# eTable 5. Quality appraisal of case reports and case series

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|  | **Domains** | **Overall quality** | **OCEBM Level** |
| **Study ID** | **1** | **2** | **3** | **4** | **5** | **6** | **7: A** | **7: P** | **8** |
| Corr et al. 20141 | Y | N | Y | N | NA | NA | Y | − | N | Poor | 5 |
| Fang, Zheng & Zhang 20182 | Y | ? | Y | N | NA | NA | N | − | N | Very poor | 5 |
| Fryer et al. 20163 | Y | ? | ? | N | NA | NA | N | N | N | Very poor | 5 |
| Gagliardi et al. 20194 | Y | N | Y | Y | NA | N | ? | Y | N | Good | 5 |
| González et al. 20205 | Y | N | Y | Y | NA | NA | Y | N | ? | Good | 5 |
| Hayashi et al. 20206 | Y | ? | Y | N | NA | NA | Y | Y | ? | Poor | 5 |
| Hovsepian et al. 20187 | Y | N | Y | N | NA | NA | N | N | ? | Very poor | 5 |
| Ito et al. 20208 | Y | ? | Y | N | NA | NA | Y | Y | ? | Poor | 5 |
| Kitamura et al. 20169 | Y | ? | Y | N | NA | NA | Y | − | ? | Poor | 5 |
| Kubota et al. 200410 | Y | N | Y | N | NA | NA | N | − | ? | Very poor | 5 |
| Lekoubou et al. 201111 | 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. 201313 | Y | ? | Y | N | NA | NA | Y 1st | N 2nd | N | N | 5 | 5 |
| Oyama et al. 202014 | Y | N | Y | N | NA | NA | Y | − | N | Poor | 5 |
| Randhawa et al. 201615 | Y | N | Y | N | NA | NA | Y | Y | N | Poor | 5 |
| Renard & Ion 202016 | Y | N | NR | NR | NA | NA | N | − | N | Very poor | 5 |
| Sakai et al. 201817 | Y | N | Y | ? | NA | NA | N | N | N | Very poor | 5 |
| Shigemi et al. 201118 | Y | N | Y | N | NA | NA | Y | N | Y | Good | 5 |
| Shimizu et al. 202019 | Y | N | ? | Y | NA | NA | Y | − | N | Poor | 5 |
| Siddiq, Widjaja & Tein 201520 | Y | ? | Y | N | NA | NA | N | Y | ? | Poor | 5 |
| Sunde et al. 201621 | Y | N | ? | N | NA | NA | N | Y | N | Very poor | 5 |
| Torre et al. 202022 | Y | N | N | N | NA | NA | N | Y | ? | Very poor | 5 |
| Ueki et al. 202023 | Y | N | Y | Y | NA | NA | ?g | − | N | Poor | 5 |
| Wang et al. 202024 | Y | ? | NR | NR | NA | NA | N | − | N | Very poor | 5 |
| Wei, Cui & Pen 201925 | Y | N | Y | N | NA | NA | Y | Y | Y | Good | 5 |
| Yoneda et al. 201226 | Y | ? | Y | N | NA | NA | N | − | ? | Very poor | 5 |
| Koga et al. 200227 | Y | ? | Y | N | NA | NA | N | N | Y | Poor | 4 |
| Calvaruso et al. 201128 | Y | ? | NR | ? | NA | NA | − | N | N | Very poor | 5 |
| Cosentino et al. 201929 | Y | ? | NR | ? | NA | NA | − | N | N | Very poor | 5 |
| Fukuda & Nagao 201930 | Y | ? | Y | N | NA | NA | − | Y | N | Poor | 5 |
| Marques-Matos 201531 | Y | ? | N | N | NA | NA | − | N | N | Very poor | 5 |
| Selim & Mehaney 201332 | Y | ? | NR | N | NA | NA | − | N | N | Very poor | 5 |
| Sun et al. 201833 | Y | N | ? | N | NA | NA | − | Y | N | Very poor | 5 |
| Suzuki et al. 201734 | 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.*

1. ‘No, where anticonvulsants/antiepileptic drugs were used; ‘Unclear’ where any other treatments were used or where other treatments were not reported.
2. ‘Yes’ where outcomes included brain imaging or semi-quantitative measures; ‘No’ where response to treatment was measured via self-reported assessment, judgement, or description.
3. ‘No’ where the outcome (improvement or deterioration) could be explained by other exposures (i.e. other treatment/s).
4. ‘NA’ as adverse drug events with a rechallenge phenomenon was not applicable.
5. ‘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.
6. ‘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).
7. Route & regime (acute or prophylactic) treatment of L-arginine was not reported

**References**

1. Corr A, Gaughan M, Moroney J, Looby S. MELAS, an important consideration in the adult population presenting with unusual and recurrent stroke-like episodes. *BMJ Case Reports*. 28 Jan 2014;(no pagination)(A160)

2. Fang GL, Zheng Y, Zhang YX. Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes in an older adult mimicking cerebral infarction: A chinese case report. *Clinical Interventions in Aging*. 2018;13:2421-2424.

