

ERN MELAS WORKING GROUPS

WG leader identified in bold

Group 1 MELAS DEFINITION (INCLUDING SLE DEFINITION)	1. Mary Kay Koenig (pedi/adult) 2. Rob Pitceathly (adult) 3. Michelangelo (adult) 4. Rita Horvath (adult) 5. Daria Diodato (ped) 6. Manuel Schiff (ped) 7. Serenella (adulti) 8. Felix Distelmaier (pediatric) 9. Chiara La Morgia (adult) 10. Michio Hirano (adult/ped) 11. Rene de Coe (pediatric/ adult) 12. Amel Karaa (peds/adult) ECR: Piervito Lopriore
Group 2 MANAGEMENT OF SLE	1. Marcello Bellusci (ped) 2. Guido Primiano (adult) 3. Daria Diodato (ped) 4. Fernando Scaglia (ped/adult) 5. Chiara La Morgia (adult) 6. Manuel Schiff (ped) 7. Serenella (adulti) 8. Bobby McFarland (paediatric) ECR: Luisa Semmler
Group 3 MANAGEMENT OF COGNITIVE AND PSYCHIATRIC ISSUES	1. Cornelia Kornblum (adult) 2. Thomas Klopstock (adult) 3. Amel Karaa (peds/adult) 4. Serenella (adulti) 5. Costanza Lamperti (adult) 6. Musumeci Olimpia (adult) 7. Mika Martikainen (adult) ECR: Luisa Semmler
Group 4 Management of headache and epilepsy	1. Michelangelo Mancuso (adult) 2. Omar Hikmat (pediatric) 3. Musumeci Olimpia (adult) 4. Guido Primiano (adult) 5. Felix Distelmaier (pediatric) 6. Bobby McFarland (paediatric) 7. Chiara La Morgia (adult) 8. Rene de Coe (pediatric/ adult) 9. Mika Martikainen (adult) ECR: Piervito Lopriore
Group 5 Management of comorbidities (cardiomyopathy, gastrointestinal....)	1. Mary Kay Koenig (pedi/adult) 2. Fernando Scaglia (pedi/adult) 3. Chiara La Morgia (adult) 4. Costanza Lamperti 5. Musumeci Olimpia (adult) 6. Michio Hirano 7. Amel Karaa (peds/adults) ECR: Luisa Semmler

