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Oral Iron Therapy for Iron Deficiency Anemia Harmful and Cold-Water Emersion Helpful for Episodic Pain in A Patient with NaV1.7 Sodium Channel Gene *SCN9A* Hyperactive A1632E Mutation

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ABSTRACT

The first patient described with both paroxysmal episodic pain disorder and erythromelalgia secondary to a unique A1632E mutation of the *SCN9A* gene demonstrated early breath-holding spells and bradycardia requiring a pacemaker. Frequent episodes of pain were helped by routine oxcarbazepine-carbamazepine therapy from an early age. Additional relief was found when she was older and could jump into the family swimming pool or take a quick cold shower to lower pain intensity. Puberty was delayed. After it started, she became moderately anemic after excess menstrual blood loss over 2 years. Episodes of intermittent pain became more severe, particularly during menstrual periods. Frequent lower leg muscle pains developed as her anemia worsened. Oral iron therapy for iron deficiency anemia led to more intense muscle pains, particularly in her legs, and intense abdominal pain. The adverse reaction was attributed to ingested iron, with positive iron Fe^{+3} group binding to her *de novo* appearing mutant glutamic acid A1632E with negative carboxyl CO_3^- that was not a part of the normal *SCN9A* gene sequence. A unit of packed red cells, followed by another 3 months later, a vegetable based iron preparation, and an iron patch successfully treated her anemia and her symptoms improved

Introduction:

Mutations in the Nav1.7 sodium channel gene *SCN9A* have been known for more than 30 years, first with congenital absence of pain,[1] and later in some patients with a painful neuropathy.[2] Also, mutations in the *SCN9A* gene produce hyperactive pain disorders termed inherited erythromelalgia (IEM) with episodic reddening and painful extremities that was "characterized by intermittent burning pain and skin redness in the feet or hands, triggered by warmth or mild exercise,"[3] and paroxysmal extreme pain disorder (PEPD) [4,5] with episodic attacks of "rectal, ocular and mandibular pain accompanied with skin flushing, triggered by bowel movement and perianal stimulation."[6] Subsequent patients with the same mutation and symptoms and multiple genetic lesions lead to one or the other disorder[7,8] and sub-variants, resistant to one drug [9] or a unique unilateral reflex dystrophy [10] have been described. Mutations in the *SCN9A* gene are usually new in a family, and inherited as an autosomal dominant disorder. Our patient had symptoms of both IEM and PEPD secondary to an A1632E mutation in the *SCN9A* gene.[6] Patch clamp studies of an *in vitro* model of the A1632E mutation showed that the physiologic expression of this mutation demonstrated findings of both disorders[6]. Subsequent patients with a) the same mutation and symptoms, [11] and b) the same locus but a single base A1632T altered mutation and only erythromelagia[12] have been described. For the latter affected patient, milder symptoms were found and the A1632T mutation failed to slow current decay-open-state inactivation and did not increase resurgent currents which contribute to the high-frequency firing dysfunction in the A1632E mutation.[12] Here we show that oral iron to treat a moderate to severe iron deficiency and menstrual loss of our patient with an A1632E mutation was toxic and severely exacerbated her abdominal and leg pain, and red cell transfusions and alternative iron therapies were needed. Cold showers and sudden pool immersion were useful in attenuating her painful episodes.

Case Report:

The original patient with gain of function A1682E mutation of the $Na_V1.7$ ion channel gene SCN9A[6] developed moderate to severe iron deficient microcytic anemia following a long period of excess menstrual periods. The early childhood clinical expression of minutes-long episodes of pain associated with constipation, reddening of the hands and feet that led to the genetic testing of the *SCN9A* gene has been described.[6] Poor feeding, bradycardia on stimulation, and episodes of apnea requiring resuscitation began shortly after birth. The bradycardia was so severe that a pacemaker was inserted at 18 months of age. Episodic reflux, projectile vomiting and a hypersensitive gag reflex led to frequent prolonged hospitalizations over her first 2 years of life. [6] This improved but was replaced by attacks of pain and erythema that usually appeared every other day, occasionally on a following day when the episodes could come on with touching or stimulation or a bowel movement. The pain was more intense if the pain-free interval was longer than 2 days. It was appreciated at an early age that splashing her with cold water and placing her in a cold shower or the family pool was extremely helpful. She learned how to swim in the family pool at 18 months of age before she could walk at 2.5 years of age.