3. Fryer RH, Bain JM, De Vivo DC. Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-Like Episodes (MELAS): A Case Report and Critical Reappraisal of Treatment Options. Case Reports

Research Support, N.I.H., Extramural. *Pediatric Neurology*. 2016;56:59-61.

4. Gagliardi D, Mauri E, Magri F, et al. Can intestinal pseudo-obstruction drive recurrent stroke-like episodes in late-onset MELAS syndrome? A case report and review of the literature. *Frontiers in Neurology*. 2019;10 (JAN) (no pagination)(38)

5. Gonzalez-Pinto Gonzalez T, Almeida Velasco J, Moreno Estebanez A, et al. Acute management of a stroke-like episode in MELAS syndrome: What should we know? *eNeurologicalSci*. September 2020;20 (no pagination)100249.

6. Hayashi Y, Iwasaki Y, Yoshikura N, et al. Clinicopathological findings of a mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes/Leigh syndrome overlap patient with a novel m.3482A>G mutation in MT-ND1. *Neuropathology*. 2020;

7. Hovsepian DA, Galati A, Chong RA, et al. MELAS: Monitoring treatment with magnetic resonance spectroscopy. Case Reports. *Acta Neurologica Scandinavica*. 2019;139(1):82-85.

8. Ito H, Fukutake S, Odake S, Okeda R, Tokunaga O, Kamei T. A MELAS patient developing fatal acute renal failure with lactic acidosis and rhabdomyolysis. *Internal Medicine*. 01 Nov 2020;59(21):2773-2776.

9. Kitamura M, Yatsuga S, Abe T, et al. L-Arginine intervention at hyper-acute phase protects the prolonged MRI abnormality in MELAS. Case Reports

Letter. *Journal of Neurology*. 2016;263(8):1666-8.

10. Kubota M, Sakakihara Y, Mori M, Yamagata T, Momoi-Yoshida M. Beneficial effect of L-arginine for stroke-like episode in MELAS. Case Reports. *Brain & Development*. 2004;26(7):481-3; discussion 480.

11. Lekoubou A, Kouame-Assouan AE, Cho TH, Luaute J, Nighoghossian N, Derex L. Effect of long-term oral treatment with L-arginine and idebenone on the prevention of stroke-like episodes in an adult MELAS patient. Case Reports. *Revue Neurologique*. 2011;167(11):852-5.

12. Minobe S, Matsuda A, Mitsuhashi T, et al. Vasodilatation of multiple cerebral arteries in early stage of stroke-like episode with MELAS. *Journal of Clinical Neuroscience*. 01 Feb 2015;22(2):407-408.

13. Mitani T, Aida N, Tomiyasu M, Wada T, Osaka H. Transient ischemic attack-like episodes without stroke-like lesions in MELAS. *Pediatric Radiology*. October 2013;43(10):1400-1403.

14. Oyama M, Iizuka T, Nakahara J, Izawa Y. Neuroimaging pattern and pathophysiology of cerebellar stroke-like lesions in MELAS with m.3243A>G mutation: a case report. Case Reports. *BMC Neurology*. 2020;20(1):167.

15. Randhawa N, Wilson L, Mann S, Sirrs S, Benavente O. Clinical Reasoning: A complicated case of MELAS. *Neurology*. 18 Oct 2016;87(16):e189-e195.

16. Renard D, Ion I. Cerebral arterial and venous MRI abnormalities in MELAS. *Acta Neurol Belg*. Apr 2020;120(2):455-456. doi:10.1007/s13760-017-0867-7

17. Sakai S, Osaki M, Hidaka M, et al. Association between stroke-like episodes and neuronal hyperexcitability in MELAS with m.3243A>G: A case report. *eNeurologicalSci*. 2018/09/01/ 2018;12:39-41. doi:<https://doi.org/10.1016/j.ensci.2018.08.003>

18. Shigemi R, Fukuda M, Suzuki Y, Morimoto T, Ishii E. L-arginine is effective in stroke-like episodes of MELAS associated with the G13513A mutation. Case Reports. *Brain & Development*. 2011;33(6):518-20.