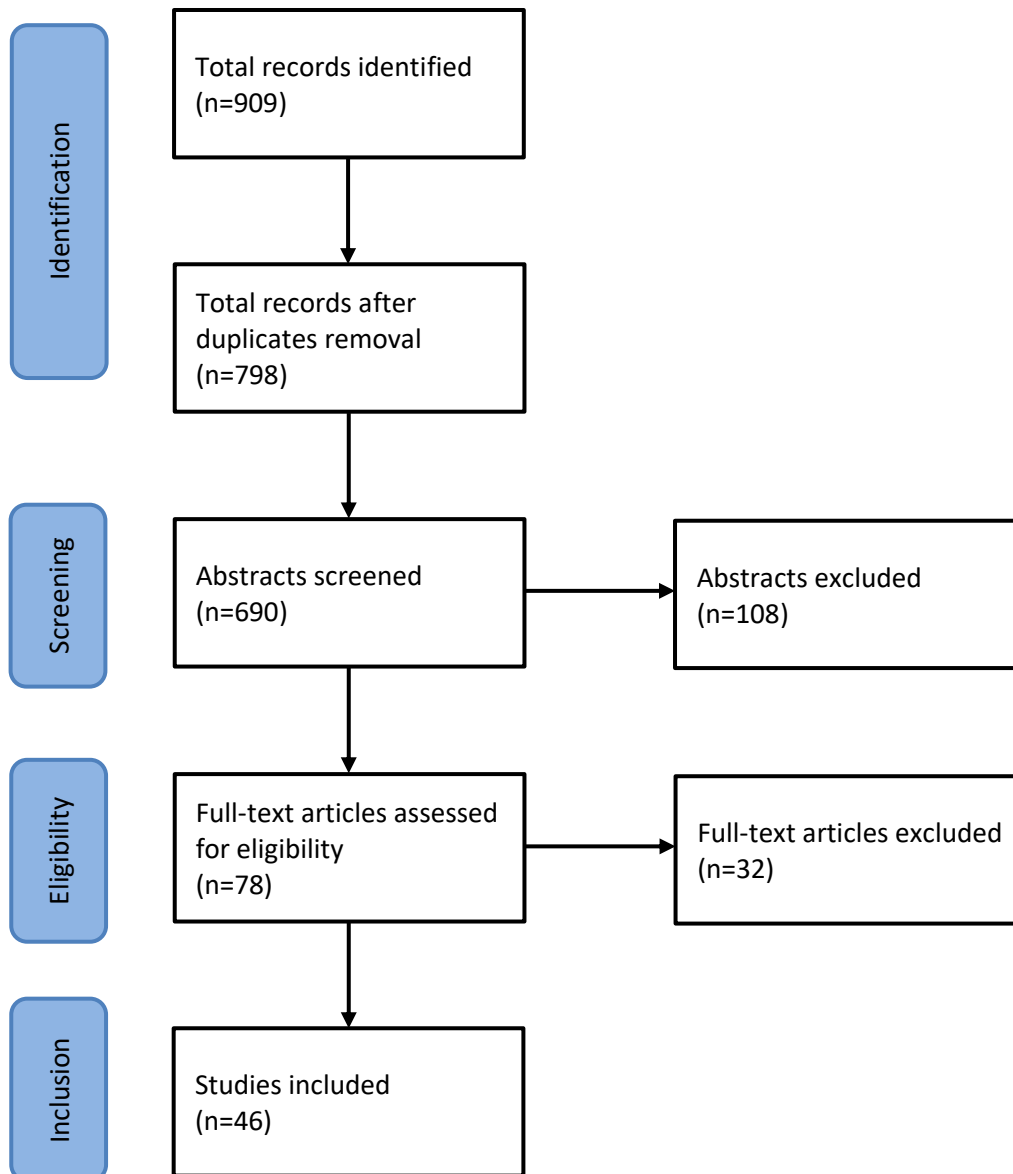
Prisma Flow Chart

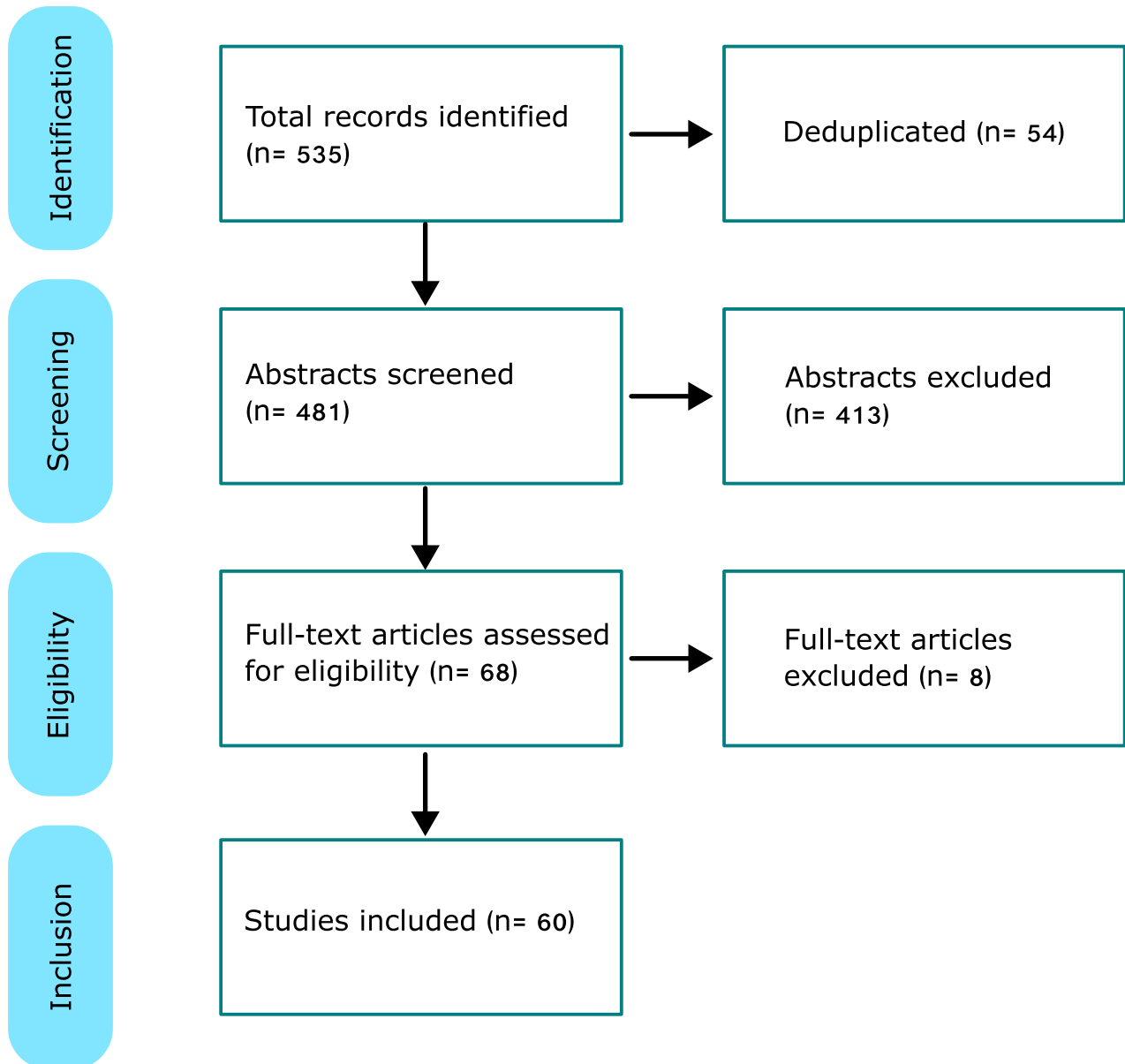
EURO-NMD MELAS Consensus

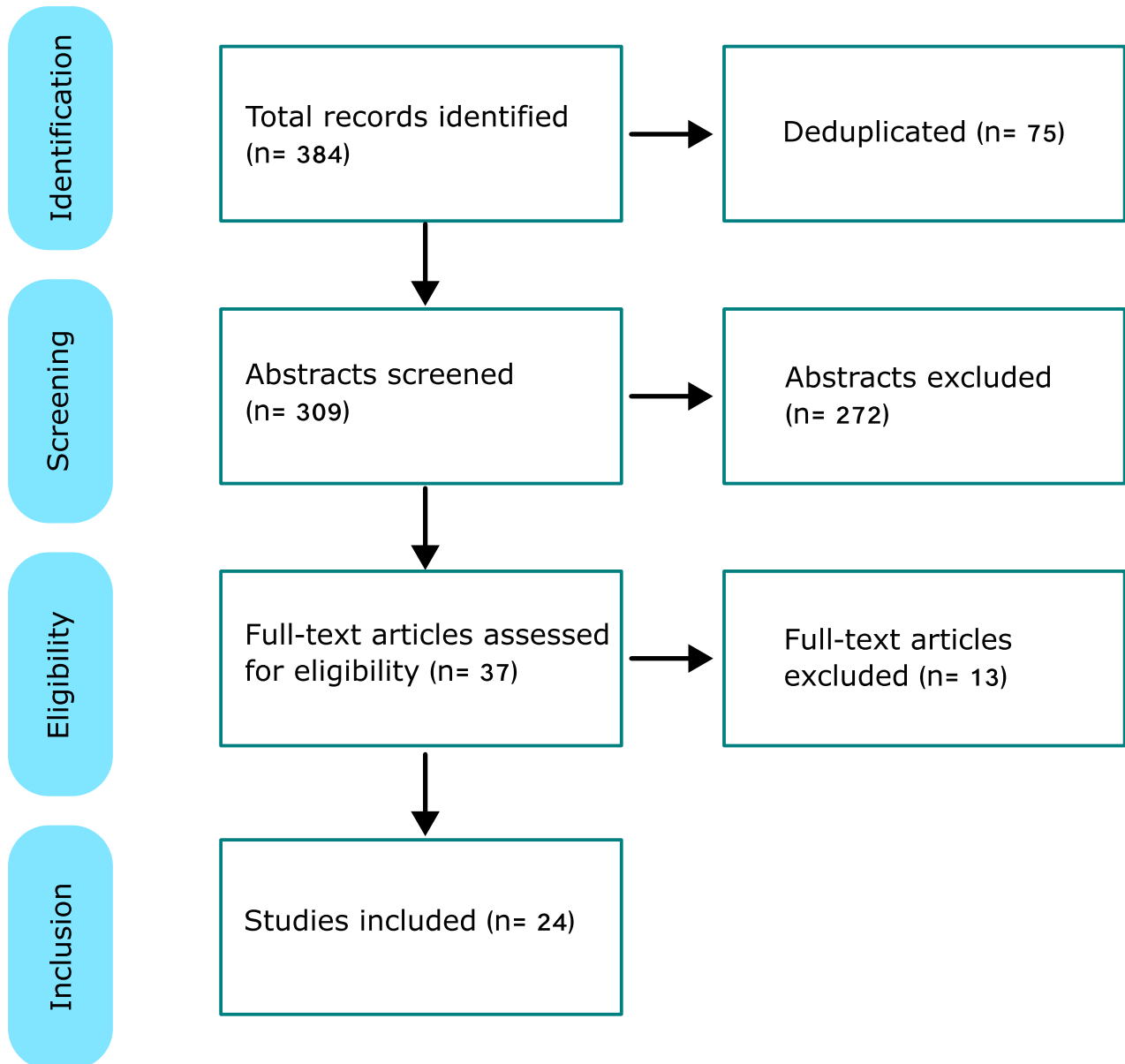
Working group 1: MELAS/SLE definition



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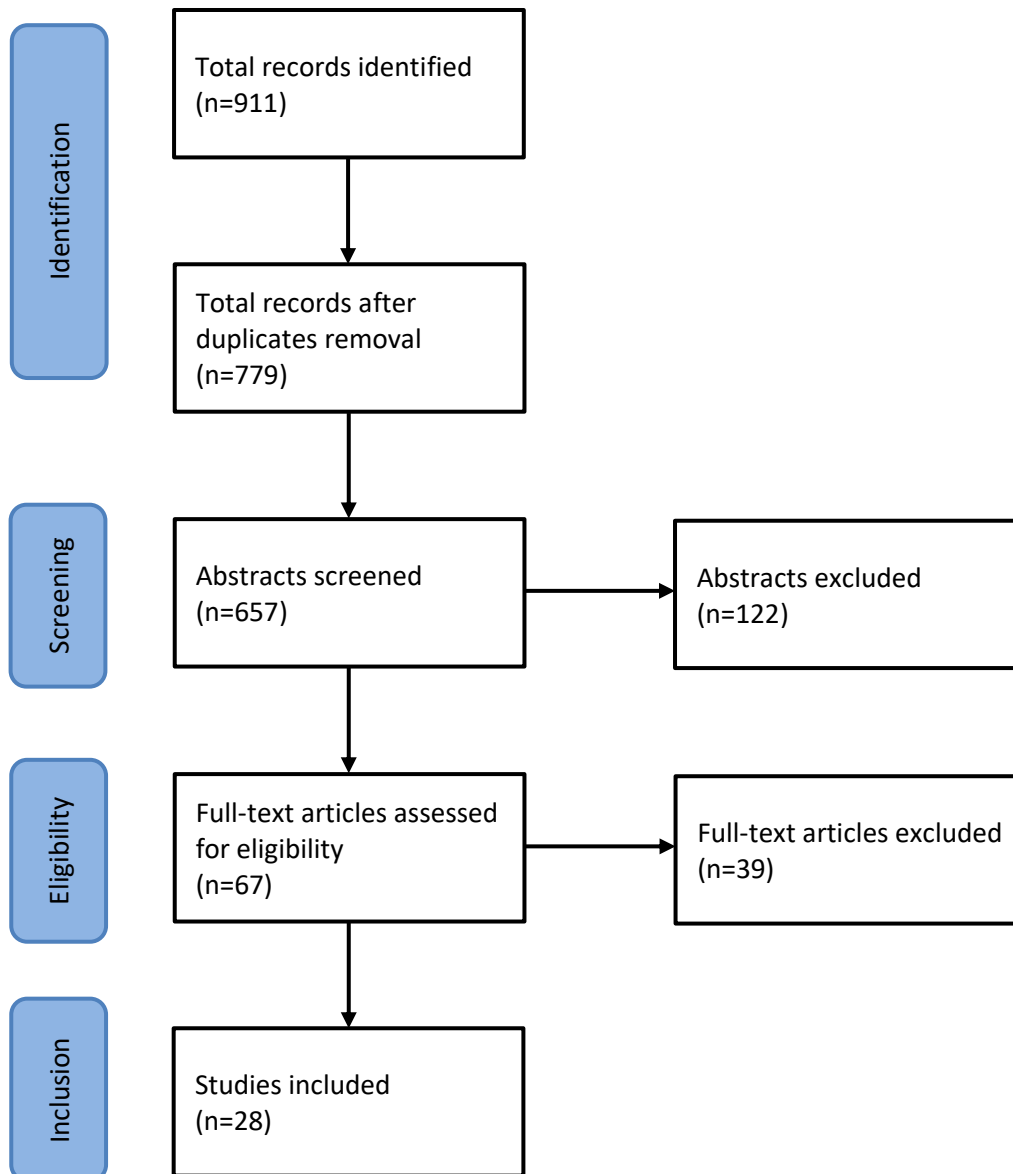
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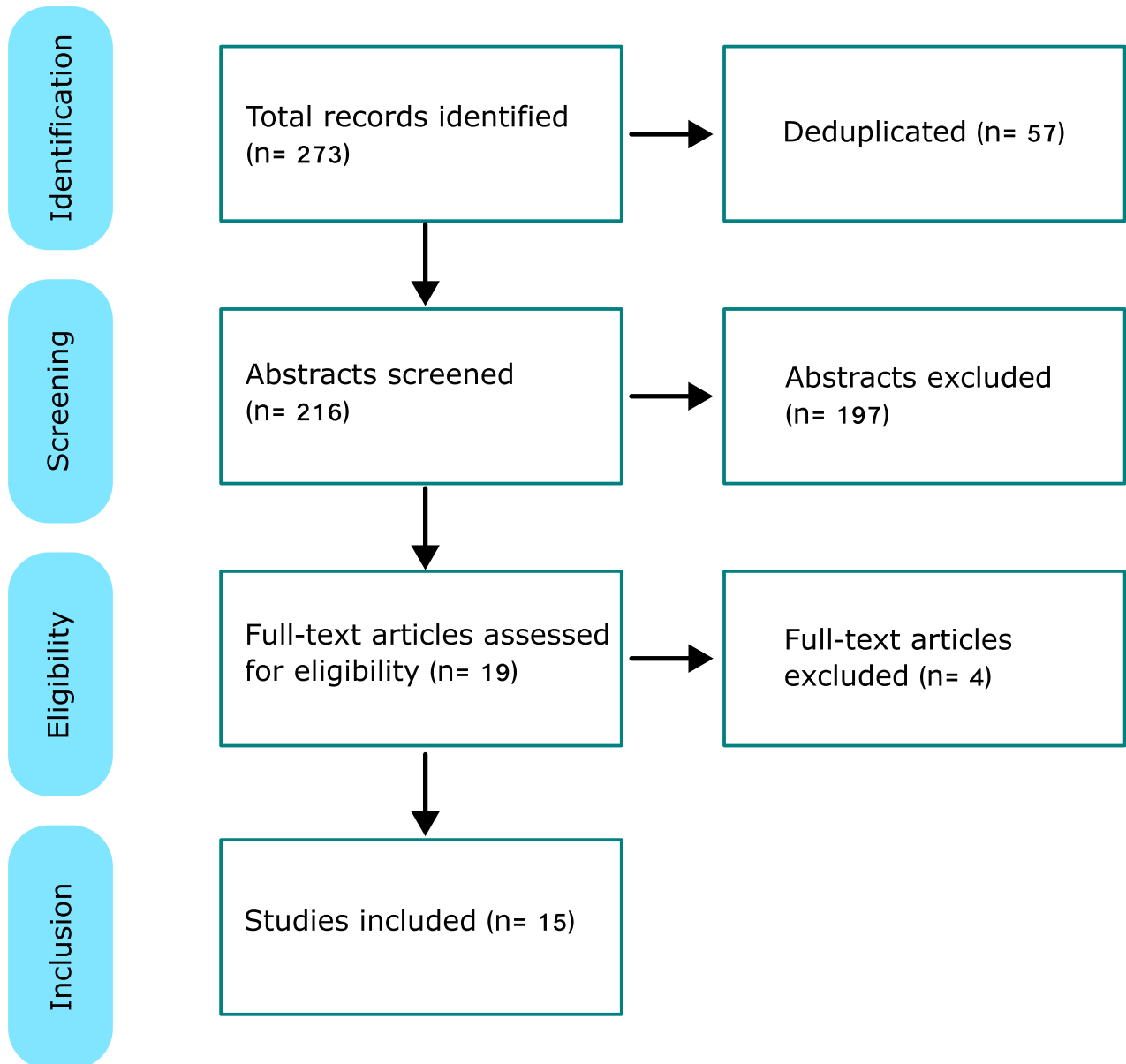
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Working group 4: Headache and Epilepsy



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Literature search strategy

We are going to search electronic databases MEDLINE via PubMed, ClinicalTrials.gov and the European Clinical Trials Register. Both MeSH terms and open search will be performed

1. From now to May 15th each WG will perform a revision of the published literature until March 31st 2025.
2. The focus of the search will be a genetically confirmed primary mitochondrial disease characterised by 1. the full clinical phenotype of MELAS or 2. by encephalopathy and at least one stroke-like episode
3. Each working group has to provide the results as *PRISMA Flowchart*, the final list of included articles must be provided as well as the queries to be voted in the first Survey
4. Mandatory strategies/aspects to be explored for WG1:
Books and documents, clinical trials, meta-analyses, randomized controlled trials, reviews and systematic reviews under the search terms (see below)

Inclusion criteria literature search for WGs:

- Peer reviewed papers: case reports, case series, case control studies, prospective or retrospective cohort studies, non-randomized uncontrolled trials, randomized control trials, reviews and systematic reviews
- Only papers with genetically confirmed MELAS (m.3243A>G, POLG etc.)

