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Case Report

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NMN Cocktail Results in Marked CADISIL Clinical Improvement along with Favorable Changes in Epigenetic Age and Inflammatory Biomarkers

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Abstract

Classic CADISIL is a rare (~1/100,000) but fatal neurologic disorder with no known treatment. Phenotypically milder cases occur more commonly (~1/1000 persons). Mitochondrial dysfunction has been documented in multiple neurodegenerative diseases including CADASIL Perhaps in part due to impaired crosstalk between mitochondrial and nuclear electron chain transfer subunit manufacture - which has been shown to respond to supraphysiologic doses of NMN. Here, an individual with "classic" CADISIL was administered a NMN cocktail with prompt amelioration of neurologic symptoms on three separate occasions. A reduction of inflammation was documented over the first treatment period. Her elevated baseline (higher than chronologic ages) DNAm GrimAges suggesting elevated mortality-morbidity risk were markedly reduced after each observed course of treatment. Her neurologic symptoms deteriorated promptly each time treatment was withdrawal. This NMN cocktail shows promise and should be studied prospectively in CADISIL patients to see if these findings are reproducible.

Keywords/Abbreviations

CADASIL NMN cocktail, DNAm GRIMAge, mitochondrial dysfunction, NOTCH3 gene, epidermal growth factor receptor (EGFr) exon 5.

Case Report

A 37-year-old hairdresser presented complaining of chronic headaches and RUE numbness with a recent inability to work, walk downstairs or drive her car due to bowel incontinence, gait imbalance (requiring cane) and RUE weakness (dropping scissors while cutting hair).

She had recently been diagnosed with multiple sclerosis based on an MRI with bilateral subcortical and periventricular confluent white matter hyper intense foci with lessor basal ganglia, thalami, pons, cerebellum, and temporal subcortical white matter hyperintensities.

She was on multiple medications for head pain, nausea, muscle spasms, loss of energy and depression (gabapentin 300 mg QID, Tylenol codeine 300/30 QID, Celebrex 200 mg QD, baclofen 10 mg TID, Emgality pen 120 mg sq q month, promethazine 50 mg supp qhs, Zofran 8 mg q8hrs, Adderall xr 20 mg and dilaudid 4 mg q4hrs prn). The patient reported cigarette and moderate daily alcohol use.

Two months later, her NOTCH3 gene test returned positive (cysteine mutation at the epidermal growth factor receptor (EGFr) exon 5). A diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) was made. Her father had a disabling psychiatric condition in his fifties and died at age 70.

CADASIL is a neuro-degenerative disorder caused by mutations in the *NOTCH3* gene that present in the second or third decade with headaches, mood and cognitive disorders. Ongoing destruction of vascular smooth muscle cells (VSMC) leads to progressive brain arteriole wall thickening, fibrosis, luminal narrowing, and lacunar infarcts - often in the basal ganglia and frontal-temporal white matter associated with focal neurological deficits, subcortical vascular type dementia and early death.

CADASIL may be diagnosed before the onset of neurologic abnormalities based on:

1. Characteristic MRI features (T_2-weighted hyperintense periventricular and deep white matter lesions)
2. Pathognomonic granular osmiophilic material in arterial walls, including skin arteries (VSMC damage is generalized).
3. Pathognomonic *NOTCH3* cysteine mutations.

280 distinct mutations within the 34 EGFr domains of the *NOTCH3* gene have been associated with the classic CADASIL phenotype (~1/100,000 prevalence). However, heterogeneity within the CADASIL phenotype is now increasingly recognized. Analysis of large international exome databases shows the frequency of cysteine altering *NOTCH3* mutations in all EGFr domains are ~1/1000 - *100-fold higher* than expected based on the prevalence of classic CADASIL. Individuals with mutations in EGFr domains 1 to 6 are predisposed to "classic" CADASIL [1] while persons with the 100-fold more common mutations in domains 7 to 34 display milder symptoms later in life with low burdens of brain white matter hyperintensities that for the most part are never attributed to CADASIL [2,3,4].

There is currently no treatment for CADASIL.
Mitochondrial dysfunction has been documented in multiple neurodegenerative diseases [5] including CADASIL [6] where VSMC mitochondria, though increased in number, have suboptimal mitochondrial membrane potentials [7].

Mitochondrial function is largely dependent on the normal expression of mitochondrial proteins, which are encoded by both mitochondrial and nuclear DNA [8]. Premature aging and age associated neurodegenerative disease have impaired crosstalk between mitochondrial and nuclear electron chain transfer subunit manufacture which has been shown to respond to supraphysiologic doses of NMN [9].

