L-arginine has been reported to be beneficial in several small series and has become common practice.[18-21] It is therefore critical to reach a correct diagnosis at the onset of a first SLE. Our clinicoradiologic criteria allow for rapid and accurate diagnosis of SLEs at their onset and timely administration of IV L-arginine, possibly diminishing disability and preventing mortality.

We suggest that our criteria be applied in any case of a young patient (<60) presenting with acute focal neurologic deficits. In light of the high diagnostic accuracy of our criteria and the relatively high drug safety profile of IV L-arginine, the use of the following algorithm should significantly shorten time to diagnosis and treatment: when probable SLE diagnostic criteria are fulfilled, a very high suspicion of a MELAS-associated SLE should prompt immediate initiation of IV L-arginine treatment without waiting for further confirmatory tests. The treating physicians should in parallel pursuit formal molecular genetic testing. When only possible SLE diagnostic criteria are fulfilled, treating physicians should search for supporting clinical evidence such as high serum lactate and/or serum lactate dehydrogenase and perform a thorough anamnesis of family history. If diagnosis is still uncertain, a repeat neuroimaging test at several days' interval should be performed. A typical spatiotemporal evolution of the lesion should lead to the diagnosis of a SLE with very high probability and the immediate initiation of IV L-arginine treatment. The suggested algorithm is illustrated in Figure 5.

Our study has several limitations that accompany the study of a rare disease. Our patient cohort was relatively small. Validation was performed by a blinded rater on the same patient cohort on which criteria were constructed. These limit the external validation of our findings, and they should be corroborated in a separate, larger cohort of patients with MELAS and SLE. In addition, our cohort included only adult patients and is therefore not applicable to the pediatric population.

In conclusion, SLEs have unique clinical and neuroimaging features. A set of clinicoradiologic criteria based on simple anamnesis and a CT at presentation can accurately diagnose SLE and lead to early administration of appropriate therapy.

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Disclosure

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Publication History

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Appendix Authors

Name	Location	Contribution
Vadim Khasminsky, MD	Department of Imaging, Rabin Medical Center, Petach Tikva; Sackler Faculty of Medicine, Tel Aviv University, Israel	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Eitan Auriel, MD	Department of Neurology, Rabin Medical Center, Petach Tikva; Sackler Faculty of Medicine, Tel Aviv University, Israel	Study concept or design

Appendix *(continued)*

Name	Location	Contribution
Judith Luckman, MD	Department of Imaging, Rabin Medical Center, Petach Tikva; Sackler Faculty of Medicine, Tel Aviv University, Israel	Major role in the acquisition of data
Ruth Eliahou, MD	Department of Imaging, Rabin Medical Center, Petach Tikva; Sackler Faculty of Medicine, Tel Aviv University, Israel	Major role in the acquisition of data
Edna Inbar, MD	Department of Imaging, Rabin Medical Center, Petach Tikva; Sackler Faculty of Medicine, Tel Aviv University, Israel	Major role in the acquisition of data
Keshet Pardo, MD	Department of Neurology, Rabin Medical Center, Petach Tikva, Israel	Analysis or interpretation of data
Yuval Landau, MD	Sackler Faculty of Medicine, Tel Aviv University; Metabolic Diseases Clinic, Schneider Children's Medical Center, Petach Tikva, Israel	Drafting/revision of the manuscript for content, including medical writing for content
Rani Barnea, MD	Department of Neurology, Rabin Medical Center, Petach Tikva; Sackler Faculty of Medicine, Tel Aviv University, Israel	Study concept or design
Maor Mermelstein, MD	Department of Neurology, Rabin Medical Center, Petach Tikva, Israel	Major role in the acquisition of data
Shahar Shelly, MD	Department of Neurology, Rambam Health Care Campus, Haifa, Israel; Department of Neurology, Mayo Clinic, Rochester, MN	Analysis or interpretation of data
Jonathan Naftali, MD	Department of Neurology, Rabin Medical Center, Petach Tikva, Israel	Major role in the acquisition of data; analysis or interpretation of data
Shlomi Peretz, MD	Department of Neurology, Rabin Medical Center, Petach Tikva; Sackler Faculty of Medicine, Tel Aviv University, Israel	Study concept or design

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