eAppendix 1. Search strategy

We searched Medline via Ovid, Embase via Ovid, Scopus, Web of Science, and CINAHL via EBSCO from inception to January 15, 2021 with no language or other restrictions imposed. We also performed backward citation searching; the reference lists of included articles and related reviews were manually screened via hand searching to identify additional studies. and searched ClinicalTrials.gov. We did not contact authors, additional experts, manufacturers, or others for additional data.

The search was first run on 12/7/2019 and updated shortly before submission of the planned manuscript in order to include the latest references (the last date the searches were carried out on all databases was January 15, 2021).

The search was undertaken by a senior medical librarian (L.E), with the search strategies peer reviewed by the investigational team, included subject expertise (neurologists, G.S.G. and Y.S.N.) prior to execution. All records from each data source were imported using bibliographic management software (EndNote) for de-duplicating, screening and managing each stage of the inclusion/exclusion article process. Duplicates were removed using EndNote's duplicate identification functionality (LE) and then manually (R.J.S.)

The search strategy used across databases were translated as closely as possible; a variety of keyword and subject heading terms were included to cover these concepts depending upon the thesaurus terms available in each database. The only search filter used was that recommended by Cochrane to identify human not animal studies at the end of both the Ovid Medline and Embase searches.

Database	Search	Search terms	Database	Search	Search terms
MEDLINE (Ovid)	1	exp Arginine/	Embase (Ovid)	1	Arginine/
	2	Citrulline/		2	Citrulline/
	3	L-arginine.mp.		3	L-arginine.mp.
	4	arginine.mp.		4	arginine.mp.
	5	L-citrulline.mp.		5	L-citrulline.mp.
	6	citrulline.mp.		6	citrulline.mp.
	7	Nitric Oxide/		7	Nitric Oxide/
	8	nitric oxide.mp.		8	nitric oxide.mp.
	9	or/1-8		9	or/1-8
	10	exp Mitochondrial Diseases/		10	"disorders of mitochondrial functions"/
	11	MELAS.mp.		11	MELAS.mp.
	12	MERRF.mp.		12	MERRF.mp.
	13	DNA Polymerase gamma/		13	DNA directed DNA Polymerase gamma/
	14	POLG.mp.		14	POLG.mp.
	15	"8344".mp.		15	"8344".mp.
	16	"3243".mp.		16	"3243".mp.
	17	DNA, Mitochondrial/		17	DNA, Mitochondrial/
	18	mitochondria*.mp.		18	mitochondria*.mp.
	19	or/10-18		19	or/10-18
	20	stroke-like episode*.mp.		20	stroke-like episode*.mp.
	21	exp Epilepsy/		21	exp Epilepsy/
	22	epilep*.mp.		22	epilep*.mp.
	23	exp Seizures/		23	exp Seizure/
	24	seizure*.mp.		24	seizure*.mp.
	25	exp Brain Diseases/		25	exp Brain Disease/
	26	encephalopath*.mp.		26	encephalopath*.mp.
	27	or/20-26		27	or/20-26
	28	9 and 19 and 27		28	9 and 19 and 27

	29	exp animals/ not humans.sh.		29	(animal$ not human$).sh,hw.
	30	28 not 29		30	28 not 29

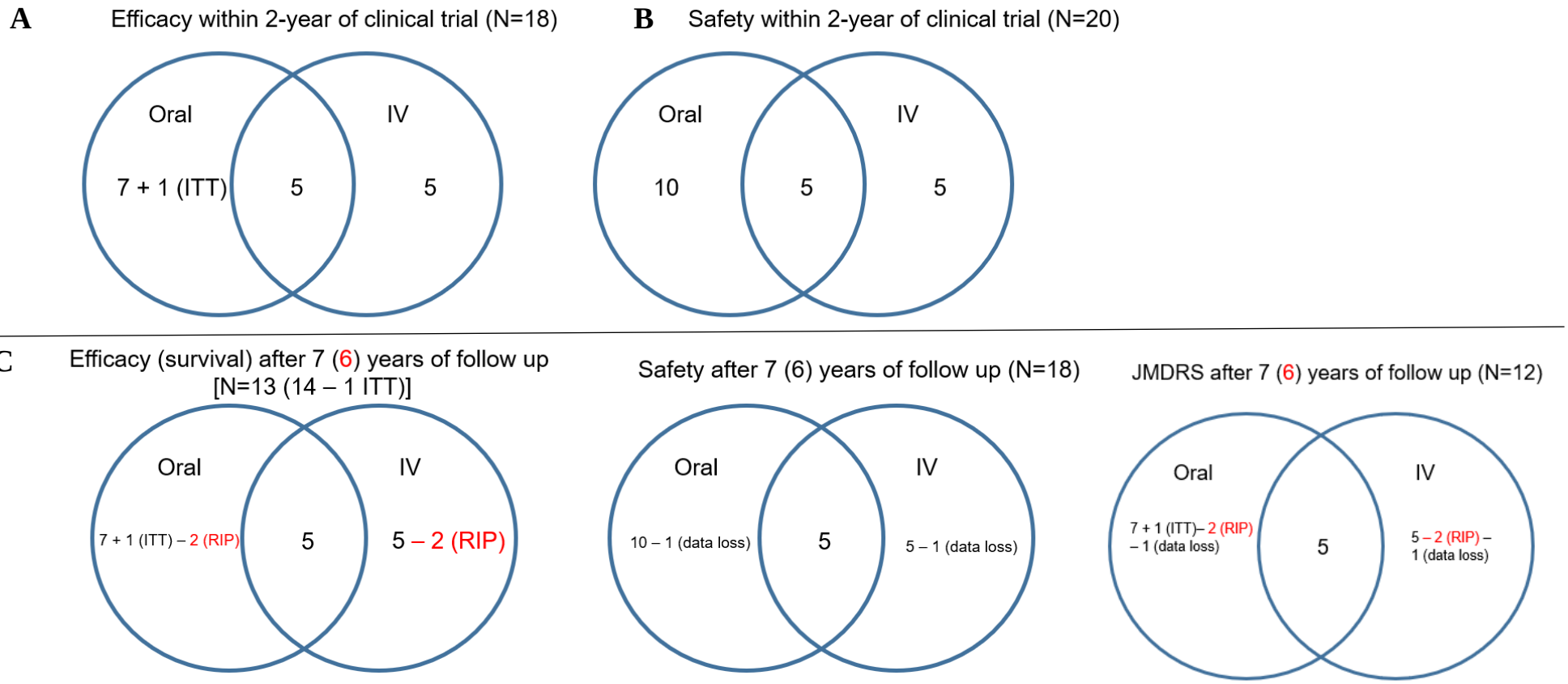
Scopus (EBSCO)
(TITLE-ABS-KEY (arginine OR citrulline OR l-arginine OR l-citrulline OR "Nitric Oxide") AND TITLE-ABS-KEY (melas OR merrf OR "DNA Polymerase gamma" OR polg OR 8344 OR 3243 OR mitochondria*) AND TITLE-ABS-KEY ("stroke-like episode*" OR epilep* OR seizure* OR "Brain Disease*" OR encephalopath*))

Web of Science (EBSCO)
TOPIC: (Arginine OR Citrulline OR L-arginine OR L-citrulline OR "Nitric Oxide") AND TOPIC: (MELAS OR MERRF OR "DNA Polymerase gamma" OR POLG OR 8344 OR 3243 OR mitochondria*) AND TOPIC: ("stroke-like episode*" OR epilep* OR Seizure* OR "Brain Disease*" OR encephalopath*)

CINAHL (EBSCO)
TX (Arginine OR Citrulline OR L-arginine OR L-citrulline OR "Nitric Oxide") AND TX (MELAS OR MERRF OR "DNA Polymerase gamma" OR POLG OR 8344 OR 3243 OR mitochondria*) AND TX ("stroke-like episode*" OR epilep* OR Seizure* OR "Brain Disease*" OR encephalopath*)