Exclusion criteria literature search for WGs 2-6:

- Papers without genetic confirmation of MELAS
- Studies that are not reporting any outcome from therapeutic intervention

WG1

Previous criteria:

Hirano 1994 (MELAS) (<https://pubmed.ncbi.nlm.nih.gov/1422200/>)

Yatsuga 2012 (MELAS) (<https://pubmed.ncbi.nlm.nih.gov/21443929/>)

Yi 2019 (SLE) (<https://pubmed.ncbi.nlm.nih.gov/32090171/>)

Yi 2022 (SLE) (<https://pubmed.ncbi.nlm.nih.gov/34927673/>)

Emmanuele 2022 (MELAS) (<https://pubmed.ncbi.nlm.nih.gov/35606253/>)

Prompt:

- MELAS Syndrome (MeSH Term) and Stroke-like episode AND/OR diagnostic criteria AND/OR definition AND/OR diagnosis
- MELAS Syndrome (MeSH Term) AND metabolic AND stroke

WG2

Prompt:

- MELAS Syndrome (MeSH Term) AND Stroke-like episode AND/OR management AND therapy AND/OR prevention

WG3

Prompt:

- MELAS Syndrome (MeSH Term) AND/OR Stroke-like episode AND mental disorders

WG4

Prompt:

- MELAS Syndrome (MeSH Term) AND/OR Stroke-like episode AND epilepsy (MeSH Term) AND/OR seizures (MeSH Term)
- MELAS Syndrome (MeSH Term) AND/OR Stroke-like episode AND headache (MeSH Term)

WG5

Prompt:

- MELAS Syndrome (MeSH Term) AND/OR Stroke-like episode AND/OR Glucose intolerance AND/OR Diabetes AND/OR Gastrointestinal* AND/OR Cardiomyopathy AND/OR Hearing AND/OR Endocrine * AND/OR Kidney failure AND/OR Visual* AND/OR Liver* AND/OR Infection AND/OR Neuropathy AND/OR Myopathy AND/OR Multi-organ failure AND/OR Rhabdomyolysis AND/OR lactic acidosis

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List_literature search WG 1 (MELAS and SLE definition)

1. Ambrogetti R, Kavanagh E, ElTayeb K. Late-onset mitochondrial encephalopathy with lactic acidosis and stroke-like episodes and the role of serial imaging. *BMJ Case Rep.* 2024 Feb 27;17(2):e259102. doi: 10.1136/bcr-2023-259102. PMID: 38417938; PMCID: PMC10900402.
2. Miyahara H, Tamai C, Inoue M, Sekiguchi K, Tahara D, Tahara N, Takeda K, Arafuka S, Moriyoshi H, Koizumi R, Akagi A, Riku Y, Sone J, Yoshida M, Ihara K, Iwasaki Y. Neuropathological hallmarks in autopsied cases with mitochondrial diseases caused by the mitochondrial 3243A>G mutation. *Brain Pathol.* 2023 Nov;33(6):e13199. doi: 10.1111/bpa.13199. Epub 2023 Aug 3. PMID: 37534760; PMCID: PMC10580013.
3. Alves CAPF, Zandifar A, Peterson JT, Tara SZ, Ganetzky R, Viaene AN, Andronikou S, Falk MJ, Vossough A, Goldstein AC. MELAS: Phenotype Classification into Classic-versus-Atypical Presentations. *AJNR Am J Neuroradiol.* 2023 May;44(5):602-610. doi: 10.3174/ajnr.A7837. Epub 2023 Apr 6. PMID: 37024306; PMCID: PMC10171385.
4. Naftali J, Mermelstein M, Landau YE, Barnea R, Shelly S, Auriel E, Peretz S. Clinical score for early diagnosis and treatment of stroke-like episodes in MELAS syndrome. *Acta Neurol Belg.* 2023 Jun;123(3):1019-1028. doi: 10.1007/s13760-023-02196-z. Epub 2023 Feb 15. PMID: 36792807.
5. Zhao Y, Yu X, Ji K, Lin Y, Xu X, Wang W, Yan C. Reversible cerebral artery constriction accompanied with stroke-like episode in MELAS: A case series. *J Neurol Sci.* 2022 Oct 15;441:120345. doi: 10.1016/j.jns.2022.120345. Epub 2022 Jul 19. PMID: 35940028.
6. Seed LM, Dean A, Krishnakumar D, Phyu P, Horvath R, Harijan PD. Molecular and neurological features of MELAS syndrome in paediatric patients: A case series and review of the literature. *Mol Genet Genomic Med.* 2022 Jul;10(7):e1955. doi: 10.1002/mgg3.1955. Epub 2022 Apr 26. PMID: 35474314; PMCID: PMC9266612.
7. Bernardo P, Pandolfi M, Vedova P, Varone A, Rubino A. Clinical presentation of a stroke-like episode in MELAS syndrome: what is the impact of epileptogenic activity? *Neurol Sci.* 2021 Aug;42(8):3463-3466. doi: 10.1007/s10072-021-05277-0. Epub 2021 May 1. PMID: 33932178.
8. Chong L, Zhenzhou L, Daokun R, Yuankui W, Hui Z, Chao Y, Yafang H, Haishan J. Vessel flow void sign and hyperintense vessel sign on FLAIR images distinguish between MELAS and AIS. *Mitochondrion.* 2021 May;58:131-134. doi: 10.1016/j.mito.2021.02.015. Epub 2021 Mar 11. PMID: 33713868.
9. 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. *BMC Neurol.* 2020 May 1;20(1):167. doi: 10.1186/s12883-020-01748-7. PMID: 32357846; PMCID: PMC7195751.
10. Chen H, Hu Q, Raza HK, Chansysouphanthong T, Singh S, Rai P, Cui G, Zhang Z, Ye X, Xu C, Liu Y, Jiang H. An analysis of the clinical and imaging features of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). *Somatosens Mot Res.* 2020 Mar;37(1):45-49. doi: 10.1080/08990220.2020.1720636. Epub 2020 Jan 30. PMID: 32000557.
11. Bhatia KD, Krishnan P, Kortman H, Klostranec J, Krings T. Acute Cortical Lesions in MELAS Syndrome: Anatomic Distribution, Symmetry, and Evolution. *AJNR Am J Neuroradiol.* 2020 Jan;41(1):167-173. doi: 10.3174/ajnr.A6325. Epub 2019 Dec 5. PMID: 31806591; PMCID: PMC6975311.
12. Lu Y, Deng J, Zhao Y, Zhang Z, Hong D, Yao S, Zhao D, Xie J, Fang H, Yuan Y, Wang Z. Patients with MELAS with negative myopathology for characteristic ragged-red fibers. *J Neurol Sci.* 2020 Jan 15;408:116499. doi: 10.1016/j.jns.2019.116499. Epub 2019 Oct 15. PMID: 31726383.
13. Wang Z, Xiao J, Xie S, Zhao D, Liu X, Zhang J, Yuan Y, Huang Y. MR evaluation of cerebral oxygen metabolism and blood flow in stroke-like episodes of MELAS. *J Neurol Sci.* 2012 Dec 15;323(1-2):173-7. doi: 10.1016/j.jns.2012.09.011. Epub 2012 Oct 11. PMID: 23062409.
14. Yatsuga S, Povalko N, Nishioka J, Katayama K, Kakimoto N, Matsuishi T, Kakuma T, Koga Y; Taro Matsuoka for MELAS Study Group in Japan. MELAS: a nationwide prospective cohort study of 96

