# eTable 3. Summary characteristics of included case reports and cohort study (N=34)

| **Study ID** | **N** | **Genetic diagnosis** | **Sex;** **Age** | **Clinical presentation**  | **Acute route**  | **Prophylaxis Y/N** | **AEDs** | **Additional treatments** | **AEs** | **Response to L-arginine treatment**  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case reports** |
| Corr et al. 20141 | 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 20182 | 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, CoQ10 | NR | ‘dramatically improved’ after 1-w. Muscle strength recovered, and there were no residual psychotic symptoms or aphasia on discharge. |
| Fryer et al. 20163 | 1 | m.3243A>G (72% hetroplasmy) | F; 8 | At 8-y, acute onset of binocular blindness with hemiparesis. V spontaneously improved over 4-d  | - | YesDose: NR | NR | *Chronic:* riboflavin, CoQ10 | 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. |
| 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, aDose: NR(with 10%dextrose-containing fluids) for 24-h | YesDose: NR | aspirin (3-w before presenting), discontinued at discharge*Acute:* dexamethasone;*Chronic:* steroid taper | Her condition improved. |
| Gagliardi et al. 20194 | 1  | m.3243A>G(13.1% hetroplasmy) | M; 50 *(dec)* | Persistence of confusion and L arm clumsiness and stiffness. *EEG, MRI, MRS* | 1; IVDose: NR | YesDose: NR | *Acute:* carbamazepine, lacosamide, phenytoin, clobazam added tolevetiracetam;*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. |
| González et al. 20205 | 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 | CoQ10 | 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. 20206 | 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; Oral0.5 g/kg/d | Yes0.5 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. 20187 | 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 | Yes0.32 g/kg/d | lacosamide, levetiracetam | *Acute:* methylprednisolone, CoQ10, 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. |
| Ito et al. 20208 | 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; IV30 g/d | Yes12 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. 20169 | 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: IV0.5 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: IV0.5 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.) |
| Kubota et al. 200410 | 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; IV0.5 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. |
| Lekoubou et al. 201111 | 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; Oral0.375 g/kg/d | Yes0.375 g/kg/dfor 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. |
| Minobe et al. 201512 | 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; NRDose: 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. 201313 | 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; NRDose: NR | No | NR | vitamin B1, 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; NR12 g/d | No | levetiracetam | acyclovir, methylprednisolone, plasma exchange, taurine, vitamin B1, 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. |
| Randhawa et al. 201615 | 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; OralDose: NR | YesDose: 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 202016 | 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; NRDose: 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; NRDose: NR | No | iacosamide  | NR | NR | NR |
| Sakai et al. 201817 | 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; IV16 g/d for 3-d (on d-3 of hospital admission) | YesDose: 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). |
| Shigemi et al. 201118 | 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 ond-1 of symptom onset (5 x over 9-d) | Yes0.2 g/kg/d bid ~d-4 of symptom onset↑ dose to 0.4 g/kg/d bid | *Acute:* diazepam | *Acute:* mannitol; *Chronic*: vitamin B1, vitamin B2, CoQ10, 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. 202019 | 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; NRDose: NR | No | levetiracetam, perampanel, lacosamide, clobazam, propofol, midazolam | CoQ10, 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. |
| Siddiq, Widjaja & Tein 201520  | 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) | YesTapered over 6-w to 1 g bid | NR | NR | *Acute* Oral: emesis  | Oral- within 24-h, rapid neurologic improvementIV- 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; IV0.5 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. |
| Sunde et al. 201621 | 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; IVDose: NR | Yes5 g bid | *Acute:* phenytoin, levetiracetam, lamotrigine;*Chronic:* phenytoin, lamotrigine, levetiracetam, clonazapan | *Acute:* IV glucose; *Chronic:* CoQ10, vitamin B12 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. 202022 | 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; Oral6 g/8-h | Yes6 g/8-h(6-w) | *Acute:* phenytoin, levetiracetam, clonazepam; *Chronic:* clonazepam, levetiracetam lacosamide | *Acute:* ubiquinol, idebenone, vitamin complexes (thiamine [B1], riboflavin [B2] 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. |