19. Shimizu J, Tabata T, Tsujita Y, et al. Propofol infusion syndrome complicated with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes: a case report. *Acute Medicine and Surgery*. 2020;7(1)e473.

20. Siddiq I, Widjaja E, Tein I. Clinical and radiologic reversal of stroke-like episodes in MELAS with high-dose L-arginine. Case Reports

Observational Study. *Neurology*. 2015;85(2):197-8.

21. Sunde K, Blackburn PR, Cheema A, et al. Case report: 5 year follow-up of adult late-onset mitochondrial encephalomyopathy with lactic acid and stroke-like episodes (MELAS). *Molecular Genetics and Metabolism Reports*. 01 Dec 2016;9:94-97.

22. Perez Torre P, Acebron-Herrera F, Garcia Barragan N, Corral Corral I. Global cerebral involvement and L-arginine use in a patient with MELAS syndrome. Afectacion encefalica global y uso de L-arginina en un paciente con sindrome de MELAS. *Neurologia*. July - August 2020;35(6):435-437.

23. Ueki K, Wakisaka Y, Nakamura K, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes due to m.3243A > G mutation in a 76-year-old woman. *Journal of the Neurological Sciences*. 15 May 2020;412 (no pagination)116791.

24. Wang S, Song T, Wang S. Mitochondrial DNA 10158T>C mutation in a patient with mitochondrial encephalomyopathy with lactic acidosis, and stroke-like episodes syndrome: A case-report and literature review (CARE-complaint). Case Reports

Review. *Medicine*. 2020;99(24):e20310.

25. Wei YP, Cui LY, Pen B. L-Arginine prevents stroke-like episodes but not brain atrophy: a 20-year follow-up of a MELAS patient. *Neurological Sciences*. Jan 2019;40(1):209-211. doi:10.1007/s10072-018-3573-1

26. Yoneda M, Ikawa M, Arakawa K, et al. In vivo functional brain imaging and a therapeutic trial of L-arginine in MELAS patients. Case Reports

Research Support, Non-U.S. Gov't

Review. *Biochimica et Biophysica Acta*. 2012;1820(5):615-8.

27. Koga Y, Ishibashi M, Ueki I, et al. Effects of L-arginine on the acute phase of strokes in three patients with MELAS. Research Support, Non-U.S. Gov't. *Neurology*. 2002;58(5):827-8.

28. Calvaruso MA, Willemsen MA, Rodenburg RJ, van den Brand M, Smeitink JAM, Nijtmans L. New mitochondrial tRNAHIS mutation in a family with lactic acidosis and stroke-like episodes (MELAS). *Mitochondrion*. September 2011;11(5):778-782.

29. Cosentino C, Contento M, Paganini M, Mannucci E, Cresci B. Therapeutic options in a patient with MELAS and diabetes mellitus: follow-up after 6 months of treatment. *Acta Diabetologica*. 01 Nov 2019;56(11):1231-1233.

30. Fukuda M, Nagao Y. Dynamic derangement in amino acid profile during and after a stroke-like episode in adult-onset mitochondrial disease: a case report. Case Reports. *Journal of Medical Case Reports [Electronic Resource]*. 2019;13(1):313.

31. Marques-Matos C, Reis J, Reis C, Castro L, Carvalho M. Mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes presenting before 50 years of age: When a stroke is not just a stroke. *JAMA Neurology*. May 2016;73(5):604-606.

32. Selim L, Mehaney D. Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes in a Japanese child: Clinical, radiological and molecular genetic analysis. *Egyptian Journal of Medical Human Genetics*. July 2013;14(3):317-322.

33. Sun X, Jiang G, Ju X, Fu H, Na. MELAS and macroangiopathy: A case report and literature review. *Medicine*. 2018;97(52):e13866-e13866. doi:10.1097/MD.0000000000013866

34. Suzuki J, Iwata M, Moriyoshi H, Nishida S, Yasuda T, Ito Y. Familial pernicious chronic intestinal pseudo-obstruction with a mitochondrial DNA A3243G mutation. *Internal Medicine*. 2017;56(9):1089-1093.

35. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med*. Apr 2018;23(2):60-63. doi:10.1136/bmjebm-2017-110853