Clinicaltrials.gov
Arginine OR Citrulline OR L-arginine OR L-citrulline OR Nitric Oxide | MELAS OR MERRF OR "DNA Polymerase gamma" OR POLG OR 8344 OR 3243 OR mitochondrial disease OR "stroke-like episode

eFigure 1. Number of patients evaluated for safety and efficacy in Koga et al. 2018 [1]



Abbreviations: ITT, intention-to-treat; JMDRS, Japanese mitochondrial disease rating scale; RIP, rest in peace

A Inter-ictal MELAS (Oral) March 09–June 11, a
N=15 patients were enrolled. N=3 patients discontinued: increased seizure frequency, concurrent pneumonia, and unverified efficacy.
Efficacy: N=13, However N=12 completed the trial [data from 1 of the 3 discontinued patients was included for analysis (assumed ITT)]
Safety: N=15
a 5 patients were also enrolled in the clinical trial of IV L-arginine

B Acute MELAS (IV) Dec 08–March 2011 b
Enrolment (N=10); Efficacy (N=10); Safety (N=10)
b 5 patients were also enrolled in the clinical trial of oral L-arginine

C Additional 6-years follow up until May 2017
Deaths: N=2 while on in the interictal (oral) trial, N=2 while in the acute (IV) trial
Efficacy: N=7 + N=5 + N=5 – N=4 (deaths); N=13
Safety: N=10 + N=5 + N=5 – N=2 (lost follow up); N=18

References

1. Koga Y, Povalko N, Inoue E, et al. Therapeutic regimen of L-arginine for MELAS: 9-year, prospective, multicenter, clinical research. Clinical Trial Multicenter Study. *Journal of Neurology*. 2018;265(12):2861-2874.

eTable 1. PRISMA 2002 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1, 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3-4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	e1 (pg. 1 - 2)
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4-5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4-5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4-5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4-5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4-5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5, Fig 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	eTable 2
Study characteristics	17	Cite each included study and present its characteristics.	eTable 3-eTable 4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	eTable 5-eTable 6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	5, Fig 2A/B
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	8-11
	23b	Discuss any limitations of the evidence included in the review.	9-10
	23c	Discuss any limitations of the review processes used.	9-10
	23d	Discuss implications of the results for practice, policy, and future research.	10-11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	1 and 3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	1 and 3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	12
Competing interests	26	Declare any competing interests of review authors.	12

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	5

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

eTable 2 PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	YES
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	YES
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	YES
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	YES
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	YES
Synthesis of results	6	Specify the methods used to present and synthesise results.	YES
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	YES
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	YES
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	YES
Interpretation	10	Provide a general interpretation of the results and important implications.	YES
OTHER			
Funding	11	Specify the primary source of funding for the review.	N/A
Registration	12	Provide the register name and registration number.	YES

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71 . For more information, visit: http://www.prisma-statement.org

eTable 3. PRISMA-S Checklist

Section/topic	#	Checklist item	Location(s) Reported
INFORMATION SOURCES AND METHODS			
Database name	1	Name each individual database searched, stating the platform for each.	3; e1 (pg. 1)
Multi-database searching	2	If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched.	N/A
Study registries	3	List any study registries searched.	4
Online resources and browsing	4	Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done.	N/A
Citation searching	5	Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, setting up email alerts for references citing included studies).	3; e1 (pg. 1)
Contacts	6	Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others.	e1 (pg. 1)
Other methods	7	Describe any additional information sources or search methods used.	4
SEARCH STRATEGIES			
Full search strategies	8	Include the search strategies for each database and information source, copied and pasted exactly as run.	e1 (pg. 1-2)
Limits and restrictions	9	Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use.	4
Search filters	10	Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used.	e1 (pg. 1-2)
Prior work	11	Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s).	N/A
Updates	12	Report the methods used to update the search(es) (e.g., rerunning searches, email alerts).	e1 (pg. 1)
Dates of searches	13	For each search strategy, provide the date when the last search occurred.	e1 (pg. 1)
PEER REVIEW			
Peer review	14	Describe any search peer review process.	e1 (pg. 1)
MANAGING RECORDS			

Total Records	15	Document the total number of records identified from each database and other information sources.	Fig 1
Deduplication	16	Describe the processes and any software used to deduplicate records from multiple database searches and other information sources.	e1 (pg. 1)

PRISMA-S: An Extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews
Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB, PRISMA-S Group.
Last updated February 27, 2020.

eTable 4. Excluded studies after full-text review

Author ID	Title	Reason for exclusion
Abraham, Abraham & Khanna, 2010[1]	Arginine extravasation leading to skin necrosis	Patients did not meet criteria for genetically confirmed diagnosis
Ebrahimi-Fakhari et al. 2015[2]	Recurrent Stroke-Like Episodes in FBXL4-Associated Early-Onset Mitochondrial Encephalomyopathy	Insufficient detail provided to ascertain if L-arginine was used for the acute or prophylactic treatment of SLEs
El-Hattab et al. 2012[3]	Restoration of impaired nitric oxide production in MELAS syndrome with citrulline and arginine supplementation	No L-arginine intervention
El-Hattab et al. 2016[4]	Impaired nitric oxide production in children with MELAS syndrome and the effect of arginine and citrulline supplementation	L-arginine was not used for the acute or prophylactic treatment of SLEs
Goto & Momoi 2004[5]	Treatment for mitochondrial diseases	No L-arginine intervention
Ikawa, Povalkoc & Koga, 2018[6]	Arginine therapy in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes	Duplicated data of previously published (and included) article (Koga et al. 2018)
Koga et al. 2006[7]	Endothelial dysfunction in MELAS improved by L-arginine supplementation	Duplicated data of previously published (and included) article (Koga et al. 2005)
Koga et al. 2007[8]	MELAS and L-arginine therapy	Duplicated data of previously published (and included) article (Koga et al. 2005)
Koga et al. 2008[9]	L-arginine therapy on MELAS	Duplicated data of previously published and included) article (Koga et al. 2005)
Liu et al. 2019[10]	Mitochondrial A3243G mutation causes mitochondrial encephalomyopathy in a Chinese patient	No L-arginine intervention
Moutaouakil et al. 2009[11]	L-arginine efficiency in MELAS syndrome. A case report	Unable to translate to English (French)
Murakami & Ono 2017[12]	MELAS: Mitochondrial encephalomyopathy, lactic acidosis and SLEs	No L-arginine intervention
Parikh et al. 2009[13]	A modern approach to the treatment of mitochondrial disease	No L-arginine intervention
Parikh et al. 2017[14]	Patient care standards for primary mitochondrial disease: A consensus statement from the mitochondrial medicine society	No L-arginine intervention
Rodan et al. 2015[15]	L-arginine Affects Aerobic Capacity and Muscle Metabolism in MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-Like Episodes) Syndrome	Patients did not meet criteria of SLEs
Rodan et al. 2020[16]	L-arginine effects on cerebrovascular reactivity, perfusion and neurovascular coupling in MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes) syndrome	L-arginine was not used for the acute or prophylactic treatment of SLEs
Song et al. 2019[17]	Twenty-one-year follow-up of variable onset MELAS syndrome with heteroplasmic mt3243A>G mtDNA mutation: A case report	Patients did not meet criteria of SLEs

Sudo, Sano, & Kawamura 2014[18]	Determination of the critical time point for efficacy of L-arginine infusion therapy in a case of MELAS with frequent SLEs	Unable to translate to English (Japanese)
Toribe 2007[19]	Usefulness of L-arginine infusion for status epilepticus in mitochondrial myopathy, encephalopathy, lactic acidosis, and SLEs	Unable to translate to English (Japanese)
Yatsuga et al. 2012[20]	MELAS: a nationwide prospective cohort study of 96 patients in Japan	No L-arginine intervention

Abbreviations: SLE, stroke-like episode
NB: Only 1 patient (patient 1) was eligible for inclusion in Suzuki et al. 2017[21] (patient 2 and 3 excluded: no L-arginine intervention);
2 patients (1 and 3) included in Renard & Ion 2020[22] (patient 2 excluded: no L-arginine intervention).