| Ueki et al. 202023 | 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; NRDose: 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. 202024 | 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;IVDose: NR | No | NR | CoQ10 | NR | NR |
| Wei, Cui & Pen 201925 | 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; IV0.5 g/kg/d for 5-d  | Yes0.2 g/kg/d (~9-y) | levetiracetam  | CoQ10, 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. |
| Yoneda et al. 201226 | 1 | m.3243A>G | M; 13 | Recurrent SLEs consisting of migraine H, vomiting andV 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; IV0.5 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 201827 | 1#1 | ND4/ND6 | NR; 6 | Unilateral ophthalmoparesis\* | 1; IV0.5 g/kg for 1-d  | Yes0.237 g/kg/d (~8-y) | NR | CoQ10, vitamin E, vitamin C, creatine, riboflavin, carnitine, folinic acid MVI | None | Yes- responded |
| 1#2 | ND5 | NR; 4 | R- upper extremity hemiplegia | 1; IV0.5 g/kg for 1-d | Yes0.15 g/kg/d (~7.5-y);citrulline Dose: NR (4.5-y) | NR | CoQ10, 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 | Yes0.3 g/kg/d (~5.5-y);citrulline Dose: NR (2-y) | NR | CoQ10, vitamin C, alpha lipoic acid, creatine, thiamine, riboflavin, folinic acid, B50, MVI, carnitine, vitamin E, biotin | 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 |
| R hemiplegia, partial S on the R | 1;IV 0.5 g/kg for 7-d | Yes, not specified | 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; IV0.25 g/kg for 1-d; 0.25 g/kg for 24-h | Yescitrulline 10g/m^2/d(~4-y) | NR | CoQ10, alpha lipoic acid, creatine, carnitine | Yes- responded |
| At 21-y. Dysarthria and dysphagia, new R hemianopsia | 1;IV0.25 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;IV0.25  | 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;IV0.47 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;IV0.485 g/kg for 1-d | No | NR | Partial- S stopped |
| At 19-y Dizziness, L-side W, fatigue | 1;IV0.436 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;IV0.5 g/kg bolus for 3-d | No | NR | CoQ10, 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;IV0.5 g/kg bolus for 1-d | Yes0.292 g/kg/d(~2-y, 5-mo.) | NR | CoQ10, vitamin C, alpha lipoic acid, biotin, folinic acid, B50, MVI, riboflavin, carnitine, niacin, niacinamide | No- did not respond |
| Worsening Cheyne-Stokes respirations \* | 1;IV0.5 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;IV0.5 g/kg bolus for 1-d | No | NR | CoQ10, vitamin C, carnitine, riboflavin | Partial: strength normalised; persistent L hyporeflexia. |
| 1#8 | mtDNA deletion | NR; 12 | Ataxia, dysmetria, worsened ophthalmoplegia, atonic episodes\* | 1;IV0.5 g/kg bolus for 5-d | No | NR | No | Atonia resolved |
| 1#9 | *SURF 1* | F; 3 *(dec)* | Cheyne-Stokes- presented with an abnormal respiratory pattern \* | 1;IV0.5 g/kg for 1-d (1-d after presenting) | Yes0.13 g/kg/d(~2-y, 4-mo.) | NR | CoQ10, vitamin E, alpha lipoic acid, B50, folinic acid, riboflavin | No- did not respond. Passed due to acute respiratory failure. |
| **Prophylaxis (only)**  |
| Calvaruso et al. 201128 | 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 | Yes1 g/d from 20-y | NR | NR | NR | NR |
| Cosentino et al. 201929 | 1 | m.3243A>G | F; 42 | History of migraine 8-mo. previously. Spatio-temporal disorientation and confusion. *MRI, B* | NA | Yes1.66 g bid | NR | *Acute:* glucocorticoids; *Chronic:* CoQ10, riboflavinOther: metformin, lispro insulin, linagliptin, enalapril | NR | NR |
| Fukuda & Nagao 201930 | 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 | Yes12 g/d, from d-253 of presenting with SLE | NR | *Chronic*: L-carnitine, CoQ10,fursultiamine, ascorbic acidOther: 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 201531 | 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 | Yes60 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. |
| Selim & Mehaney 201332 | 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 Vdisturbance, mostly R-HH. Mild R-hemiparesis.*MRI, MRA, B* | NA | Yes0.5 g bid | NR | NR | NR | NR |
| Sun et al. 201833 | 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 | YesDose: NR. (nearly 1-y) | valproic acid sodium | aspirin, a statin, CoQ10, 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. 201734 | 1#1 | m.3243A>G | F; 23*(dec)* | 1st SLE at 10-y (H, vomiting, blurred V).*MRI B* | NA | Yes | NR | l-carnitine, CoQ10 | 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); CoQ10, Coenzyme Q10; 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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