- patients in Japan. *Biochim Biophys Acta*. 2012 May;1820(5):619-24. doi: 10.1016/j.bbagen.2011.03.015. Epub 2011 Apr 2. PMID: 21443929.
15. Ito H, Mori K, Harada M, Minato M, Naito E, Takeuchi M, Kuroda Y, Kagami S. Serial brain imaging analysis of stroke-like episodes in MELAS. *Brain Dev*. 2008 Aug;30(7):483-8. doi: 10.1016/j.braindev.2008.01.003. Epub 2008 Mar 4. PMID: 18289816.
 16. Abe K, Yoshimura H, Tanaka H, Fujita N, Hikita T, Sakoda S. Comparison of conventional and diffusion-weighted MRI and proton MR spectroscopy in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like events. *Neuroradiology*. 2004 Feb;46(2):113-7. doi: 10.1007/s00234-003-1138-2. Epub 2003 Dec 12. PMID: 14673554.
 17. Iizuka T, Sakai F, Kan S, Suzuki N. Slowly progressive spread of the stroke-like lesions in MELAS. *Neurology*. 2003 Nov 11;61(9):1238-44. doi: 10.1212/01.wnl.0000091888.26232.fe. PMID: 14610127.
 18. Ohshita T, Oka M, Imon Y, Watanabe C, Katayama S, Yamaguchi S, Kajima T, Mimori Y, Nakamura S. Serial diffusion-weighted imaging in MELAS. *Neuroradiology*. 2000 Sep;42(9):651-6. doi: 10.1007/s002340000335. PMID: 11071437.
 19. Hirano M, Ricci E, Koenigsberger MR, Defendini R, Pavlakis SG, DeVivo DC, DiMauro S, Rowland LP. Melas: an original case and clinical criteria for diagnosis. *Neuromuscul Disord*. 1992;2(2):125-35. doi: 10.1016/0960-8966(92)90045-8. PMID: 1422200.
 20. Ng YS, Bindoff LA, Gorman GS, Horvath R, Klopstock T, Mancuso M, Martikainen MH, McFarland R, Nesbitt V, Pitceathly RDS, Schaefer AM, Turnbull DM. Consensus-based statements for the management of mitochondrial stroke-like episodes. *Wellcome Open Res*. 2019 Dec 13;4:201. doi: 10.12688/wellcomeopenres.15599.1. PMID: 32090171; PMCID: PMC7014928.
 21. Mickelsson N, Hirvonen J, Martikainen MH. Clinical features and treatment of stroke-like episodes in mitochondrial disease: a cohort-based study. *J Neurol*. 2024 Dec 12;272(1):47. doi: 10.1007/s00415-024-12745-y. PMID: 39666093; PMCID: PMC11638336.
 22. Serra G, Piccinu R, Tondi M, Muntoni F, Zeviani M, Mastropaolo C. Clinical and EEG findings in eleven patients affected by mitochondrial encephalomyopathy with MERRF-MELAS overlap. *Brain Dev*. 1996 May-Jun;18(3):185-91. doi: 10.1016/0387-7604(95)00147-6. PMID: 8836498.
 23. Xu S, Jiang J, Chang L, Zhang B, Zhu X, Niu F. Multisystem clinicopathologic and genetic analysis of MELAS. *Orphanet J Rare Dis*. 2024 Dec 24;19(1):487. doi: 10.1186/s13023-024-03511-4. PMID: 39719631; PMCID: PMC11668008.
 24. Wang R, Hu B, Sun C, Geng D, Lin J, Li Y. Metabolic abnormality in acute stroke-like lesion and its relationship with focal cerebral blood flow in patients with MELAS: Evidence from proton MR spectroscopy and arterial spin labeling. *Mitochondrion*. 2021 Jul;59:276-282. doi: 10.1016/j.mito.2021.06.012. Epub 2021 Jun 27. PMID: 34186261.
 25. Emmanuele V, Ganesh J, Vladutiu G, Haas R, Kerr D, Saneto RP, Cohen BH, Van Hove JLK, Scaglia F, Hoppel C, Rosales XQ, Barca E, Buchsbaum R, Thompson JL, DiMauro S, Hirano M; North American Mitochondrial Disease Consortium (NAMDC). Time to harmonize mitochondrial syndrome nomenclature and classification: A consensus from the North American Mitochondrial Disease Consortium (NAMDC). *Mol Genet Metab*. 2022 Jun;136(2):125-131. doi: 10.1016/j.ymgme.2022.05.001. Epub 2022 May 13. PMID: 35606253; PMCID: PMC9341219.
 26. Ng YS, Lax NZ, Blain AP, Erskine D, Baker MR, Polvikoski T, Thomas RH, Morris CM, Lai M, Whittaker RG, Gebbels A, Winder A, Hall J, Feeney C, Farrugia ME, Hirst C, Roberts M, Lawthom C, Chrysostomou A, Murphy K, Baird T, Maddison P, Duncan C, Poulton J, Nesbitt V, Hanna MG, Pitceathly RDS, Taylor RW, Blakely EL, Schaefer AM, Turnbull DM, McFarland R, Gorman GS. Forecasting stroke-like episodes and outcomes in mitochondrial disease. *Brain*. 2022 Apr 18;145(2):542-554. doi: 10.1093/brain/awab353. PMID: 34927673; PMCID: PMC9014738.
 27. Wang W, Zhao Y, Xu X, Ma X, Sun Y, Lin Y, Zhao Y, Xu Z, Wang J, Ren H, Wang B, Zhao D, Wang D, Liu F, Li W, Yan C, Ji K. A different pattern of clinical, muscle pathology and brain MRI findings in MELAS with mt-ND variants. *Ann Clin Transl Neurol*. 2023 Jun;10(6):1035-1045. doi: 10.1002/acn3.51787. Epub 2023 May 23. PMID: 37221696; PMCID: PMC10270267.

28. Cox BC, Pearson JY, Mandrekar J, Gavrilova RH. The clinical spectrum of MELAS and associated disorders across ages: a retrospective cohort study. *Front Neurol.* 2023 Dec 14;14:1298569. doi: 10.3389/fneur.2023.1298569. PMID: 38156086; PMCID: PMC10753009.
29. van Eijdsden RG, Eijssen LM, Lindsey PJ, van den Burg CM, de Wit LE, Rubio-Gozalbo ME, de Die CE, Ayoubi T, Sluiter W, de Coo IF, Smeets HJ. Termination of damaged protein repair defines the occurrence of symptoms in carriers of the m.3243A > G tRNA(Leu) mutation. *J Med Genet.* 2008 Aug;45(8):525-34. doi: 10.1136/jmg.2008.057497. Epub 2008 May 2. PMID: 18456717.
30. Haast RAM, Ivanov D, IJsselstein RJT, Salleveld SCEH, Jansen JFA, Smeets HJM, de Coo IFM, Formisano E, Uludağ K. Anatomic & metabolic brain markers of the m.3243A>G mutation: A multi-parametric 7T MRI study. *Neuroimage Clin.* 2018 Jan 31;18:231-244. doi: 10.1016/j.nicl.2018.01.017. PMID: 29868447; PMCID: PMC5984598.
31. Ng YS, Gorman GS. Stroke-like episodes in adult mitochondrial disease. *Handb Clin Neurol.* 2023;194:65-78. doi: 10.1016/B978-0-12-821751-1.00005-1. PMID: 36813321.
32. Distelmaier F, Klopstock T. Neuroimaging in mitochondrial disease. *Handb Clin Neurol.* 2023;194:173-185. doi: 10.1016/B978-0-12-821751-1.00016-6. PMID: 36813312.
33. Mastrangelo M, Ricciardi G, Giordo L, Michele M, Toni D, Leuzzi V. Stroke and stroke-like episodes in inborn errors of metabolism: Pathophysiological and clinical implications. *Mol Genet Metab.* 2022 Jan;135(1):3-14. doi: 10.1016/j.ymgme.2021.12.014. Epub 2021 Dec 23. PMID: 34996714.
34. Yokota Y, Hara M, Akimoto T, Mizoguchi T, Goto YI, Nishino I, Kamei S, Nakajima H. Late-onset MELAS syndrome with mtDNA 14453G→A mutation masquerading as an acute encephalitis: a case report. *BMC Neurol.* 2020 Jun 17;20(1):247. doi: 10.1186/s12883-020-01818-w. PMID: 32552696; PMCID: PMC7298965.
35. Shi Y, Dong G, Pan H, Tai H, Zhou Y, Wang A, Niu S, Chen B, Wang X, Zhang Z. Stroke-like episodes in patients with adult-onset neuronal intranuclear inclusion disease and patients with late-onset MELAS: A comparative study. *Ann Clin Transl Neurol.* 2024 Dec;11(12):3125-3136. doi: 10.1002/acn3.52219. Epub 2024 Oct 4. PMID: 39367621; PMCID: PMC11651200.
36. Zhang X, Qiu S, Yang L, Li Y, Xu L, Xu N, Mi C, Li M. A novel heterozygous ATP1A2 pathogenic variant in a Chinese child with MELAS-like alternating hemiplegia. *Mol Genet Genomic Med.* 2023 May;11(5):e2146. doi: 10.1002/mgg3.2146. Epub 2023 Feb 7. PMID: 36749827; PMCID: PMC10178798.
37. Pizzamiglio C, Bugiardini E, Macken WL, Woodward CE, Hanna MG, Pitceathly RDS. Mitochondrial Strokes: Diagnostic Challenges and Chameleons. *Genes (Basel).* 2021 Oct 19;12(10):1643. doi: 10.3390/genes12101643. PMID: 34681037; PMCID: PMC8535945.
38. Liao NY, Liao KK, Liao YC, Lee YC. Mitochondrial DNA m.3243A>G mutation rarely causes CADASIL-like phenotype. *Neurobiol Aging.* 2021 Jan;97:145.e5-145.e6. doi: 10.1016/j.neurobiolaging.2020.08.016. Epub 2020 Aug 27. PMID: 32950272.
39. Nikolaus M, Tietze A, Schweizer L, Kaindl AM, Stenzel W, Schuelke M, Knierim E. Fulminant cerebral venous thrombosis associated with the m.3243A>G MELAS mutation: A new guise for an old disease. *Brain Dev.* 2019 Nov;41(10):901-904. doi: 10.1016/j.braindev.2019.07.002. Epub 2019 Jul 22. PMID: 31345444.
40. Snyder MT, Manor J, Gijavanekar C, Mizerik E, Kralik SF, Elsea SH, Machol K, Emrick L, Scaglia F. Heteroplasmic pathogenic m.12315G>A variant in MT-TL2 presenting with MELAS syndrome and depletion of nitric oxide donors. *Am J Med Genet A.* 2024 Mar;194(3):e63461. doi: 10.1002/ajmg.a.63461. Epub 2023 Nov 12. PMID: 37953071.
41. 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). *Medicine (Baltimore).* 2020 Jun 12;99(24):e20310. doi: 10.1097/MD.00000000000020310. PMID: 32541454; PMCID: PMC7302614.
42. Lamperti C, Diodato D, Lamantea E, Carrara F, Ghezzi D, Mereghetti P, Rizzi R, Zeviani M. MELAS-like encephalomyopathy caused by a new pathogenic mutation in the mitochondrial DNA encoded cytochrome c oxidase subunit I. *Neuromuscul Disord.* 2012 Nov;22(11):990-4. doi: 10.1016/j.nmd.2012.06.003. Epub 2012 Jul 23. PMID: 22832341.

43. Menotti F, Brega A, Diegoli M, Grasso M, Modena MG, Arbustini E. A novel mtDNA point mutation in tRNA(Val) is associated with hypertrophic cardiomyopathy and MELAS. *Ital Heart J.* 2004 Jun;5(6):460-5. PMID: 15320572.
44. Zhao Y, Xu Z, Yan C, Ji K. Unraveling the Diagnostic Puzzle: Minor Stroke-Like Lesions and Normal Muscle Histopathology in MELAS Syndrome. *Stroke.* 2024 Apr;55(4):e127-e130. doi: 10.1161/STROKEAHA.123.045984. Epub 2024 Feb 16. PMID: 38362757.
45. De Coo IF, Renier WO, Ruitenbeek W, Ter Laak HJ, Bakker M, Schägger H, Van Oost BA, Smeets HJ. A 4-base pair deletion in the mitochondrial cytochrome b gene associated with parkinsonism/MELAS overlap syndrome. *Ann Neurol.* 1999 Jan;45(1):130-3. doi: 10.1002/1531-8249(199901)45:1<130::aid-art21>3.3.co;2-q. PMID: 9894888.
46. de Coo IF, Sistermans EA, de Wijs IJ, Catsman-Berrevoets C, Busch HF, Scholte HR, de Klerk JB, van Oost BA, Smeets HJ. A mitochondrial tRNA(Val) gene mutation (G1642A) in a patient with mitochondrial myopathy, lactic acidosis, and stroke-like episodes. *Neurology.* 1998 Jan;50(1):293-5. doi: 10.1212/wnl.50.1.293. PMID: 9443499.

