

# A multi-faceted lifestyle intervention for m.8344A>G associated multiple symmetric lipomatosis (MSL): Report of a successful patient initiated novel therapy

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## Abstract

An adult female patient carrying the mitochondrial DNA m.8344A>G mutation (86% heteroplasmy in urine) had multiple symmetric lipomatosis (MSL) as the primary disease manifestation, as did two of her siblings. Relatedly, her daughter developed severe cardiomyocyte lipid deposition culminating in fatal infantile histiocytoid cardiomyopathy. Other family members had typical neurologic manifestations of the mitochondrial disease syndrome (myoclonic epilepsy with ragged red fibres) without MSL.

The patient required major lipoma reduction surgery after a rapid rate of lipoma progression starting in the 6th decade of life. Following a difficult recovery from the surgical procedure, the patient independently researched an alternative therapy for her disease. The lifestyle intervention was multi-faceted (dietary, physical activity, meditation) and progressive over the course of two years. It was informed by her personal review of the medical literature in addition to consultation with multiple individuals including family members, professors, social media user groups, and her metabolic disease clinic health care professionals.

A carbohydrate reduced (5 – 10% of calories) modified ketogenic diet was a major part of the treatment regimen owing to its incidental success in MSL management when her brother started similar dietary therapy for management of glioblastoma multiforme. Intermittent fasting was also implemented and progressed over two years. Exercise regimens and return to work protocols were further incorporated. The outcome of her multi-faceted intervention was extremely positive in all of the targeted outcomes: weight loss (82 → 58 kg), lipoma size stabilization and then reduction by 50% in transverse diameter as measured by serial MRI, improvement in physical activity and strength, improvement in laboratory markers of insulin resistance (fasting glucose 107 mg/dL to 93 mg/dL), and improved subjective sense of well being accompanied by a return to full time work. Two years into the progression of her self-designed therapy, she continues with her dramatic improvements in subjective and objective measures of health.

In summary, a potential non-surgical therapy for mitochondrial disease associated MSL appears feasible over the short term. The success of the lifestyle intervention in MSL therapy is unprecedented and, importantly, fully patient initiated. The success of this novel therapy provides potential insight into the mechanism of MSL exacerbation: suggesting insulin resistance or other lifestyle modifiable factors as mediators of disease progression.

## Patient photos

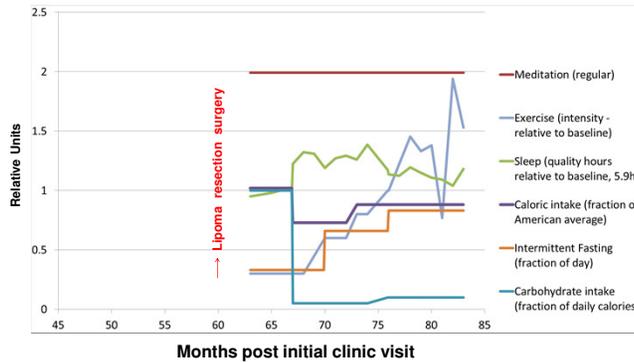


67 months (initiation of lifestyle intervention)

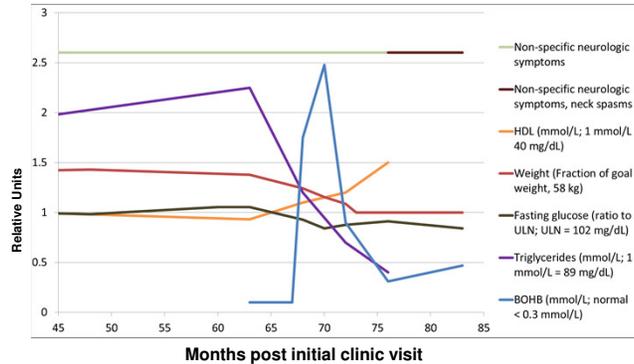
75 months (8 months post lifestyle intervention)

91 months (24 months post lifestyle intervention)

## Interventions (patient initiated)



## Outcomes (Significant changes)

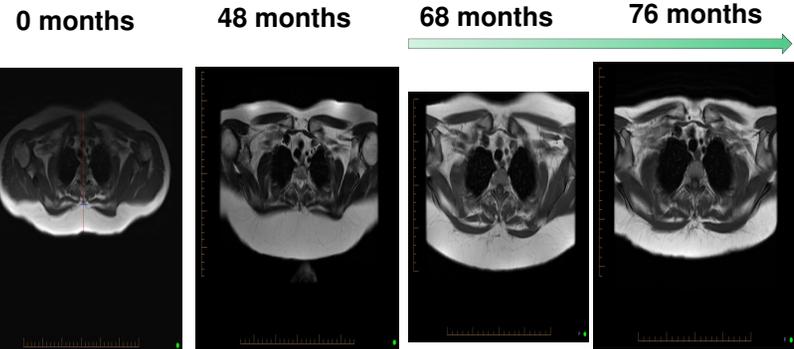


## MRI measurements of dorsal cervical lipoma

Year	Months followed in clinic	Transverse diameter of lipoma*	Transverse diameter of thorax*	Relative lipoma size (ratio of transverse diameter of lipoma / trans thoracic, %)*
2011	0	1.0	9.6	11%
2015	48	2.3	12.5	18%
2016	60	- Surgery (remote from lipoma measurement site)		
2016	67	- Initiation of lifestyle intervention		
2017	68	3.9	12.1	32%
2017	72	3.6	12.1	30%
2017	76	2.5	11.9	21%
2018	83	1.9	13.9	13%

\*See MRI image figure legend for a description of the MRI measurements

## Representative MRI images of dorsal mid-cervical lipoma



The representative axial MRI images over time since first clinic visit are taken at the same anatomic landmarks. Measurements of the transverse diameter of the thorax were taken as shown on the "0 months" image; the red line indicates the transverse diameter of the thorax, while the blue line indicates the demarcation of the anterior most aspect of the lipoma for measurement purposes. The green arrow indicates the onset of the multiple lifestyle interventions.