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eTable 5. Summary characteristics of included case reports and cohort study (N=34)

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophyl axis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
Case reports										
Corr et al. 2014[1]	1	m.3243A>G	M; 48	3-d history of brief generalised tonic–clonic S; 1-w word finding difficulty and speech apraxia with ↓ fine motor skills. Bilateral LL and R-UL and orolabial dyspraxia. Difficulty conversing, expressive and receptive dysphasia. Ataxic gait; impaired UL/LL coordination. *B, CT, MRI, MRS*	n=1; Regime: NR; Dose: NR	No	Yes, not specified	Aggressively hydrated; enteral feeding; diabetic medication	NR	Speech and gait improved over the 3-w admission. ADL impacted, so referred to a neurological rehabilitation centre- there was almost complete recovery of neurological function.
Fang, Zheng & Zhang 2018[2]	1	m.3243A>G	F; 63	Acute psychosis and R-sided hemiparesis. Mixed non-fluent aphasia. *B, EEG, MRI, CT*	n=1; Regime: NR; Dose: NR for 1-w	No	NR	Aspirin and atorvastatin (prior to diagnosis), vitamin E, CoQ_{10}	NR	'dramatically improved' after 1-w. Muscle strength recovered, and there were no residual psychotic symptoms or aphasia on discharge.
Fryer et al. 2016[3]	1	m.3243A>G (72% hetroplasmy)	F; 8	At 8-y, acute onset of binocular blindness with hemiparesis. V spontaneously improved over 4-d	-	Yes Dose: NR	NR	*Chronic:* riboflavin, CoQ_{10}	NR	Discharged with a persistent L hemiparesis. She had progressive cognitive deficits, including episodes of speaking nonsense words and other incoherent speech patterns, memory problems, and difficulty completing tasks.

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophylaxis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
				At 10-y, 11-d after taking aspirin- H, nausea, emesis, blurred V, slurred speech. Worsened H and R arm shaking. All extremities moved spontaneously (more on the L); intermittent R arm and leg trembling and R-sided sensory disturbance. *MRI, B, CT*	n=1; IV, a Dose: NR (with 10% dextrose-containing fluids) for 24-h	Yes Dose: NR		aspirin (3-w before presenting), discontinued at discharge *Acute:* dexamethasone; *Chronic:* steroid taper		Her condition improved.
Gagliardi et al. 2019[4]	1	m.3243A>G (13.1% hetroplasmy)	M; 50 *(dec)*	Persistence of confusion and L arm clumsiness and stiffness. *EEG, MRI, MRS*	1; IV Dose: NR	Yes Dose: NR	*Acute:* carbamazepine, lacosamide, phenytoin, clobazam added to levetiracetam; *Chronic:* levetiracetam	*Acute:* dexamethasone; *Chronic:* ubidecarenone, riboflavin, insulin	NR	3-mo. after discharge, presented with new onset-acute confusion, V illusion, H and disoriented. R superior quadrantopsia with previous L-HH. Face-blindness, V agnosia, L UL apraxia and mild anomic aphasia. MRI- partial resolution of previous R cortical lesion and new SLE. Following mo., ideomotor decline; disorientation, psychomotor agitation, speech disturbance with confabulation and cortical-blindness; a new L lateral temporal and occipital lesion (MRI). Despite ↑ oral L-arginine dose and acute IV L-arginine, non-convulsive status epilepticus (NCSE) developed- requiring additional AEDs. No recovery, patient died 1-mo. later.

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophylaxis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
González et al. 2020[5]	1	m.3243A>G	M; 38	Speech impairment, irritability (2-w), H (4-d). Expressive language disorder, L-HH, astereognosis and L distal arm W. *B, CT, EEG*	1; IV (bolus, 30 g + 30 g (24-h infusion with 10% dextrose) for 3-d	Yes. 7 g tid	levetiracetam	CoQ_{10}	NR	NCSE status was resolved only after adding IV lacosamide. MRI 1-mo. after clinical onset showed a partial resolution of the lesions.
Hayashi et al. 2020[6]	1	m.3482A>G	F; 41 *(dec)*	History of multiple SLEs since 16-y. Akinetic mutism 2-mo. prior to admission. *B, MRI, MRS*	1; Oral 0.5 g/kg/d	Yes 0.5 g/kg/d until death (5-mo.)	NR	Not given taurine or other supplements (not specified)	NR	Improved consciousness- she could reply to simple orders within 4-w after treatment. No SLEs for 5-mo. preceding death due to aspiration pneumonia. Postmortem revealed bilateral cerebral atrophy predominantly in L occipital lobe and cerebellar atrophy.
Hovsepian et al. 2018[7]	1	m.3243A>G	F; 46	Experienced a S 7-y prior followed by 6-y asymptomatic period before presenting. Abnormal L hand movements, jaw jerking, difficulty following complex commands, impaired attention, memory, and extinction to L side stimulation. *B, MRS, MRI*	1; IV 0.5 g/kg/d for 7-d	Yes 0.32 g/kg/d	lacosamide, levetiracetam	*Acute:* methylprednisolone, CoQ_{10}, riboflavin, vitamin C	NR	Within a few days, improved delayed recall, and resolution of abnormal movements. Glasgow Outcome Score (from 3 to 4); modified Rankin Scale for Neurologic Disability (from 4 to 3). At 3-d into acute treatment, ↓ lactate peak and an elevated NAA/Cho ratio (MRS); ↓ FLAIR signal (MRI) 8-d after acute treatment, persistent or continued improvement.

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophylaxis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
Ito et al. 2020[8]	1	m.3243A>G (37% hetroplasmy)	M; 2 SLEs at 25-y and 30-y *(dec)*	At 25-y, H, vomiting, and aphasia. *B, MRI* At 30-y- H, vomiting, apraxia. *B, ECG, MRI*	2; IV 30 g/d	Yes 12 g/d (after 1st SLE)	NR	Not given: aminoglycoside, valproic acid, or dichloroacetate	NR	1st SLE- Gradual improvement. 2nd SLE- At 38-d, most of the abnormal MR signals had disappeared. However, patient developed serious acute renal failure with lactic acidosis, followed by rhabdomyolysis. Multiple cardiopulmonary arrests and sudden deterioration resulted in death 10-d after presenting.
Kitamura et al. 2016[9]	2	m.3243A>G (79% hetroplasmy in urine)	F; 7	History of SLE at 5.5-y. L-sided L-side hemianopia and hemiconvulsion, H, vomiting.	1: IV 0.5 g/kg (60-min of symptom onset)	No	Not used	NR	NR	All clinical symptoms disappeared within 30-min. MRI at 18-h after symptom onset showed high intensity signal in bilateral cerebellar cortex and right posterior cortex. MRI normalised at 1-w and 1-mo. later.
		m.3243A>G (45% hetroplasmy in urine)	F; 32	History of 2 SLEs. L hemiconvulsion, H and vomiting.	1: IV 0.5 g/kg at (60-min of symptom onset)	No	Yes, not specified	NR	NR	Hemi-convulsion was getting worse to generalized convulsion, however, S and vomiting disappeared within 120-min after L-arginine followed by AEDs. MRI at 2 and 9-h after symptom onset showed signal change in R parietal lobe with restricted diffusion. MRI normalised (1-w and 1-mo.)