The patient began a liquid NMN cocktail (NMN, Na+, betaine and food grade H2O2) taken fasting morning and early evening after full informed consent from patient and her half-sister (by a different father). She improved within days, including the ability to walk without a cane, walk downstairs on her own and drive her car again. She felt clearer mentally, became more self-sufficient and was able to perform more routine daily tasks including cutting hair on a limited basis. She noted no untoward side effects.

The patients initial mDNA GRIM age was 44.5 (7.1 years older than her chronologic age). CRP and IL-6 at 1-, 2- and 3-months follow-up respectively showed decreases from 5.69 initially to 0.57, 0.67 and 0.47 mg/dL and 3.8 initially to 3.3, na, and 2.4 pg/mL.
Unfortunately, she suffered multiple personal life setbacks, became homeless, and was then lost to follow-up. She presented 6 months later with persistent home and family life instability and worsened neurologic and psychiatric status. She was unable to commit to a regular daily schedule of treatments and regular evaluations.

18 months after the initial three-month course of the NMN cocktail, the patient's personal life stabilized and she abstained from cigarettes and alcohol. Some medications (i.e., muscle relaxants/anti-spasmodics and ketamine treatment) were discontinued. She and her new fiancé agreed to monitor her mood, anxiety, concentration, driving and exercise ability, pain, appetite. After a 2-week baseline observation period she was re prescribed a double dose of the NMN cocktail. Based on the contemporaneously completed daily symptom charts, she markedly improved in all measures within two weeks.

After 2 months on the double dose NMN cocktail, the cocktail was discontinued with the consent of the patient to test if her improvements were "real" vs placebo effect and test the duration of the effects. She deteriorated in all measures within days.
In the patient's words:

Mood: *While taking the cocktail, I'm more motivated, cheerful, happy, energetic, cognitively aware, less quick to become agitated…*
Off, I'm hot tempered, slower in speech, mobility and thought process … way more emotional and quicker to snap!!!
Anxiety: *ON, I am much more relaxed. … OFF for the last two weeks, I had worst anxiety. Bad withdrawals from getting off? I felt as I used to before the 3 months of cocktail, pretty miserable in all ways!*
Concentration: *On daily cocktail, my brain fog is substantially lifted, as though the heavens opens … I can listen better, stay aware, present, and in the moment. Off the cocktail, the struggle can be so crippling, fighting to make sense of the simplest thoughts or memory!*
Driving: *… definitely able to drive on cocktail … not now that I've been off cocktail for two weeks … increased vertigo, disabling drop in depth perception and decreased clarity of mind.*
Exercise: *My ability to exercise is greatly improved while taking cocktail … endurance longer … able to take two Pilates classes in a day. When off - I'm barely able to take 1-2 classes per week, literally a 10 down to a 1.*
Pain: *On cocktail my pain more manageable. The brain neuropathy was better. Off, I have to rely more on pain meds and spend way more time in bed.*
Appetite: *ON my appetite was strong, I gained 20 lbs. OFF, I've experienced more nausea, out of bed and randomly while working out. Vertigo is also a major struggle. My bladder and poop issues (incontinence) are also back*
Medication adjustments: *Able to get off Adderall on cocktail … OFF I have stayed off Adderall except for a few days. But it has definitely been a struggle - slim to no energy. I'm drinking more coffee which doesn't sit well with my system…*

After 1 month off the NMN cocktail, the cocktail was restarted at the same "single" dose that appeared to be effective during her initial 3-month treatment. She improved neurologically but she was not able to function to the level of the prior two-month trial. Her dose was increased to a double dose and over the next several weeks her neurologic status returned to the best it had been during the second two-month treatment period.

Figure 1 if desired: **Serial representative MRI cuts: 5/28/19, 10/19/2019, 7/08/20, 3/22/2022, 8/24/22 - stable signal abnormalities.**