Reference list – included articles WG 2 MELAS Consensus – Management of SLE

1. Alenezi, A. F., Almelahi, M. A., Fekih-Romdhana, F., & Jahrami, H. A. (2022). Delay in diagnosing a patient with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome who presented with status epilepticus and lactic acidosis: a case report. *Journal of Medical Case Reports [Electronic Resource]*, 16(1), 361. doi:<https://dx.doi.org/10.1186/s13256-022-03613-2>
2. Berbel-Garcia, A., Barbera-Farre, J. R., Etesam, J. P., Salio, A. M., Cabello, A., Gutierrez-Rivas, E., & Campos, Y. (2004). Coenzyme Q 10 improves lactic acidosis, strokelike episodes, and epilepsy in a patient with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes). *Clin Neuropharmacol*, 27(4), 187-191. doi:10.1097/01.wnf.0000137862.67131.bf
3. Bi, W. L. M. A., Baehring, J. M. M. D., & Lesser, R. L. M. D. (2006). Evolution of Brain Imaging Abnormalities in Mitochondrial Encephalomyopathy With Lactic Acidosis and Stroke-Like Episodes. *Journal of Neuro-Ophthalmology*, 26(4), 251-256. Retrieved from <https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovfth&AN=00041327-200612000-00004>
4. Chen, J. C., Tsai, T. C., Liu, C. S., & Lu, C. T. (2007). Acute hearing loss in a patient with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS). *Acta Neurol Taiwan*, 16(3), 168-172.
5. Choi, H. S., Lee, J. H., Lee, S. H., & Lee, Y. M. (2018). Avascular necrosis after long-term glucocorticoid treatment in MELAS: a cautionary note. *J Inherit Metab Dis*, 41(2), 277-278. doi:10.1007/s10545-017-0110-y
6. Clinical Long Term Evaluation of Glutamine Supplement in MELAS (Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like Episodes) Syndrome in Order to Prevent Neurological Damage. (2022). Retrieved from <https://clinicaltrials.gov/study/NCT05255328>. Available from National Library of Medicine (US) <https://clinicaltrials.gov/study/NCT05255328>
7. Clinical Trial of Ketogenic Diet in the Treatment of Mitochondrial Encephalomyopathy With Lactic Acidosis and Stroke-like Episodes(MELAS). (2023). Retrieved from <https://clinicaltrials.gov/study/NCT06013397>. Available from National Library of Medicine (US) <https://clinicaltrials.gov/study/NCT06013397>
8. Corda, D., Rosati, G., Deiana, G. A., & Sechi, G. (2006). "Erratic" complex partial status epilepticus as a presenting feature of MELAS. *Epilepsy Behav*, 8(3), 655-658. doi:10.1016/j.yebeh.2005.12.011
9. Curtò, N., Tremolizzo, L., Mattavelli, L., Piatti, M. L., Marzorati, L., Guerra, L., . . . Ferrarese, C. (2006). A case of Melas (A3243G) on chronic dichloroacetate treatment. *Eur Neurol*, 55(1), 37-38. doi:10.1159/000091424
10. El-Hattab, A. W., Emrick, L. T., Hsu, J. W., Chanprasert, S., Almannai, M., Craigen, W. J., . . . Scaglia, F. (2016). Impaired nitric oxide production in children with MELAS syndrome and the effect of

- arginine and citrulline supplementation. *Mol Genet Metab*, 117(4), 407-412. doi:10.1016/j.ymgme.2016.01.010
11. El-Hattab, A. W., Hsu, J. W., Emrick, L. T., Wong, L. J., Craigen, W. J., Jahoor, F., & Scaglia, F. (2012). Restoration of impaired nitric oxide production in MELAS syndrome with citrulline and arginine supplementation. *Mol Genet Metab*, 105(4), 607-614. doi:10.1016/j.ymgme.2012.01.016
 12. Emmanuele, V. M. D., Sotiriou, E. M. D., Rios, P. G. P., Ganesh, J. M. D., Ichord, R. M. D., Foley, A. R. M. D., . . . DiMauro, S. M. D. (2013). A Novel Mutation in the Mitochondrial DNA Cytochrome b Gene (MTCYB) in a Patient With Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes Syndrome. *Journal of Child Neurology*, 28(2), 236-242. Retrieved from <https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovfto&AN=0004811-201328020-00010>
 13. Farrar, M. A., Lin, C. S., Krishnan, A. V., Park, S. B., Andrews, P. I., & Kiernan, M. C. (2010). Acute, reversible axonal energy failure during stroke-like episodes in MELAS. *Pediatrics*, 126(3), e734-739. doi:10.1542/peds.2009-2930
 14. Fryer, R. H., Bain, J. M., & De Vivo, D. C. (2016). Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-Like Episodes (MELAS): A Case Report and Critical Reappraisal of Treatment Options. *Pediatr Neurol*, 56, 59-61. doi:10.1016/j.pediatrneurol.2015.12.010
 15. Ganetzky, R. D., & Falk, M. J. (2018). 8-year retrospective analysis of intravenous arginine therapy for acute metabolic strokes in pediatric mitochondrial disease. *Molecular Genetics & Metabolism*, 123(3), 301-308. doi:<https://dx.doi.org/10.1016/j.ymgme.2018.01.010>
 16. Gonzalez-Pinto Gonzalez, T., Almeida Velasco, J., Moreno Estebanez, A., Agirre Beitia, G., Cabral Martinez, L., Diaz Cuervo, I., & Martinez Arroyo, A. (2020). Acute management of a stroke-like episode in MELAS syndrome: What should we know? *eNeurologicalSci*, 20, 100249. doi:<https://dx.doi.org/10.1016/j.ensci.2020.100249>
 17. He, F., Ye, L., Miao, P., Zhou, J., Ding, Y., & Wang, S. (2023). Long-term ketogenic diet therapy improves mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS): A case report. *CNS: Neuroscience & Therapeutics*, 29(9), 2717-2720. Retrieved from <https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovftz2&AN=01445395-202309000-00030>
 18. Hovsepian, D. A., Galati, A., Chong, R. A., Mazumder, R., DeGiorgio, C. M., Mishra, S., & Yim, C. (2019). MELAS: Monitoring treatment with magnetic resonance spectroscopy. *Acta Neurol Scand*, 139(1), 82-85. doi:10.1111/ane.13027
 19. Ikawa, M., Povalko, N., & Koga, Y. (2020). Arginine therapy in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes. *Curr Opin Clin Nutr Metab Care*, 23(1), 17-22. doi:10.1097/mco.0000000000000610
 20. Ikejiri, Y. M., Mori, E. M., Ishii, K. M., Nishimoto, K. M., Yasuda, M. M., & Sasaki, M. P. (1996). Idebenone improves cerebral mitochondrial oxidative metabolism in a patient with MELAS. *Neurology*, 47(2), 583-585. Retrieved from <https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovftb&AN=0006114-199608000-00048>
 21. Jung, I., Park, S. H., & Kim, D. W. (2015). Mitochondrial encephalopathy, lactic acidosis, and stroke-like episode syndrome presenting with prolonged visual aura. *J Clin Neurol*, 11(1), 104-105. doi:10.3988/jcn.2015.11.1.104
 22. Kaufmann, P., Engelstad, K., Wei, Y., Jhung, S., Sano, M. C., Shungu, D. C., . . . De Vivo, D. C. (2006). Dichloroacetate causes toxic neuropathy in MELAS: a randomized, controlled clinical trial. *Neurology*, 66(3), 324-330. doi:10.1212/01.wnl.0000196641.05913.27
 23. Kitamura, M., Yatsuga, S., Abe, T., Povalko, N., Saiki, R., Ushijima, K., . . . Koga, Y. (2016). L-Arginine intervention at hyper-acute phase protects the prolonged MRI abnormality in MELAS. *J Neurol*, 263(8), 1666-1668. doi:10.1007/s00415-016-8069-4
 24. Koga, Y., Akita, Y., Nishioka, J., Yatsuga, S., Povalko, N., Katayama, K., & Matsuishi, T. (2007). MELAS and L-arginine therapy. *Mitochondrion*, 7(1-2), 133-139. doi:10.1016/j.mito.2006.11.006

25. Koga, Y., Ishibashi, M., Ueki, I., Yatsuga, S., Fukiyama, R., Akita, Y., & Matsuishi, T. (2002). Effects of L-arginine on the acute phase of strokes in three patients with MELAS. *Neurology*, 58(5), 827-828. doi:10.1212/wnl.58.5.827
26. Koga, Y., Povalko, N., Inoue, E., Nakamura, H., Ishii, A., Suzuki, Y., . . . Fujii, K. (2018). Therapeutic regimen of L-arginine for MELAS: 9-year, prospective, multicenter, clinical research. *J Neurol*, 265(12), 2861-2874. doi:10.1007/s00415-018-9057-7
27. Kubota, M., Sakakihara, Y., Mori, M., Yamagata, T., & Momoi-Yoshida, M. (2004). Beneficial effect of L-arginine for stroke-like episode in MELAS. *Brain Dev*, 26(7), 481-483; discussion 480. doi:10.1016/j.braindev.2004.01.006
28. Lahiri, D., Sawale, V. M., Banerjee, S., Dubey, S., Roy, B. K., & Das, S. K. (2019). Chorea-ballism as a dominant clinical manifestation in heteroplasmic mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome with A3251G mutation in mitochondrial genome: a case report. *J Med Case Rep*, 13(1), 63. doi:10.1186/s13256-018-1936-0
29. Lekoubou, A., Kouamé-Assouan, A. E., Cho, T. H., Luauté, J., Nighoghossian, N., & Derex, L. (2011). Effect of long-term oral treatment with L-arginine and idebenone on the prevention of stroke-like episodes in an adult MELAS patient. *Rev Neurol (Paris)*, 167(11), 852-855. doi:10.1016/j.neurol.2011.02.038
30. Li, P. G., Tang, Y. N., Zheng, S. S., Chen, W. K., & Lu, L. P. (2016). Dandy-Walker Malformation and Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like Episode Syndrome: Is There a Causal or Coincidental Association? *Chin Med J (Engl)*, 129(5), 620-621. doi:10.4103/0366-6999.176984
31. Li, Y. M. D. P., Lin, J. M. D. P., Sun, C. M. D. P., Zhao, C. M. D. P., & Li, H. M. D. P. (2017). Increased cerebral blood flow as a predictor of episodes in MELAS using multimodal MRI. *Journal of Magnetic Resonance Imaging*, 46(3), 915-918. Retrieved from <https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovfts&AN=01445455-201709000-00030>
32. Liu, X.-Q., Shen, S.-Q., Yang, G.-C., & Liu, Q. (2019). Mitochondrial A3243G mutation causes mitochondrial encephalomyopathy in a Chinese patient: Case report. *Medicine*, 98(19). Retrieved from https://journals.lww.com/md-journal/fulltext/2019/05100/mitochondrial_a3243g_mutation_causes_mitochondrial.55.aspx
33. Lu, J., & Huang, Y. (2013). Childhood mitochondrial encephalomyopathies: clinical course, diagnosis, neuroimaging findings, mtDNA mutations and outcome in six children. *Ital J Pediatr*, 39, 60. doi:10.1186/1824-7288-39-60
34. Majamaa, K., Rusanen, H., Remes, A. M., Pyhtinen, J., & Hassinen, I. E. (1996). Increase of blood NAD⁺ and attenuation of lactacidemia during nicotinamide treatment of a patient with the MELAS syndrome. *Life Sci*, 58(8), 691-699. doi:10.1016/s0024-3205(96)80008-7
35. Mori, M., Yamagata, T., Goto, T., Saito, S., & Momoi, M. Y. (2004). Dichloroacetate treatment for mitochondrial cytopathy: long-term effects in MELAS. *Brain Dev*, 26(7), 453-458. doi:10.1016/j.braindev.2003.12.009
36. Napolitano, A., Salvetti, S., Vista, M., Lombardi, V., Siciliano, G., & Giraldi, C. (2000). Long-term treatment with idebenone and riboflavin in a patient with MELAS. *Neurol Sci*, 21(5 Suppl), S981-982. doi:10.1007/s100720070015
37. Ni Cathain, D., Browne, E., Skehan, K., & Boyle, K. (2021). MELAS syndrome: an acute stroke-like episode complicated by renal tubular acidosis. *BMJ Case Rep*, 14(11). doi:10.1136/bcr-2021-245898
38. Oguro, H., Iijima, K., Takahashi, K., Nagai, A., Bokura, H., Yamaguchi, S., & Kobayashi, S. (2004). Successful treatment with succinate in a patient with MELAS. *Intern Med*, 43(5), 427-431. doi:10.2169/internalmedicine.43.427
39. Ohsawa, Y., Hagiwara, H., Nishimatsu, S. I., Hirakawa, A., Kamimura, N., Ohtsubo, H., . . . Sunada, Y. (2019). Taurine supplementation for prevention of stroke-like episodes in MELAS: a multicentre, open-label, 52-week phase III trial. *J Neurol Neurosurg Psychiatry*, 90(5), 529-536. doi:10.1136/jnnp-2018-317964