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophylaxis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
Kubota et al. 2004[10]	1	m.3243A>G	F; 16	History of 4 prior SLEs from 14-y. R-sided hemiconvulsion. S every 2-3-min (1-min, and occasionally progressed to secondary generalized S. Altered consciousness. R-sided hemiparesis and sensory loss. *MRI*	1; IV 0.5 g/kg (5-h of symptom onset)	No	diazepam, midazolam	prednisolone, glycerol, edalavone	None	After 1-h, the S disappeared, and consciousness gradually recovered. Within 24-h consciousness disturbance and R-sided sensori-motor problems disappeared.

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophylaxis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
Lekoubou et al. 2011[11]	1	m.3243A>G (15% hetroplasmy in blood)	F; 38	1-mo history of disorientation, behavioral and speech disturbances, brief L-sided tonic head deviation with unresponsiveness to verbal and painful stimuli. Persistent confusion and delusions. *B, MRI*.	3; Oral 0.375 g/kg/d	Yes 0.375 g/kg/d for 27-mo. in total (5-mo. x 2 and 17-mo.)	levetiracetam	idebenone	None	Clinical status gradually improved over 5-mo. The patient still exhibited action slowing but was well-oriented. No deficit of memory, language, visuo-spatial or executive function. NMDAS from 54 (on treatment initiation) to 25 (at 5-mo.). 10-d after stopping L-arginine and idebenone: Recurrent V impairment and confusional state. L hemiparesis and L hemianopsia. MRI- new lesions. Despite some residual V and language impairments, independence remained for most days. 48-h after a 2nd treatment discontinuation, L heminanopsia worsened and L hemibody sensory deficit developed. MRI- extension of the lesions to the R pulvinar and marked bilateral parietal and occipital atrophy. After 17-mo., cognitive impairment gradually improved, no recurrent epileptic seizures. Orientated with a well-adapted behaviour but exhibited persistent action slowing, constructional apraxia, L hemianopsia and sensory deficit.

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophyl axis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
Minobe et al. 2015[12]	1	m.3243A>G	F; 22	16-d history of H, aphasia, V disturbance, partial S. R-HH and conjugate eye deviation to the R, which was considered to indicate a simple partial S. *MRI, CT, EEG*.	1; NR Dose: NR	No	NR	vitamin B	NR	Yes. Reported symptoms gradually improved after the use of L-arginine. MRI, CT angiography and CT perfusion showed ↓ dilation of the blood vessels and hyperperfusion (13-d after treatment).
Mitani et al. 2013[13]	1	m.3243A>G	F; 2 SLEs at 8-y	1st SLE: 2-d history of fever and clonic S. H, blindness. R-HH 2nd SLE: On d-40 after presenting, complete blindness, H, repeated clonic S. *MRI, MRS*	2; NR Dose: NR	No	NR	vitamin B_1, edaravone, glycerin	NR	Yes. 1st SLE: On d-11, still reported H, and MRI revealed a high-intensity signal lesion with MRS showing a high lactate peak and large ↓ in NAA/Cr. Symptoms disappeared by 4-w and R-HH at discharge. 2nd SLE: Symptoms improved within 24-h. On d-44 (4-d after SLE), MRS showed a ↓ in Lac peak in the R occipital lobe.
Oyama et al. 2020 [14]	1	m.3243A>G (17% hetroplasmy in blood)	M; 47	Admitted with acute onset sensory aphasia. On d-45, cerebellar ataxia, and dysarthria. Mute and somnolent a few days later. *MRI, EEG, B*	1; NR 12 g/d	No	levetiracetam	acyclovir, methylprednisolone, plasma exchange, taurine, vitamin B_1, carnitine	None	Yes. She became able to follow simple commands. Follow-up MRI at 4-mo. after admission showed diffuse brain atrophy including the cerebellum; modified Rankin Scale at 9-mo. was 4, with residual cognitive deficits.

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophylaxis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
Randhawa et al. 2016[15]	1	m.3243A>G (23% hetroplasmy in blood)	F; 48	L-HH which progressed to cortical blindness plus L- U extremity paranesthesia over 3-w. H, generalised tonic clonic S. *CT, EEG, MRI*	1; Oral Dose: NR	Yes Dose: NR	levetiracetam, phenytoin	*Acute:* acyclovir; Chronic: vitamin cocktail, including citrulline; Other: tacrolimus	None	Yes. 6-w after presenting, patient was no longer cortically blind. She had mild residual L-HH and encephalopathy; and optic ataxia. Some improvement in low attenuation of the bilateral occipito-parietal regions (CT).
Renard & Ion 2020[16]	1 #1	m.3243A>G	M; 32	History of S. SLE in the absence of clinical or EEG abnormalities in favour of epilepsy. *MRI*	1; NR Dose: NR	No	topiramate	NR	NR	NR
	1 #3	m.3243A>G	F; 54	History of epilepsy. SLE in the absence of clinical or EEG abnormalities in favour of epilepsy. *MRI*	1; NR Dose: NR	No	iacosamide	NR	NR	NR
Sakai et al. 2018[17]	1	m.3243A>G	F; 53	Walking instability 10-d before admission. H and writing difficulty. R-HH, truncal ataxia. *B, CT, MRI, MRA*	1; IV 16 g/d for 3-d (on d-3 of hospital admission)	Yes Dose: NR	levetiracetam on d-10 of hospital admission	*Acute:* unfractionated heparin	NR	Day after IV treatment (d-4), neurological symptoms deteriorated with the additional development of pure alexia and Gerstmann's syndrome; on d-5, EEG showed intermittent slow wave of 4-5Hz predominantly in the L parieto-occipital lobe); on d-8, DWI-positive lesions further expanded, with hyperperfusion in the L parieto-occipital lobes (SPECT).

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophylaxis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
Shigemi et al. 2011[18]	1	m.13513G>A	M; 15	Previous SLE 2-y earlier. Generalized convulsions, R-HH, and Gerstmann syndrome. 2-y later, sudden R-HH and gait disturbance. *B, MRI*.	1; IV 0.5 g/kg on d-1 of symptom onset (5 x over 9-d)	Yes 0.2 g/kg/d bid ~d-4 of symptom onset ↑ dose to 0.4 g/kg/d bid	*Acute:* diazepam	*Acute:* mannitol; *Chronic*: vitamin B_1, vitamin B_2, CoQ_{10}, dichloroacetate	None	After 1st IV L-arginine, V fields improved but after 30-h, gradual incomplete paralysis of the R limbs and generalized convulsions developed which stopped after diazepam. IV L-arginine was re-administered- 2-h later, the patient was alert and could move his R hand. Incomplete paralysis of R lower limb on treatment d-5, 6 and 9. Symptoms improved immediately upon switching to IV L-arginine.
Shimizu et al. 2020[19]	1	m.3271T>C	F; 24	Impaired consciousness and myoclonus in the extremities, mandible, and trunk (persisted for 2-w). Diagnosed NCSE. UL and LL bilateral muscle W. *B, MRI, EEG.*	1; NR Dose: NR	No	levetiracetam, perampanel, lacosamide, clobazam, propofol, midazolam	CoQ_{10}, L-carnitine	NR	Patient developed propofol infusion syndrome when treated for status epilepticus; L-arginine had been given prior to the development of refractory S.