**Patient self-directed therapy** for severe MSL predicted to require serial surgical interventions: After discussion with the clinic staff, and completion of her own investigation, this patient opted to pursue the following minimally invasive interventions to control her MSL:

- Reduce her caloric intake for 6 months to achieve a goal weight of 58 kg (BMI 21.8) as compared to baseline of 82 kg (BMI 30.9) for her height of 1.63 m. Total caloric intake for 1<sup>st</sup> 6 months (1400 kcal/day), 2<sup>nd</sup> 6 months (1690 kcal/day).
- Reduce her carbohydrate intake as a percentage of daily calories indefinitely (< 10% of total caloric intake), while increasing fat (70%) and protein (20%). Concurrently administer nutrient supplements to meet her daily allowance of vitamins and minerals, and use of home made yoghurt to optimize bowel microbiome.
- Time restrict her caloric intake to an 8 hour period within each day for the first three months and to within a 4 hour period for the next 9 months. After that, she planned to further restrict the time of caloric intake to one meal per day.
- Increase her physical activity: physical therapy guided stretching and aerobics for two 30 min periods daily. By month four she progressed to daily aerobic and yoga sessions in addition to the physiotherapy prescribed exercises. By month 9, she was vigorously increasing her strengthening program with guidance from a personal trainer.
- Participate in regular scheduled meditation
- Monitor her daily nutrition (MyFitnessPal™), sleep schedule (Sleep Cycle™), physical activity, and weight regularly.
- Collaborate with the clinic in monitoring via regular clinical exams, serum electrolytes and routine chemistry testing, nutritional blood test monitoring. Serial MRI scans were ordered to assess efficacy of lipoma growth reduction.

**Outcomes:** As shown, there were marked improvements in overall health and lipoma size that reversed trends present over the previous 6 years.

There were new neurologic symptoms including a new onset head spasm that is stable and non-progressive. Subjectively, the patient had remarkable benefits that facilitated a full return to the workforce post-surgery and marked increase in daily activity.

**Interpretation:** The multi-faceted intervention was effective in achieving the patients goals over the 1.5 years of the study. The patient continues the intervention in all regards with continued reduction in lipoma size at 2 years.

The unknown mechanism behind the development of MSL in select MERRF pedigrees was not explored in this study. However, the co-incidence of histiocytoid cardiomyopathy and MSL in this MERRF pedigree raises the question of the existence of a genetically inherited predisposition (beyond the mitochondrial m.8344A>G mutation), to both of these rare MERRF manifestations of excess lipid storage.

The mechanism behind the late onset deterioration of pre-existing MSL in MERRF patients is also unknown. The timing in this patient, and in her two siblings, coincides with the onset of insulin resistance. This patient's self-initiated therapy includes interventions known to improve insulin sensitivity: increased exercise and weight reduction. Intermittent fasting and a reduced carbohydrate diet may also contribute to improved insulin sensitivity by controlling satiety or by other mechanisms. Markers of insulin resistance including the fasting glucose measurements improved in this specific patient after initiation of these multiple interventions. Thus, there is a strong possibility that insulin resistance modulates lipoma growth in MERRF associated MSL as interventions to reduce insulin resistance, reversed a steady trend towards worsening MSL. This hypothesis is further supported by her brother's anecdotal description of MSL improvement with a carbohydrate reduced diet, that initially inspired her to initiate her own therapeutic intervention. Previously, MSL has been treated exclusively with surgery when severe enough to require therapy.

While the interventions have improved insulin resistance, it is not definite that this is the specific mechanism for improvement in this patient's MSL. Ketogenesis may also be contributory; however, the degree of ketosis in this patient is not clearly associated with the improvement in her MSL.

In addition, the lifestyle induced improvement in the MSL phenotype was associated with some undesirable outcomes: alopecia (transient), recurrent benign positional vertigo, constipation, and a new onset movement disorder characterized by head tremor vs neck muscle spasm. Detailed neurologic assessments and brain MRI scans have not confirmed that she has a new neurologic phenotype but this possibility remains.

**In conclusion,** this case report identifies a unique means to improve the MSL phenotype. However, much remains to be studied to determine regarding the multi-faceted intervention in this context: a) the sustainability of the effect of the interventions (assuming the patient can sustain the interventions), b) the subcomponent(s) of the multi-faceted intervention which are of greatest impact, c) the mechanism for improvement of the phenotype, and d) the safety of the intervention in the near and long term, when implemented in the setting of impaired mitochondrial metabolism.