40. Pérez-Cruz, E., González-Rivera, C., & Valencia-Olvera, L. (2022). Immunonutrition for the acute treatment of MELAS syndrome. *Endocrinol Diabetes Nutr (Engl Ed)*, 69(2), 144-148. doi:10.1016/j.endien.2022.02.006
41. Ramesh, R., Hariharan, S., & Sundar, L. (2023). Stroke-Like Episodes and Epilepsy in a Patient with COQ8A-Related Coenzyme Q10 Deficiency. *Annals of Indian Academy of Neurology Nov Dec*, 26(6), 980-982. Retrieved from <https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovftz2&AN=02223306-202326060-00023>
42. Rikimaru, M., Ohsawa, Y., Wolf, A. M., Nishimaki, K., Ichimiya, H., Kamimura, N., . . . Sunada, Y. (2012). Taurine ameliorates impaired the mitochondrial function and prevents stroke-like episodes in patients with MELAS. *Intern Med*, 51(24), 3351-3357. doi:10.2169/internalmedicine.51.7529
43. Rodan, L. H., Poubanc, J., Fisher, J. A., Sobczyk, O., Mikulis, D. J., & Tein, I. (2020). L-arginine effects on cerebrovascular reactivity, perfusion and neurovascular coupling in MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes) syndrome. *PLoS One*, 15(9), e0238224. doi:10.1371/journal.pone.0238224
44. Sage-Schwaede, A., Engelstad, K., Salazar, R., Curcio, A., Khandji, A., Garvin, J. H., Jr., & De Vivo, D. C. (2019). Exploring mTOR inhibition as treatment for mitochondrial disease. *Ann Clin Transl Neurol*, 6(9), 1877-1881. doi:10.1002/acn3.50846
45. Shigem, R., Fukuda, M., Suzuki, Y., Morimoto, T., & Ishii, E. (2011). L-arginine is effective in stroke-like episodes of MELAS associated with the G13513A mutation. *Brain Dev*, 33(6), 518-520. doi:10.1016/j.braindev.2010.07.013
46. Shinkai, T., Nakashima, M., Ohmori, O., Terao, T., & Nakamura, J. (2000). Coenzyme Q10 Improves Psychiatric Symptoms in Adult-Onset Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis and Stroke-Like Episodes: A Case Report. *Australian and New Zealand Journal of Psychiatry*, 34(6), 1034-1035. Retrieved from <https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovftd&AN=0000929-200034060-00024>
47. Siddiq, I., Widjaja, E., & Tein, I. (2015). Clinical and radiologic reversal of stroke-like episodes in MELAS with high-dose L-arginine. *Neurology*, 85(2), 197-198. doi:10.1212/wnl.0000000000001726
48. Smith, K. M. D., Chiu, S. M. D., Hunt, C. M. D., Chandregowda, A. P., Babovic-Vuksanovic, D. M. D., & Keegan, B. M. M. D. (2019). Late-onset Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like Episodes Presenting With Auditory Agnosia. *Neurologist*, 24(3), 90-92. Retrieved from <https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovftu&AN=00127893-201905000-00004>
49. Snyder, M. T., Manor, J., Gijavanekar, C., Mizerik, E., Kralik, S. F., Elsea, S. H., . . . Scaglia, F. (2024). Heteroplasmic pathogenic m.12315G>A variant in MT-TL2 presenting with MELAS syndrome and depletion of nitric oxide donors. *Am J Med Genet A*, 194(3), e63461. doi:10.1002/ajmg.a.63461
50. Steriade, C., Andrade, D. M., Faghfoury, H., Tarnopolsky, M. A., & Tai, P. (2014). Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) may respond to adjunctive ketogenic diet. *Pediatr Neurol*, 50(5), 498-502. doi:10.1016/j.pediatrneurol.2014.01.009
51. Sudo, A., Sasaki, M., Sugai, K., & Matsuda, H. (2004). Therapeutic effect and [123I]IMP SPECT findings of sodium dichloroacetate in a patient with MELAS. *Neurology*, 62(2), 338-339. doi:10.1212/01.wnl.0000103443.61141.76
52. Sun, X., Jiang, G., Ju, X., & Fu, H. (2018). MELAS and macroangiopathy: A case report and literature review. *Medicine*, 97(52). Retrieved from https://journals.lww.com/md-journal/fulltext/2018/12280/melas_and_macroangiopathy_a_case_report_and.66.aspx
53. Taieb, G., Juntas-Morales, R., & Renard, D. (2017). Progression of stroke-like lesions along the cortico-ponto-cerebellar tract. *Acta Neurologica Belgica*, 117(1), 309-310. doi:10.1007/s13760-016-0671-9
54. Tanaka, J., Nagai, T., Arai, H., Inui, K., Yamanouchi, H., Goto, Y., . . . Okada, S. (1997). Treatment of mitochondrial encephalomyopathy with a combination of cytochrome C and vitamins B1 and B2. *Brain Dev*, 19(4), 262-267. doi:10.1016/s0387-7604(97)00573-1

55. Van Karnebeek, C. D. M., Waters, P. J., Sargent, M. A., Mezey, M. M., Wong, L.-J., Wang, J., & Stockler-Ipsiroglu, S. (2011). Expanding the clinical phenotype of the mitochondrial m.13513G>A mutation with the first report of a fatal neonatal presentation. *Developmental Medicine & Child Neurology*, 53(6), 565-568. Retrieved from <https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovftl&AN=0003434-201106000-00020>
56. Walcott, B. P., Edlow, B. L., Xia, Z., Kahle, K. T., Nahed, B. V., & Schmahmann, J. D. (2012). Steroid responsive A3243G mutation MELAS: clinical and radiographic evidence for regional hyperperfusion leading to neuronal loss. *Neurologist*, 18(3), 159-170. doi:10.1097/NRL.0b013e318247bcd8
57. Wei, Y., Cui, L., & Pen, B. (2019). L-Arginine prevents stroke-like episodes but not brain atrophy: a 20-year follow-up of a MELAS patient. *Neurol Sci*, 40(1), 209-211. doi:10.1007/s10072-018-3573-1
58. Yesilbas, O., Sengenc, E., Olbak, M. E., Bako, D., Nizam, O. G., Seyithanoglu, M. H., . . . Aydin, K. (2022). First Case of MELAS Syndrome Presenting with Local Brain Edema Requiring Decompressive Craniectomy. *Turk Neurosurg*, 32(1), 155-159. doi:10.5137/1019-5149.Jtn.34196-21.4
59. Yoneda, M., Ikawa, M., Arakawa, K., Kudo, T., Kimura, H., Fujibayashi, Y., & Okazawa, H. (2012). In vivo functional brain imaging and a therapeutic trial of L-arginine in MELAS patients. *Biochim Biophys Acta*, 1820(5), 615-618. doi:10.1016/j.bbagen.2011.04.018
60. Zieglgänsberger, D., & Finsterer, J. (2025). Presentation, Treatment, and Outcome of a First Stroke-like Episode in a Carrier of the Compound Heterozygous Variants c.695G_A and c.2209G_C in POLG: A Case Report. *Cureus*, 17(2), e78428. doi:10.7759/cureus.78428

Reference list – included articles WG 3 MELAS Consensus – Management of psychiatric and cognitive issues

1. Apostolova, L. G., White, M., Moore, S. A., & Davis, P. H. (2005). Deep white matter pathologic features in watershed regions: a novel pattern of central nervous system involvement in MELAS. *Arch Neurol*, 62(7), 1154-1156. doi:10.1001/archneur.62.7.1154
2. Bernardo, P., Pandolfi, M., Vedova, P., Varone, A., & Rubino, A. (2021). Clinical presentation of a stroke-like episode in MELAS syndrome: what is the impact of epileptogenic activity? *Neurological Sciences*, 42(8), 3463-3466. doi:10.1007/s10072-021-05277-0
3. Bi, W. L. M. A., Baehring, J. M. M. D., & Lesser, R. L. M. D. (2006). Evolution of Brain Imaging Abnormalities in Mitochondrial Encephalomyopathy With Lactic Acidosis and Stroke-Like Episodes. *Journal of Neuro-Ophthalmology*, 26(4), 251-256. Retrieved from <https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovfth&AN=0041327-200612000-00004>
4. Chen, W. T., Lin, Y. S., Wang, Y. F., & Fuh, J. L. (2019). Adult onset MELAS Syndrome Presenting as A Mimic of Herpes Simplex Encephalitis. *Acta Neurologica Taiwanica*, 28(2), 46-51. Retrieved from <https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med16&AN=31867706>
5. Chu, C. S., Chu, C. L., Liu, H. E., & Lu, T. (2012). Regain of visuospatial capacity after coenzyme Q10 in a patient with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes: a case report. *Acta Neuropsychiatrica*, 24(3), 186-188. doi:<https://dx.doi.org/10.1111/j.1601-5215.2011.00620.x>
6. Clinical Trial of Ketogenic Diet in the Treatment of Mitochondrial Encephalomyopathy With Lactic Acidosis and Stroke-like Episodes(MELAS). (2023). Retrieved from <https://clinicaltrials.gov/study/NCT06013397>. Available from National Library of Medicine (US) <https://clinicaltrials.gov/study/NCT06013397>