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophyl axis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
Siddiq, Widjaja & Tein 2015[20]	1	m.3243A>G (32% hetroplasmy in blood)	M; SLE at 10-y, 2-mo.	Encephalopathy with R-sided focal S, receptive aphasia, R-superior quadrantanopia. R hemiparesis. At 3-mo. he had memory, processing, and word-finding difficulties but no focal W or field defect. *MRI, MRS*	1; Oral 0.5 g/kg/d divided tid converted to IV 0.5 g/kg/d divided tid (24-h). ↓ to 0.2 g/kg/d divided tid (48-h)	Yes Tapered over 6-w to 1 g bid	NR	NR	*Acute* Oral: emesis	Oral- within 24-h, rapid neurologic improvement IV- symptoms resolved. Chronic- At 3 mo., no field defect or focal W, steady improvement in speech, cognitive processing, and memory.
			SLEs at 13-y	Upper respiratory tract infection and emesis; hospitalized for hydration. 6-d later, H with transient diplopia, partial R VI nerve palsy, and V. *MRI*	1; IV 0.5 g/kg/d divided tid (24-h). ↓ to 0.2 g/kg/d	-	NR	NR	NR	Within 24-h, complete resolution of symptoms. MRI after 3-d- complete resolution of the pontine lesion, but the basal ganglia, R occipital pole, and L superior temporal gyrus were unchanged.

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophyl axis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
Sunde et al. 2016[21]	1	m.3243A>G (31% hetroplasmy in blood)	F; 49	Generalized tonic-clonic S and multiple confusional spells. History of 4 SLEs (between 49 and 50-y), resulting in mild neurologic deficits, predominantly involving language fluency. *CT, MRI*	1; IV Dose: NR	Yes 5 g bid	*Acute:* phenytoin, levetiracetam, lamotrigine; *Chronic:* phenytoin, lamotrigine, levetiracetam, clonazapan	*Acute:* IV glucose; *Chronic:* CoQ_{10}, vitamin B_{12} vitamin C, vitamin E calcium with vitamin D	NR	Responded (on multiple therapies). No major events. However, she has persistent neurological deficits including word findings difficulties, despite being on L-arginine.
Torre et al. 2020[22]	1	m.3243A>G	M; 61	20-mo. prior- episode compatible with secondarily generalised focal-onset S with status epilepticus. Asymptomatic until sudden V loss affecting the L hemifield. L-HH; slight dysmetria during L finger-to-nose. Declined in the following days- cortical blindness, deafness, global aphasia. Psychomotor agitation, continuous jargon aphasia and unmotivated actions. *B, MRI*	1; Oral 6 g/8-h	Yes 6 g/8-h (6-w)	*Acute:* phenytoin, levetiracetam, clonazepam; *Chronic:* clonazepam, levetiracetam lacosamide	*Acute:* ubiquinol, idebenone, vitamin complexes (thiamine [B_1], riboflavin [B_2] vitamin C2, vitamin E; *Chronic:* vitamin complexes	NR	His condition improved to a certain extent at discharge (6-w). He was able to follow simple instructions and produce short, coherent sentences. His V improved slightly. Speech impairment with paraphasia persisted.

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophyl axis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
Ueki et al. 2020[23]	1	m.3243A>G	F; 76	Encephalopathy accompanied by SLEs and NCSE. Hearing disability was worsening and unable to communicate. Sensory aphasia and R unilateral spatial neglect, R central facial hemiparesis, impaired consciousness. After 4-d, W (R UL and LL). *MRI, MRA, EEG, CT, MRS*	1; NR Dose: NR	No	levetiracetam, carbamazepine, lacosamide, midazolam, perampanel	heparin, aspirin, edaravone, ubidecarenone, ascorbic acid, fursultiamine, levocarnitine	NR	Had to give multiple AEDs to control NCSE. Patient had sensory aphasia as a sequela- requiring transfer to rehabilitation hospital.
Wang et al. 2020[24]	1	m.10158T>C	F; 22	Previously hospitalised at 19-y (convulsion with consciousness loss) and 21-y (H, R-side hemianopsia and blurred V). At 22-y, convulsion with loss of consciousness. *MRI, B, EEG*	1; IV Dose: NR	No	NR	CoQ_{10}	NR	NR
Wei, Cui & Pen 2019[25]	1	m.3243A>G (35% hetroplasmy in blood)	F; 24 *(dec)*	Residual symptoms remaining after at least 5 SLEs with hemiparesis, hemianopsia, or acute psychosis. *MRI, EEG*	1; IV 0.5 g/kg/d for 5-d	Yes 0.2 g/kg/d (~9-y)	levetiracetam	CoQ_{10}, multivitamins	None	NR for acute use. Despite continuous L-arginine, the patient's general condition gradually worsened, including cognition, mental condition, and extent of multisystem involvement. Diffuse brain atrophy became more remarkable. She died of multiple organ failure.

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophylaxis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
Yoneda et al. 2012[26]	1	m.3243A>G	M; 13	Recurrent SLEs consisting of migraine H, vomiting and V disturbance (homonymous hemianopsia) at 9-y. Comatose and needed ventilation support. Recurrent partial complex S (L arm to whole body). Absent brainstem responses. *MRI, B*	1; IV 0.5 g/kg for 30-min	No	NR	NR	NR	After 15-min after IV had started, he showed voluntary movements in his face and extremities. 6-h after the infusion, consciousness improved from deep coma to somnolence. He became alert and no longer required artificial ventilator support 36-h after the infusion had started.↓lactate at 36-h.
Cohort study										
Ganetzky & Falk 2018[27]	1 #1	ND4/ND6	NR; 6	Unilateral ophthalmoparesis *	1; IV 0.5 g/kg for 1-d	Yes 0.237 g/kg/d (~8-y)	NR	CoQ_{10}, vitamin E, vitamin C, creatine, riboflavin, carnitine, folinic acid MVI	None	Yes- responded
	1 #2	ND5	NR; 4	R- upper extremity hemiplegia	1; IV 0.5 g/kg for 1-d	Yes 0.15 g/kg/d (~7.5-y); citrulline Dose: NR (4.5-y)	NR	CoQ_{10}, EP1743, folinic acid, MVI, riboflavin		No- did not respond
	1 #3	POLG	NR; 8	New partial S activity	1; IV 0.5 g/kg for 1-d	Yes 0.3 g/kg/d (~5.5-y); citrulline Dose: NR (2-y)	NR	CoQ_{10}, vitamin C, alpha lipoic acid, creatine, thiamine, riboflavin, folinic acid, B50, MVI, carnitine,		No- did not respond. Required prolonged inpatient rehabilitation after SLE.
				L hemiplegia, depressed mental status	1; IV 0.5 g/kg for 3-d		NR			Yes- responded

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophyl axis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
				R hemiplegia, partial S on the R	1; IV 0.5 g/kg for 7-d		Yes, not specified	vitamin E, biotin		Unclear due to multiple simultaneous interventions.
	1 #4	MT-TV	NR; 19-23	At 23-y. R hemiplegia, ataxia, poverty of Speech, V floaters, dysmetria.	1; IV 0.25 g/kg for 1-d; 0.25 g/kg for 24-h	Yes citrulline 10g/m^2 /d (~4-y)	NR	CoQ_{10}, alpha lipoic acid, creatine, carnitine		Yes- responded
				At 21-y. Dysarthria and dysphagia, new R hemianopsia	1; IV 0.25 g/kg for 1-d; 0.25 g/kg for 24-h		NR			No- did not respond
				At 20-y. Head titubation, tremors for about 1-h *	1; IV 0.25		NR			Yes- responded. Required prolonged inpatient rehabilitation after SLE.
				At 20-y. L-sided hemianopsia, L hemiplegia, new partial S with deviation of the head to the L	1; IV 0.47 g/kg for 2-d; 0.25 g/kg for 2-d		NR			Partial: improved hemiplegia
				At 19-y R hemianopsia, R eye deviation, new partial S with deviation of the head to the R	1; IV 0.485 g/kg for 1-d	No	NR			Partial- S stopped