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Patient 33

DATE	Age Chronologic	Mos on Cockta	DNAmGrimAge BasedRealAge AGE	DELTA	Epigenetic Ag (Zhang) AGE	DELTA	DNAmAge Hannum AGE	DELTA	DNAm PhenoAge AGE	DELTA	DNAm AgeSkinBlooc AGE	DELTA	DNAm Age AGE	DELTA	DNAm PACK YRS	CRP HS	IL-6	HEAD MRI	Clinical course
																		5/28/19	
																		10/19/19	
6/25/20	37.4	0	44.5	7.1	56.1	18.7	24.5	-12.9	28.7	-8.7	32.6	-4.8	28.9	-8.5	23.2	5.7	3.8		
6/25/20	START NMN COCKTAIL																		
																		7/8/20	improvement
7/21/20	37.4	1														0.6	3.3		(single dose)
8/13/20	37.5	2														0.7	na		
9/17/20	37.6	3														0.5	2.4		
9/18/20	STOP NMN COCKTAIL																		
4/7/21	38.1	0	46.8	8.7	57.3	19.2	28.4	-9.7	28.5	-9.6	38.3	0.2	38.9	0.8	17.6				
																		3/22/22	
3/26/22	39.1	0	48.2	9.1	58.7	19.6	34.4	-4.7	57.0	17.9	34.6	-4.5	36.2	-2.9	39.7				
4/8/22	START NMN COCKTAIL																		
5/5/22	39.2	1	43.2	4.0	57.7	18.5	33.1	-6.1	41.7	2.4	32.0	-7.2	40.6	1.4	31.1				improvement
6/22/22	STOP NMN C																		(double dose)
																			Prompt deteriorati
7/26/22	START NMN COCKT																		
7/26/22	39.4	0	45.0	5.5					31.3	-8.1	34.8	-4.7	41.2	1.8	17.1				mild improvement
																		8/24/22	(single dose)
10/14/22	39.7	3	45.1	5.4					29.7	-10.0	33.6	-6.0	41.6	2.0	13.0				marked improveme
12/20/22	39.8	5	41.0	1.2					26.9	-13.0	38.2	-1.7	44.5	4.7	6.3				(double dose)
2/28/23	40.0	7	39.2	-0.8					23.7	-16.4	37.6	-2.4	44.4	4.3	5.1				

Age acceleration																			
First 1.7 yrs		3.7		2.6		9.9		28.3		2.0		7.3		16.5	('pack yr acceleration')				
(6/25/20 to 3/26/22)		Baseline 6/25/20																	
2nd course EGA®		-5.0		-1.0		-1.3		-15.4		-2.6		4.4		-8.6					
4/8/22 to 5/5/22		Baseline 3/26/22																	
3rd course EGA®		-9.0						-33.4		3.1		8.2		-34.6					
7/26/22 to 2/28/23		Baseline 3/26/22																	

TABLE 1: Effect of NMN Cocktail on Inflammation Markers and Epigenetic Age.

Discussion

DNAm GrimAge (units of years) is a composite biomarker based on seven DNAm surrogates and a DNAm-based estimator of smoking pack-years is a strong predictor of time-to-death (10). DNAm GRIM Age shows the expected relationship with lifestyle factors including healthy diet and educational attainment.

A DNAm GrimAge higher than chronologic age is grim news suggesting an elevated mortality-morbidity risk. This patient's initial GRIM age was accelerated by 7.1 years (37.4 to 44.5) (TABLE 1) consistent with her stressful life, use of cigarettes, lack of fitness, binge alcohol use, elevated baseline inflammation and her MRI abnormalities. Over the initial 1.7 years of observation (she received 3 months of the NMN cocktail at the beginning of this period), her GRIM age further accelerated 3.7 years – 2 years more than expected for normal aging.

One month into her second course of the NMN cocktail, again simultaneous to clinical improvements, the patients DNAm GrimAge dropped by 5.1 years. At 0, 3, 5 and 7 months into her third course of treatment, yet again with simultaneous clinical improvements, her DNAm GrimAge dropped 6.6, 7.6, 9 and 11.4 years respectively. On two separate occasions, within the first several weeks following discontinuation of the NMN cocktail, the patient noted her baseline neurologic complaints had returned.

Summary

Classic CADISIL is a rare (~1/100,000) but fatal neurologic disorder with no known treatment. Phenotypically milder cases occur more commonly (~1/1000 persons). Here, an individual with "classic" CADISIL was administered a NMN cocktail with prompt amelioration of neurologic symptoms on three separate occasions. A reduction of inflammation was documented over the first treatment period. Her elevated baseline (higher than chronologic ages) DNAm GRIMAges suggesting elevated mortality-morbidity risk were markedly reduced after each observed course of treatment. Her neurologic symptoms deteriorated promptly each time treatment was withdrawal.

This NMN cocktail shows promise and should be studied prospectively in CADISIL patients to see if these findings are reproducible.

Note: Funding: None to declare

Declaration of Interest: None to declare, my brother (Joel Huizenga) holds the 2015 patent "RESETTING BIOLOGICAL PATHWAYS FOR DEFENDING AGAINST AND REPAIRING DETERIORATION FROM HUMAN AGING

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