7. Corda, D., Rosati, G., Deiana, G. A., & Sechi, G. (2006). "Erratic" complex partial status epilepticus as a presenting feature of MELAS. *Epilepsy & Behavior*, 8(3), 655-658. doi:10.1016/j.yebeh.2005.12.011
8. De Luca, R., Russo, M., Leonardi, S., Spadaro, L., Cicero, C., Naro, A., . . . Calabro, R. S. (2016). Advances in the Treatment of MELAS Syndrome: Could Cognitive Rehabilitation Have a Role? *Applied Neuropsychology. Adult*, 23(1), 61-64. doi:<https://dx.doi.org/10.1080/23279095.2014.960522>
9. Dickerson, B. C., Holtzman, D., Grant, P. E., & Tian, D. (2005). Case records of the Massachusetts General Hospital. Case 36-2005. A 61-year-old woman with seizure, disturbed gait, and altered mental status. *N Engl J Med*, 353(21), 2271-2280. doi:10.1056/NEJMcp059032
10. Fang, G. L., Zheng, Y., & Zhang, Y. X. (2018). Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes in an older adult mimicking cerebral infarction: a Chinese case report. *Clinical Interventions In Aging*, 13, 2421-2424. doi:<https://dx.doi.org/10.2147/CIA.S186636>
11. Ge, Y. X., Shang, B., Chen, W. Z., Lu, Y., & Wang, J. (2017). Adult-onset of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome with hypothyroidism and psychiatric disorders. *eNeurologicalSci*, 6, 16-20. doi:<https://dx.doi.org/10.1016/j.ensci.2016.11.005>
12. Ghosh, R., Dubey, S., Bhuin, S., Lahiri, D., Ray, B. K., & Finsterer, J. (2022). MELAS with multiple stroke-like episodes due to the variant m.13513G>A in MT-ND5. *Clinical Case Reports*, 10(2), e05361. doi:<https://dx.doi.org/10.1002/ccr3.5361>
13. Gonzalez-Pinto Gonzalez, T., Almeida Velasco, J., Moreno Estebanez, A., Agirre Beitia, G., Cabral Martinez, L., Diaz Cuervo, I., & Martinez Arroyo, A. (2020). Acute management of a stroke-like episode in MELAS syndrome: What should we know? *eNeurologicalSci*, 20, 100249. doi:<https://dx.doi.org/10.1016/j.ensci.2020.100249>
14. Ju Seok, R., Sook Joung, L., In Young, S., Tae Sung, K., & Han Ik, Y. (2009). Depressive episode with catatonic features in a case of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). *J Child Neurol*, 24(10), 1307-1309. doi:10.1177/0883073809334380
15. Lacey, C. J., & Salzberg, M. R. (2008). Obsessive-compulsive disorder with mitochondrial disease. *Psychosomatics*, 49(6), 540-542. doi:10.1176/appi.psy.49.6.540
16. Lahiri, D., Sawale, V. M., Banerjee, S., Dubey, S., Roy, B. K., & Das, S. K. (2019). Chorea-ballism as a dominant clinical manifestation in heteroplasmic mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome with A3251G mutation in mitochondrial genome: a case report. *Journal of Medical Case Reports [Electronic Resource]*, 13(1), 63. doi:<https://dx.doi.org/10.1186/s13256-018-1936-0>
17. Montano, V., Simoncini, C., LoGerfo, A., Siciliano, G., & Mancuso, M. (2021). Catatonia as prominent feature of stroke-like episode in MELAS. *Neurological Sciences*, 42(1), 383-385. doi:10.1007/s10072-020-04638-5
18. Mori, M., Yamagata, T., Goto, T., Saito, S., & Momoi, M. Y. (2004). Dichloroacetate treatment for mitochondrial cytopathy: long-term effects in MELAS. *Brain & Development*, 26(7), 453-458. doi:<https://dx.doi.org/10.1016/j.braindev.2003.12.009>
19. Namer, I. J., Wolff, V., Dietemann, J. L., & Marescaux, C. (2014). Multimodal imaging-monitored progression of stroke-like episodes in a case of MELAS syndrome. *Clinical Nuclear Medicine*, 39(3), e239-240. doi:<https://dx.doi.org/10.1097/RLU.0b013e318286bd6f>
20. Phase 2b Randomized, Double-blind, Placebo-controlled Crossover Study Evaluating the Efficacy and Safety of Zagociguat in Participants With MELAS (PRIZM). (2024). Retrieved from <https://clinicaltrials.gov/study/NCT06402123>. Available from National Library of Medicine (US) <https://clinicaltrials.gov/study/NCT06402123>
21. Shinkai, T., Nakashima, M., Ohmori, O., Terao, T., Nakamura, J., Hiramatsu, N., . . . Tsuji, S. (2000). Coenzyme Q10 improves psychiatric symptoms in adult-onset mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes: a case report. *Aust N Z J Psychiatry*, 34(6), 1034-1035. doi:10.1080/000486700286
22. Thomeer, E. C., Verhoeven, W. M., van de Vlasakker, C. J., & Klompenhouwer, J. L. (1998). Psychiatric symptoms in MELAS; a case report. *J Neurol Neurosurg Psychiatry*, 64(5), 692-693. doi:10.1136/jnnp.64.5.692

23. Tran, N. Q., Phan, C. C., Vuong, T. B., Tran, T. V., & Ma, P. T. (2023). Acute onset of diabetes and rapid cognitive decline in a patient with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome. *Endocrinology, Diabetes & Metabolism Case Reports*, 2, 01. doi:<https://dx.doi.org/10.1530/EDM-22-0416>
24. Yokota, Y., Hara, M., Akimoto, T., Mizoguchi, T., Goto, Y. I., Nishino, I., . . . Nakajima, H. (2020). Late-onset MELAS syndrome with mtDNA 14453G->A mutation masquerading as an acute encephalitis: a case report. *BMC Neurology*, 20(1), 247. doi:<https://dx.doi.org/10.1186/s12883-020-01818-w>

List literature search WG 4 (management of headache and epilepsy)

1. Maeda K, Tsuboi H, Hosoda N, Fukumoto J, Fujita S, Ichino N, Osakabe K, Sugimoto K, Furukawa G, Ishihara N. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) with high-frequency oscillations on scalp EEG: A case report. *Epilepsy Behav Rep*. 2025 Feb 13;29:100754. doi: 10.1016/j.ebr.2025.100754. PMID: 40041622; PMCID: PMC11879601.
2. Gao R, Gu L, Zuo W, Wang P. Comprehensive predictors of drug-resistant epilepsy in MELAS: clinical, EEG, imaging, and biochemical factors. *BMC Neurol*. 2025 Feb 14;25(1):64. doi: 10.1186/s12883-025-04046-2. PMID: 39953503; PMCID: PMC11827305.
3. Yang X, Sun A, Ji K, Wang X, Yang X, Zhao X. Clinical features of epileptic seizures in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes. *Seizure*. 2023 Mar;106:110-116. doi: 10.1016/j.seizure.2023.02.014. Epub 2023 Feb 18. PMID: 36827862.
4. Seed LM, Dean A, Krishnakumar D, Phyu P, Horvath R, Harijan PD. Molecular and neurological features of MELAS syndrome in paediatric patients: A case series and review of the literature. *Mol Genet Genomic Med*. 2022 Jul;10(7):e1955. doi: 10.1002/mgg3.1955. Epub 2022 Apr 26. PMID: 35474314; PMCID: PMC9266612.
5. Primiano G, Vollono C, Dono F, Servidei S. Drug-resistant epilepsy in MELAS: safety and potential efficacy of lacosamide. *Epilepsy Res*. 2018 Jan;139:135-136. doi: 10.1016/j.epilepsyres.2017.12.001. Epub 2017 Dec 6. PMID: 29223780.
6. Lee HN, Eom S, Kim SH, Kang HC, Lee JS, Kim HD, Lee YM. Epilepsy Characteristics and Clinical Outcome in Patients With Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS). *Pediatr Neurol*. 2016 Nov;64:59-65. doi: 10.1016/j.pediatrneurol.2016.08.016. Epub 2016 Aug 26. PMID: 27671241.
7. Whittaker RG, Devine HE, Gorman GS, Schaefer AM, Horvath R, Ng Y, Nesbitt V, Lax NZ, McFarland R, Cunningham MO, Taylor RW, Turnbull DM. Epilepsy in adults with mitochondrial disease: A cohort study. *Ann Neurol*. 2015 Dec;78(6):949-57. doi: 10.1002/ana.24525. Epub 2015 Nov 17. PMID: 26381753; PMCID: PMC4737309.
8. Demarest ST, Whitehead MT, Turnacioglu S, Pearl PL, Gropman AL. Phenotypic analysis of epilepsy in the mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes-associated mitochondrial DNA A3243G mutation. *J Child Neurol*. 2014 Sep;29(9):1249-56. doi: 10.1177/0883073814538511. Epub 2014 Jul 17. PMID: 25038129.
9. Kaufman KR, Zuber N, Rueda-Lara MA, Tobia A. MELAS with recurrent complex partial seizures, nonconvulsive status epilepticus, psychosis, and behavioral disturbances: case analysis with literature review. *Epilepsy Behav*. 2010 Aug;18(4):494-7. doi: 10.1016/j.yebeh.2010.05.020. Epub 2010 Jun 26. PMID: 20580320.
10. Corda D, Rosati G, Deiana GA, Sechi G. "Erratic" complex partial status epilepticus as a presenting feature of MELAS. *Epilepsy Behav*. 2006 May;8(3):655-8. doi: 10.1016/j.yebeh.2005.12.011. Epub 2006 Feb 10. PMID: 16473046.
11. Feddersen B, Bender A, Arnold S, Klopstock T, Noachtar S. Aggressive confusional state as a clinical manifestation of status epilepticus in MELAS. *Neurology*. 2003 Oct 28;61(8):1149-50. doi: 10.1212/01.wnl.0000092497.53706.1b. PMID: 14581687.