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophyl axis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
				At 19-y Dizziness, L-side W, fatigue	1; IV 0.436 g/kg for 1-d; 0.20 g/kg over 24-h for 1-d	No	Yes, not specified			Unclear due to multiple simultaneous interventions
	1 #5	ND4	M, 13	Choreiform movements, abnormal Sp, ataxia, new clinical S, depressed mental status	1; IV 0.5 g/kg bolus for 3-d	No	NR	CoQ_{10}, biotin, B50, MVI		No- did not respond
	1 #6	NDUFS8	F, 2.9 *(dec)*	Cheyne-Stokes respirations, concerning for stroke in central respiratory centre *	1; IV 0.5 g/kg bolus for 1-d	Yes 0.292 g/kg/d (~2-y, 5-mo.)	NR	CoQ_{10}, vitamin C, alpha lipoic acid, biotin, folinic acid, B50, MVI, riboflavin, carnitine, niacin, niacinamide		No- did not respond
				Worsening Cheyne-Stokes respirations *	1; IV 0.5 g/kg bolus every 8-h for 3-d					No- did not respond
	1 #7	*FBXL4*	NR; 1.7	Left facial, UE and LE hemiplegia	1; IV 0.5 g/kg bolus for 1-d	No	NR	CoQ_{10}, vitamin C, carnitine, riboflavin		Partial: strength normalised; persistent L hyporeflexia.
	1 #8	mtDNA deletion	NR; 12	Ataxia, dysmetria, worsened ophthalmoplegia, atonic episodes *	1; IV 0.5 g/kg bolus for 5-d	No	NR	No		Atonia resolved

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophylaxis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
	1 #9	*SURF 1*	F; 3 *(dec)*	Cheyne-Stokes-presented with an abnormal respiratory pattern *	1; IV 0.5 g/kg for 1-d (1-d after presenting)	Yes 0.13 g/kg/d (~2-y, 4-mo.)	NR	CoQ_{10}, vitamin E, alpha lipoic acid, B50, folinic acid, riboflavin		No- did not respond. Passed due to acute respiratory failure.
Prophylaxis (only)										
Calvaruso et al. 2011[28]	1	m.12146 A>G	M; 20	History of SLEs at 12 & 15-y (acute, progressive encephalopathy with increased intracranial pressure, V field defects, and status epilepticus). *CT, MRI, B*	NA	Yes 1 g/d from 20-y	NR	NR	NR	NR
Cosentino et al. 2019[29]	1	m.3243A>G	F; 42	History of migraine 8-mo. previously. Spatio-temporal disorientation and confusion. *MRI, B*	NA	Yes 1.66 g bid	NR	*Acute:* glucocorticoids ; *Chronic:* CoQ_{10}, riboflavin Other: metformin, lispro insulin, linagliptin, enalapril	NR	NR

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophylaxis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
Fukuda & Nagao 2019[30]	1	m.3243A>G	M; 55	Loss of consciousness, bilateral convulsion S. UL and LL were paralyzed and did not respond to painful stimuli. L-HH diminished after 1-d. *MRI, B*	NA	Yes 12 g/d, from d-253 of presenting with SLE	NR	*Chronic*: L-carnitine, CoQ_{10},fursultiamine, ascorbic acid Other: diabetic ketoacidosis treatment- fluid resuscitation, insulin infusion, potassium. glargine , lispro, glimepiride	None	Yes. Brain lesions almost disappeared by d-302 (49-d) and no further SLEs.
Marques-Matos 2015[31]	1	m.3243A>G (15% hetroplasmy in blood; 70% in muscle)	M; >50	5-y history of stepwise loss of executive and somatosensory functions (interpreted as 2 previous SLEs). *CT, MRI, EEG, B*	NA	Yes 60 mg/d	Previously taking valproate (discontinued)	Previously: aspirin, risperidone, memantine and dipyridamole (discontinued), started quetiapine. Aspirin prescribed with L-arginine.	NR	Yes. Minimized the iatrogenic cognitive symptoms.

Study ID	N	Genetic diagnosis	Sex; Age	Clinical presentation	Acute route	Prophyl axis Y/N	AEDs	Additional treatments	AEs	Response to L-arginine treatment
Selim & Mehaney 2013[32]	1	m.3243A>G	M; 10	5-y history of recurrent episodes of H, nausea and V; associated with R-side W with difficulties in language and memory and V disturbance, mostly R-HH. Mild R-hemiparesis. *MRI, MRA, B*	NA	Yes 0.5 g bid	NR	NR	NR	NR
Sun et al. 2018[33]	1	m.3243A>G	M; 38	R hemiparesis, cortical blindness on R half side of eyes for 1-mo. History of migraine H for 20-y. 3-y prior, L hemiparesis and L cortical blindness (recovered), with recurrent S from then on. *MRI, MRA, B*	NA	Yes Dose: NR. (nearly 1-y)	valproic acid sodium	aspirin, a statin, CoQ_{10}, vitamin C	NR	Unclear. No SLEs and his V field defect improved. Occasional S but less than before, now needs family care. However, simultaneous AED treatment.
Suzuki et al. 2017[34]	1 #1	m.3243A>G	F; 23 *(dec)*	1st SLE at 10-y (H, vomiting, blurred V). *MRI B*	NA	Yes	NR	l-carnitine, CoQ_{10}	NR	While treated, she was repeatedly admitted to hospital because of SLEs such as H, V, and convulsions. At 6-mo after admission, died from aspiration pneumonia due to vomiting.

Treatment is related to L-arginine, unless otherwise specified. Age relates to of SLE(s) treatment.
a IV treatment administered included L-arginine and l-citrulline
* Clinical presentation is not typical of mitochondrial SLE.
Abbreviations: AEs, adverse events; B, biochemical (plasma/serum/blood/CSF); CoQ_{10}, Coenzyme Q_{10}; d, day; *dec,* deceased; F, females; H, headache; L, left; LL, lower limb; L-HH; left homonymous hemianopsia; m, month; M, male; MRS, magnetic resonance spectroscopy; MVI, multiple vitamin infusion; NAA/Cho, N-acetylaspartate/Choline; NCSE, non-convulsive status epilepticus; NMDAS, Newcastle mitochondrial disease activity scale; NR, not reported; R, right; R-HH; right homonymous hemianopsia; S, seizure(s); SLE, stroke-like episodes; UL, upper limb; V, vision/visual; w, week; W, weakness; y, year; ↑, increase/d; ↓, decrease

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eTable 6. Summary characteristics of included open-label trials (N=3)

Study ID	n	Genetic diagnosis	Sex; age (y)	Clinical presentation	L-arginine treatment	AEDs or other treatments	AEs	Response to treatment
Koga et al. 2002 [1]	3	m.3243A>G (87% hetroplasmy in muscle)	F; 17	Periodic vomiting. Extensive basal ganglial calcification	16 9; IV L-arginine 0.5 g/kg as a 10% solution (over 15-min) Placebo 4; 5% dextrose (0.5 g/kg) 3; D-arginine (in a 10% solution) Treatment within 1-h of symptom onset	NR	None	At 24-h, significant improvements (p<0.05) in L-arginine vs. placebo treated SLEs as follows: headache (5/9 vs 1/7), clinical disability (5/9 vs 0/7), nausea (4/9 vs 1/7), vomiting (6/9 vs 1/7). Teichopsia did not improve (1/9 vs 0/7), persisting for several days. At 30-min after L-arginine, uptake in the decreased rCBF in the ischemic region was improved on SPECT (↑ was < 13% of the increase on the contralateral side). At 24-h, plasma lactate and pyruvate improved (no change in CSF).
		m.3243A>G (74% hetroplasmy in muscle)	F; 18	Generalized muscle W, periodic vomiting and hemiparesis. Extensive basal ganglial calcification				
		m.3243A>G (58% hetroplasmy in muscle)	M; 15	Hemiblindness, hemiconvulsions, and vomiting. Extensive basal ganglial calcification				
Koga et al. 2005 [2]	24	m.3243A>G (68 ± 16% heteroplasmy in muscle)	8M, 16F; 19.6 ± 12.5 (8.2–30.3) Control group compared at baseline n=72 27M, 45F; 21.5 ± 10.4 (4.3–35.4)	SLEs fulfilled the criteria the following criteria: migraine headache, vomiting, convulsion, and transient blindness with brain image suggesting focal brain abnormality.	34 22 IV L-arginine 0.5 g/kg as a 10% solution within 1-h of symptom onset Placebo 8; 5% dextrose (0.5 g/kg) 4; D-arginine (in a 10% solution) Oral use in N=6 patients 4-24 g (0.15-0.3 g/kg/d) for 18-mo.	NR	Headache when L-arginine was infused too rapidly in 2 patients	*Acute:* At 24-h, significant improvements (p<0.05) in SLEs were as follows: headache (21/22 vs 1/12), clinical disability (20/22 vs 1/12), nausea (22/22 vs 1/22), vomiting (22/22 vs 1/22), hemi-blindness (transient) (7/7 vs 1/4), teichopsia (19/22 vs 0/12) *Chronic:* Significant reduction in the frequency of SLEs compared to pre-supplementation (0.09 ± 0.09 vs 0.78 ± 0.42, p<0.05); significant reduction in the severity of SLEs after treatment (0.17 ± 0.18 vs 2.04 ± 0.34)

Study ID	n	Genetic diagnosis	Sex; age (y)	Clinical presentation	L-arginine treatment	AEDs or other treatments	AEs	Response to treatment
Koga et al. 2018 [3]	20	m.3243A>G	*Acute:* N=4 patients enrolled in IV L-arginine only (and who had taken L-arginine other than the study intervention prior to the study). Additional N=5 patients enrolled in oral and IV L-arginine † N=10 patients started and completed 2-y IV trial. 8M; 17.2 ± 5.1 (at baseline) N= 2 patients died during follow up; N=8 completed 7-y follow up	Eligibility patients developed an ictus of SLEs within the previous 6-h.	3 patients treated with IV L-arginine in 7 SLEs (unclear how many SLEs per patient) IV 0.5 g/kg as a 10% solution (over 1-h) within 6-h of symptom onset Additional dose of 0.5 g/kg after 2-h if symptoms did not improve (received IV when developing an ictus of SLE)	Previous use: N=10 1 AED: N=2 (20%); 2 AEDs: N=4 (40%); ≥ 3 AEDs: N=4 (40%)	6/10 patients had AEs. Fever: N=5/10 patients (50%); ↓ hematocrit (N=3; 30%); ↓ hemoglobinuria (N=3; 30%). Patients recovered without treatment. 6 episodes of moderate AEs: fever (n=4), epilepsy (n=1), bleeding at the injection site (n=1); causality with L-arginine was denied. 1 episode of severe seizures developed in a patient who had been prone to develop seizures since before the trial. 2 patients died during 7-y follow up due to renal failure and sudden death	The improvement rates of the co-primary endpoints, H and nausea / vomiting, at 2, 6, 12, and 24-h after completion of the initial IV administration increased with time: for H, 25% (n=2/8), 12.5% (n=1/8), 50% (n=4/8), and 62.5% (n=5/8), respectively; nausea/vomiting, 50% (n=3/6), 40% (n=2/5), 80% (n=4/5), and 80% (n=4/5), respectively. The changes in 4 other stroke-like symptoms were NR. By the end of 7-y follow up: clear progression of disease burden (JMDRS), 24.2 +/- 12.7 vs 10.2 +/- 8.48). The distribution of SLE frequency in patients was NR.
			Chronic: N=15 started the trial. However, baseline demographics presented for N=13. N=3 discontinued; N=12 completed 2-y trial [data presented for N=13, as N=1 intention-to-treat (ITT)]. Of these, 7M; 22.7 ± 12.5 N=2 patients died during follow up; N=10 completed 7-y follow up (data presented for N=11, as N=1 ITT). Of these, 7M; 30.6 ± 12.7	Eligibility patients if they developed SLEs in the last 2-y	0.3-0.5 g/kg/d in 3 divided doses to maintain plasma arginine concentrations to 100 µmol/L (for 2-y)	Previous use: 1 AED: N=8 (61.5%); 2 AEDs: N=3 (23.1%); ≥ 3 AEDs: N=2 (15.4%)	Nasopharyngitis, n=10/15 patients (66.7%). 7 episodes of severe AEs: drug hypersensitivity, increased AST, ALT, CPK, metabolic acidosis, arrhythmias, and volvulus. All recovered or became alleviated due to the discontinuation or withdrawal (7 among a total of 10 patients) 3 discontinued (2-y) trial treatment due to the ↑ frequency of epileptic seizures, concurrent pneumonia, and unverified efficacy. N=2 patients died during 7-y follow up due to sudden death and renal and heart failure	By the end of 2-y: The distribution of SLE frequency in patients was as follows: none (n=5), one (n=2), two (n=2), three or more (n=4). The interictal phase was not significantly extended (p>0.05). By the end of 7-y follow up: clear progression of disease burden (measured by JMDRS; 24.2 +/- 12.7 vs 10.2 +/-8.48). The distribution of SLE frequency in patients was NR.

Abbreviations: AEs, adverse events; AST, aspartate aminotransferase; F, female; h, hour; JMDRS, Japanese mitochondrial disease rating scale; M, male; NR, not-reported; rCBF, regional cerebral blood flow; SLE, stroke-like episodes; W, weakness; y, year

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eTable 7 Quality appraisal of case reports and case series

	Domains										
Study ID	**1**	**2**	**3**	**4**	**5**	**6**	**7: A**	**7: P**	**8**	**Overall quality**	**OCEBM Level**
Corr et al. 2014[1]	Y	N	Y	N	NA	NA	Y	–	N	Poor	5
Fang, Zheng & Zhang 2018[2]	Y	?	Y	N	NA	NA	N	–	N	Very poor	5
Fryer et al. 2016[3]	Y	?	?	N	NA	NA	N	N	N	Very poor	5
Gagliardi et al. 2019[4]	Y	N	Y	Y	NA	N	?	Y	N	Good	5
González et al. 2020[5]	Y	N	Y	Y	NA	NA	Y	N	?	Good	5
Hayashi et al. 2020[6]	Y	?	Y	N	NA	NA	Y	Y	?	Poor	5
Hovsepian et al. 2018[7]	Y	N	Y	N	NA	NA	N	N	?	Very poor	5
Ito et al. 2020[8]	Y	?	Y	N	NA	NA	Y	Y	?	Poor	5
Kitamura et al. 2016[9]	Y	?	Y	N	NA	NA	Y	–	?	Poor	5
Kubota et al. 2004[10]	Y	N	Y	N	NA	NA	N	–	?	Very poor	5
Lekoubou et al. 2011[11]	Y	N	Y	N	NA	NA	N	Y	?	Poor	5
Minobe et al. 2015 [12]	Y	?	Y	N	NA	NA	Y	–	N	Poor	5
Mitani et al. 2013[13]	Y	?	Y	N	NA	NA	Y 1st / N 2nd	N	N	5	5
Oyama et al. 2020[14]	Y	N	Y	N	NA	NA	Y	–	N	Poor	5
Randhawa et al. 2016[15]	Y	N	Y	N	NA	NA	Y	Y	N	Poor	5
Renard & Ion 2020[16]	Y	N	NR	NR	NA	NA	N	–	N	Very poor	5
Sakai et al. 2018[17]	Y	N	Y	?	NA	NA	N	N	N	Very poor	5
Shigemi et al. 2011[18]	Y	N	Y	N	NA	NA	Y	N	Y	Good	5
Shimizu et al. 2020[19]	Y	N	?	Y	NA	NA	Y	–	N	Poor	5
Siddiq, Widjaja & Tein 2015[20]	Y	?	Y	N	NA	NA	N	Y	?	Poor	5
Sunde et al. 2016[21]	Y	N	?	N	NA	NA	N	Y	N	Very poor	5
Torre et al. 2020[22]	Y	N	N	N	NA	NA	N	Y	?	Very poor	5
Ueki et al. 2020[23]	Y	N	Y	Y	NA	NA	?[g]	–	N	Poor	5
Wang et al. 2020[24]	Y	?	NR	NR	NA	NA	N	–	N	Very poor	5
Wei, Cui & Pen 2019[25]	Y	N	Y	N	NA	NA	Y	Y	Y	Good	5
Yoneda et al. 2012[26]	Y	?	Y	N	NA	NA	N	–	?	Very poor	5
Koga et al. 2002[27]	Y	?	Y	N	NA	NA	N	N	Y	Poor	4
Calvaruso et al. 2011[28]	Y	?	NR	?	NA	NA	–	N	N	Very poor	5
Cosentino et al. 2019[29]	Y	?	NR	?	NA	NA	–	N	N	Very poor	5
Fukuda & Nagao 2019[30]	Y	?	Y	N	NA	NA	–	Y	N	Poor	5
Marques-Matos 2015[31]	Y	?	N	N	NA	NA	–	N	N	Very poor	5
Selim & Mehaney 2013[32]	Y	?	NR	N	NA	NA	–	N	N	Very poor	5
Sun et al. 2018[33]	Y	N	?	N	NA	NA	–	Y	N	Very poor	5
Suzuki et al. 2017[34]	Y	?	N	N	NA	NA	–	?	N	Very poor	5