12. Canafoglia L, Franceschetti S, Antozzi C, Carrara F, Farina L, Granata T, Lamantea E, Savoiardo M, Uziel G, Villani F, Zeviani M, Avanzini G. Epileptic phenotypes associated with mitochondrial disorders. *Neurology*. 2001 May 22;56(10):1340-6. doi: 10.1212/wnl.56.10.1340. PMID: 11376185.
13. Fujimoto S, Mizuno K, Shibata H, Kanayama M, Kobayashi M, Sugiyama N, Ban K, Ishikawa T, Itoh T, Togari H, Wada Y. Serial electroencephalographic findings in patients with MELAS. *Pediatr Neurol*. 1999 Jan;20(1):43-8. doi: 10.1016/s0887-8994(98)00088-5. PMID: 10029259.
14. Mancuso M, Papadopoulou MT, Ng YS, Ardisson A, Bellusci M, Bertini E, Di Vito L, Evangelista T, Fons C, Hikmat O, Horvath R, Klopstock T, Kornblum C, Lamperti C, Licchetta L, Molnar MJ, Varhaug KN, O'Callaghan M, Pressler RM, Schiff M, Servidei S, Szabo N, Gorman GS, Cross JH, Rahman S. Management of seizures in patients with primary mitochondrial diseases: consensus statement from the InterERNs Mitochondrial Working Group. *Eur J Neurol*. 2024 Jul;31(7):e16275. doi: 10.1111/ene.16275. Epub 2024 Apr 4. PMID: 38576261; PMCID: PMC11235721.
15. Finsterer J, Wakil SM. Stroke-like episodes, peri-episodic seizures, and MELAS mutations. *Eur J Paediatr Neurol*. 2016 Nov;20(6):824-829. doi: 10.1016/j.ejpn.2016.08.002. Epub 2016 Aug 13. PMID: 27562097.
16. Rahman S. Mitochondrial disease and epilepsy. *Dev Med Child Neurol*. 2012 May;54(5):397-406. doi: 10.1111/j.1469-8749.2011.04214.x. Epub 2012 Jan 28. PMID: 22283595.
17. Steele HE, Chinnery PF. Mitochondrial Causes of Epilepsy: Evaluation, Diagnosis, and Treatment. *Semin Neurol*. 2015 Jun;35(3):300-9. doi: 10.1055/s-0035-1552624. Epub 2015 Jun 10. PMID: 26060910.
18. Iizuka T, Sakai F, Endo M, Suzuki N. Response to sumatriptan in headache of MELAS syndrome. *Neurology*. 2003 Aug 26;61(4):577-8. doi: 10.1212/01.wnl.0000078931.87815.b3. PMID: 12939448.
19. Terrin A, Bello L, Valentino ML, Caporali L, Sorarù G, Carelli V, Maggioni F, Zeviani M, Pegoraro E. The relevance of migraine in the clinical spectrum of mitochondrial disorders. *Sci Rep*. 2022 Mar 10;12(1):4222. doi: 10.1038/s41598-022-08206-z. PMID: 35273322; PMCID: PMC8913605.
20. Naegel S, Burow P, Holle D, Stoevesandt D, Heintz S, Thaele A, Zierz S, Kraya T. Erenumab for migraine prevention in a patient with mitochondrial encephalopathy, lactate acidosis, and stroke-like episodes syndrome: A case report. *Headache*. 2021 Apr;61(4):694-696. doi: 10.1111/head.14101. Epub 2021 Mar 29. PMID: 33779998.
21. Burow P, Meyer A, Naegel S, Watzke S, Zierz S, Kraya T. Headache and migraine in mitochondrial disease and its impact on life-results from a cross-sectional, questionnaire-based study. *Acta Neurol Belg*. 2021 Oct;121(5):1151-1156. doi: 10.1007/s13760-021-01630-4. Epub 2021 Mar 8. PMID: 33683636; PMCID: PMC8443488.
22. Tiehuis LH, Koene S, Saris CGJ, Janssen MCH. Mitochondrial migraine; a prevalence, impact and treatment efficacy cohort study. *Mitochondrion*. 2020 Jul;53:128-132. doi: 10.1016/j.mito.2020.05.004. Epub 2020 May 25. PMID: 32464279.
23. Kraya T, Deschauer M, Joshi PR, Zierz S, Gaul C. Prevalence of Headache in Patients With Mitochondrial Disease: A Cross-Sectional Study. *Headache*. 2018 Jan;58(1):45-52. doi: 10.1111/head.13219. Epub 2017 Nov 15. Erratum in: *Headache*. 2018 Feb;58(2):358. doi: 10.1111/head.13259. PMID: 29139113.
24. Cevoli S, Pallotti F, La Morgia C, Valentino ML, Pierangeli G, Cortelli P, Baruzzi A, Montagna P, Carelli V. High frequency of migraine-only patients negative for the 3243 A>G tRNA^{Leu} mtDNA mutation in two MELAS families. *Cephalalgia*. 2010 Aug;30(8):919-27. doi: 10.1177/0333102409354654. Epub 2010 Mar 12. PMID: 20656703.
25. Vollono C, Primiano G, Della Marca G, Losurdo A, Servidei S. Migraine in mitochondrial disorders: Prevalence and characteristics. *Cephalalgia*. 2018 May;38(6):1093-1106. doi: 10.1177/0333102417723568. Epub 2017 Aug 1. PMID: 28762753.
26. Primiano G, Rollo E, Romozzi M, Calabresi P, Servidei S, Vollono C. Preventive migraine treatment in mitochondrial diseases: a case report of erenumab efficacy and literature review. *Neurol Sci*. 2022 Dec;43(12):6955-6959. doi: 10.1007/s10072-022-06391-3. Epub 2022 Sep 13. Erratum in: *Neurol Sci*. 2023 Feb;44(2):789. doi: 10.1007/s10072-022-06462-5. PMID: 36097203.

27. Silvestro M, Orologio I, Trojsi F, Tessitore A, Tedeschi G, Russo A. Effectiveness and safety of CGRP monoclonal antibodies in migraine related to mitochondrial diseases in patients with NARP and PEO syndromes. *Clin Neurol Neurosurg*. 2023 Mar;226:107611. doi: 10.1016/j.clineuro.2023.107611. Epub 2023 Jan 27. PMID: 36753861.
28. Kaltseis K, Indelicato E, Broessner G, Boesch S. Case report: Monoclonal CGRP-antibody treatment in a migraine patient with a mutation in the mitochondrial single-strand binding protein (SSBP1). *Front Neurol*. 2022 Sep 15;13:958463. doi: 10.3389/fneur.2022.958463. PMID: 36203974; PMCID: PMC9531672.

Reference list – included articles WG 5 MELAS Consensus – Management of comorbidities

1. Endres, D., Süß, P., Maier, S. J., Friedel, E., Nickel, K., Ziegler, C., . . . Tebartz van Elst, L. (2019). New Variant of MELAS Syndrome With Executive Dysfunction, Heteroplasmic Point Mutation in the MT-ND4 Gene (m.12015T>C; p.Leu419Pro) and Comorbid Polyglandular Autoimmune Syndrome Type 2. *Front Immunol*, 10, 412. doi:10.3389/fimmu.2019.00412
2. Ito, H., Fukutake, S., Otake, S., Okeda, R., Tokunaga, O., & Kamei, T. (2020). A MELAS Patient Developing Fatal Acute Renal Failure with Lactic Acidosis and Rhabdomyolysis. *Intern Med*, 59(21), 2773-2776. doi:10.2169/internalmedicine.4922-20
3. Jian-Ren, L. (2005). Precipitation of stroke-like event by chickenpox in a child with MELAS syndrome. *Neurol India*, 53(3), 323-325. doi:10.4103/0028-3886.16932
4. Kawano, Y., Taniguchi, A., Narita, Y., Kagawa, K., Harada, T., & Shindo, A. (2024). Effective Management of Chronic Intestinal Pseudo-Obstruction in MELAS Using Acotiamide: A Case Report. *Case Reports in Neurology*, 16(1), 288-293. doi:<https://dx.doi.org/10.1159/000541012>
5. Ng, Y. S., Feeney, C., Schaefer, A. M., Holmes, C. E., Hynd, P., Alston, C. L., . . . Gorman, G. S. (2016). Pseudo-obstruction, stroke, and mitochondrial dysfunction: A lethal combination. *Annals of Neurology*, 80(5), 686-692. doi:<https://dx.doi.org/10.1002/ana.24736>
6. Ni Cathain, D., Browne, E., Skehan, K., & Boyle, K. (2021). MELAS syndrome: an acute stroke-like episode complicated by renal tubular acidosis. *BMJ Case Rep*, 14(11). doi:10.1136/bcr-2021-245898
7. Noguchi, A., Shoji, Y., Matsumori, M., Komatsu, K., & Takada, G. (2005). Stroke-like episode involving a cerebral artery in a patient with MELAS. *Pediatr Neurol*, 33(1), 70-71. doi:10.1016/j.pediatrneurol.2005.01.013
8. Pérez-Cruz, E., González-Rivera, C., & Valencia-Olvera, L. (2022). Immunonutrition for the acute treatment of MELAS syndrome. *Endocrinol Diabetes Nutr (Engl Ed)*, 69(2), 144-148. doi:10.1016/j.endien.2022.02.006
9. Ramesh, R., Hariharan, S., & Sundar, L. (2023). Stroke-Like Episodes and Epilepsy in a Patient with COQ8A-Related Coenzyme Q10 Deficiency. *Ann Indian Acad Neurol*, 26(6), 980-982. doi:10.4103/aian.aian_511_23
10. Sen, K., Harrar, D., Hahn, A., Wells, E. M., & Gropman, A. L. (2021). Management considerations for stroke-like episodes in MELAS with concurrent COVID-19 infection. *J Neurol*, 268(11), 3988-3991. doi:10.1007/s00415-021-10538-1
11. Shimizu, J., Tabata, T., Tsujita, Y., Yamane, T., Yamamoto, Y., Tsukamoto, T., . . . Eguchi, Y. (2020). Propofol infusion syndrome complicated with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes: a case report. *Acute Med Surg*, 7(1), e473. doi:10.1002/ams2.473
12. Snyder, M. T., Manor, J., Gijavanekar, C., Mizerik, E., Kralik, S. F., Elsea, S. H., . . . Scaglia, F. (2024). Heteroplasmic pathogenic m.12315G>A variant in MT-TL2 presenting with MELAS syndrome and depletion of nitric oxide donors. *American Journal of Medical Genetics. Part A*, 194(3), e63461. doi:10.1002/ajmg.a.63461
13. Taieb, G., Juntas-Morales, R., & Renard, D. (2017). Progression of stroke-like lesions along the cortico-ponto-cerebellar tract. *Acta Neurologica Belgica*, 117(1), 309-310. doi:10.1007/s13760-016-0671-9

14. Tawankanjanachot, I., Channarong, N. S., & Phanthumchinda, K. (2005). Auditory symptoms: a critical clue for diagnosis of MELAS. *J Med Assoc Thai*, 88(11), 1715-1720.
15. Zhao, Y., Yu, X., Ji, K., Lin, Y., Xu, X., Wang, W., & Yan, C. (2022). Reversible cerebral artery constriction accompanied with stroke-like episode in MELAS: A case series. *J Neurol Sci*, 441, 120345. doi:10.1016/j.jns.2022.120345