Tool for evaluating the methodological quality of case reports and case series (Murad, et al. 2018) [35]
Abbreviations: A, acute; NA, not applicable; N, no; NR, not reported; OCEBM, Oxford Centre for Evidence-Based Medicine Levels of Evidence; P, prophylactic; Y, yes; ?, unclear
– article did not include acute or prophylactic treatment (therefore no follow up of respective regime reported).

The overall quality appraisal (within) for each article was classified according to the number of questions satisfied across any domains of Ascertainment, Causality, and Reporting; ≥ 3 questions satisfied= 'good quality'; 2 questions= 'poor quality'; one or fewer questions= 'very poor'.

Selection
1. Does the patient(s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?
Ascertainment
2. Was the exposure adequately ascertained?[a]
3. Was the outcome adequately ascertained?[b]
Causality
4. Were other alternative causes that may explain the observation ruled out?[c]
5. Was there a challenge/rechallenge phenomenon?[d]
6. Was there a dose–response effect?
7. Was follow-up long enough for outcomes to occur?[e]

Reporting

8. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?[f]

Items 4-6 are mostly relevant to cases of adverse drug events.

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a. 'No, where anticonvulsants/antiepileptic drugs were used; 'Unclear' where any other treatments were used or where other treatments were not reported.
b. 'Yes' where outcomes included brain imaging or semi-quantitative measures; 'No' where response to treatment was measured via self-reported assessment, judgement, or description.
c. 'No' where the outcome (improvement or deterioration) could be explained by other exposures (i.e. other treatment/s).
d. 'NA' as adverse drug events with a rechallenge phenomenon was not applicable.
e. 'Yes' if follow-up was performed within an acceptable length of time; 2-4 weeks (Acute treatment). For prophylactic- there is no literature on an optimal follow up duration to determine the efficacy. 'Yes' refers to follow up of any length.
f. 'No' where route of administration or dose of L-arginine (acute or prophylactic treatment) was inadequately reported; 'Unclear' where the timing of treatment in relation to the stroke-like episode was not reported. 'Unclear' where details related to AED treatment were not reported i.e. type of AED, administration, or regime).
g. Route & regime (acute or prophylactic) treatment of L-arginine was not reported

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eTable 8 Quality appraisal for all other non-randomised controlled trials

Study ID	Ganetzky & Falk 2018[1]	Koga et al. 2005[2]	Koga et al. 2018[3]	Overall bias (between)
1. Representative sample	N	Y	Y	Low
2. Inclusion/exclusion criteria clearly defined	Y	?	?	Unclear
3. Participants at similar disease progression	N	N	N	High
4. Selection of participants consecutive	?	?	?	Unclear
5. Data collection undertaken prospectively	N	Y	Y	Low
6. Groups comparable	NA	NA	NA	NA
7. Intervention clearly defined	Y	Y	Y	Low
8. Intervention delivered by experienced person	Y	Y	Y	Low
9. Intervention delivered in an appropriate setting	Y	Y	Y	Low
10. Important outcomes considered	?	?	?	Unclear
11. Objective outcome measures used	?	?	?	Unclear
12. Main outcome blind	N	N	N	High
13. Follow-up long enough	N	N Y A P	N Y A P	High
14. Information on non-respondents, dropouts	Y	NA	Y	Low
15. Withdrawals unlikely to introduce bias	N	NA	N	High
16. Length of follow-up similar between groups	NA	NA	NA	NA
17. Important prognostic factors identified	N	N	Y	High
18. Analyses adjusted for confounders	N	N	N	High
Overall bias (within)	High	High	High	
OCEBM Level	3	3	3	

The 2012 risk-of-bias checklist for non-randomized studies by Brazzelli et al. 2012[4]. Abbreviations: A, acute; NA, not applicable; N, no; OCEBM, Oxford Centre for Evidence-Based Medicine Levels of Evidence [5]; P, prophylactic; Y, yes; ?, unclear

A study was judged to have an overall high risk of bias if their analyses did not adjust for (nor reporte), the influence of confounders as deemed by the investigators (i.e. use of AED/s), and if participant withdrawals were likely to introduce bias.

1. Were participants a representative sample selected from a relevant patient population (e.g. randomly selected from those seeking treatment despite age, duration of disease, primary or secondary disease and severity of disease)?[a]
2. Were the inclusion/exclusion criteria of participants clearly described?[b]
3. Were participants entering the study at a similar point in their disease progression (i.e. severity of disease)?[c]
4. Was selection of patients consecutive?
5. Was data collection undertaken prospectively?
6. Were the groups comparable on demographic characteristics and clinical features?
7. Was the intervention (and comparison) clearly defined?[d]
8. Was the intervention undertaken by someone experienced at performing the procedure?
9. Were the staff, place and facilities where the patients were treated appropriate for performing the procedure (e.g. access to back-up facilities in hospital or special clinic)?
10. Were any of the important outcomes considered (i.e. clinical effectiveness, cost-effectiveness, learning curves)?[e]
11. Were objective (valid and reliable) outcome measures used, including satisfaction scale?[f]
12. Was the assessment of main outcomes blind?
13. Was follow-up long enough (≥ 1 year) to detect important effects on outcomes of interest?
14. Was information provided on non-respondents, dropouts?
15. Were the characteristics of withdrawals/dropouts similar to those that completed the study and therefore unlikely to cause bias?
16. Was length of follow-up similar between comparison groups
17. Were the important prognostic factors identified (e.g. age, duration of disease, disease severity)?[g]
18. Were the analyses adjusted for confounding factors?

Items specific to comparative groups (6, 16) were deemed 'NA', where studies did not have a comparison arm.

a. 'No, where patients had MELAS, or where clinical presentation of stroke-like episode/s treated were not conventional.
b. 'Unclear' if only one of either inclusion or exclusion criteria are clearly described.
c. 'No' where there is limited information provided on the disease burden.
d. 'No' where route of administration or dose of L-arginine (acute or prophylactic treatment) was inadequately reported; 'Unclear' where the timing of treatment in relation to the stroke-like episode/s was not reported.
e. 'Unclear' where other important measures such as imaging and EEG were not consistently performed.
f. 'Unclear' where no standardised tools or rating scale/s used for the assessment of response.
g. 'Yes' if two or more than two factors were identified.

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