Jumping into the family swimming pool with her clothes on became a frequent practice. Cold showers and swimming in a cold pool were associated with a good feeling even in the absence of episodic pain and erythema. Slow growth led to a diagnosis of hypothyroidism at age 13 and thyroid medication was started. Puberty was late, and estrogen was started at age 16. She had her first menstrual period at age 18. Her symptoms were much worse and included muscle pains when she had a period. Painful episodes worsened further when she became anemic at age 20. Breath holding spells returned, and she would have severe shaking spells with her pain episodes. Oral iron 500 mg/day was administered and led to acute, one day prolonged abdominal pain cramping and diarrhea, and the oral iron was discontinued. Hemoglobin was 5.9, HCT: 26.9 % (L), MCV: 59 fL (L), MCH: 16.2 pg (L), MCHC: 27.5 g/dL (L) and blood IRON: 15 mcg/dL (L), TIBC: 512 mcg/dL (H), IRON SATURATION: 3 % (L), FERRITIN: 10 ng/mL (L). The red cells were microcytic, and she received a transfusion of packed red cells. Three months later, a second transfusion was given, and testing showed an improved HGB of 7.4 g/dL (L) with microcytic red cells. A higher hematocrit improved her attacks of pain and erythromelagia. Her iron deficiency improved further with vegetable-based liquid iron product (Floravital iron) and an iron patch (Vitamin Patch Club). As an aside, intravenous iron sucrose increases the blood hemoglobin levels more rapidly than oral ferrous-sulphate in women with postpartum iron deficiency anemia [13] but was not tried since it might have larger, systemic negative effects. Her hemoglobin rose to 11.6 g/dL with a third unit of packed red cells, and her muscle pains improved. Oral cannabis products helped her tolerate an anticipated painful crisis and helped her sleep.

Discussion:

ORAL IRON PRECIPITATED A SEVERE PAINFUL CRISIS

Acute excess generalized pain, particularly abdominal pain, was associated with treatment of iron deficiency with the administration of oral iron. It would be expected that the iron would also affect pain fibers even in areas of low *SCN9A* gene expression like the gastrointestinal tract, where NaV1.7 channel activity has been detected in the mouse. [14,15] And intravenous iron therapy[13] used for post-partum women might an additional risk. It has been known for a long time that gain of function/pain generating *SCN9A* mutations can be investigated *in vitro* in nerve tissue using laboratory generated mutated genes. Patch clamp studies of an experimental model of the A1632E mutation demonstrated that its physiologic *in vitro* expression demonstrated findings of both Erythromelalgia (IEM) and Paroxysmal pain (PEPD) disorders[6] and was a "gain of function" mutation. A key physiologic aspect of the paroxysmal pain disorder was that this mutation "depolarizes (17mV) the voltage

dependence of fast inactivation, slows fast inactivation, and prevents full inactivation, resulting in persistent inward currents similar to (other activating) PEPD mutations."[6] A subsequent patient with a A1632T mutation at the same locus and only erythromelagia was also hyperactive *in vitro*, with depolarizing shifts in both steady-state fast inactivation and slow inactivation but no effect on channel activation.[12] The A1632E mutation showed "hyperpolarizing shifts in activation produce IEM, whereas depolarizing shifts in fast inactivation produce PEPD," leading to "main gating change (of the mutation) is a strongly enhanced persistent current"[6] which would be enhanced by the addition of administered positively charged iron, binding to the patient abnormal glutamic acid now at the active site of the *SCN9A* gene not found in control subjects. A second possibility, is that exogenous iron accentuates the underlying pathology of the mutation, "impaired binding of the sodium channel "inactivation particle", which further "inhibits proper functioning of the recently proposed allosteric fast inactivation mechanism."[16] The Na_v 1.7 channels form dimers and the disease-associated persistent current through Na_v 1.7/A1632E channels (that) depends on their functional dimerization status" suggesting dysfunctional influence on the dimers involved in protein gating mechanism. [16] Still, it is more likely that exogenous iron further pathologically affected an already dysfunctional process with the voltage of the sodium channel further depolarized, inactivation prevented, and persistent inward currents accelerated. This led to prolonged episodes of pain carried out by positive charged iron (Fe^{+++}) binding to the negative charge (CO_3^{---}) of glutamic acid (A1632E), the mutational change alanine to glutamic acid of *SCN9A* gene at the functional active alpha subunit site of voltage-gated sodium channel 1.7 (NaV1.7).[6]

Intravenous packed red cells, an oral vegetable iron preparation and cutaneous iron patches were successful in treating her anemia.

ICE WATER, COLD SHOWERS AND A COLD SWIMMING POOL LESSENED PAIN ATTACKS

The patient found relief in the acute application of ice/cold water that has been described for patients with erythromelagia [17, 18] but not described for patients with paroxysmal pain. And relief was found with a cold shower or pool immersion even in the absence of a painful crisis. One would think that the central core of distressful pain in a patient in PPD would not be as amenable for symptom relief as that found in patients with IE, but at least for this patient with both hyperexcitable IE and PED, the impact of cold-water relief was immediate.

MULTIPLE DRUGS APPLIED IN EXPERIMENTAL MODELS FOR SODIUM CHANNEL DISORDERS

Multiple drugs and potential therapeutic approaches have been used to affect the NaV 1.7 sodium channel experimentally starting early with the wide spread early use of carbamizine, mexiletine and similar drugs.[5,6,19, 20]

Multiple potential therapeutic have been suggested by laboratory instigated research studies, including (R)-(3-fluoropyrrolidin-1-yl)(-((5-(trifluoromethyl) pyridin-2-yl)oxy)quinolin-2-yl)methanone,[21] guanfacine, an α2A-adrenergic receptor agonist,[22,23] the anti-epileptic drug lacosamide which enhances slow-inactivation of NaV1.7 channel, [24] selective peptide toxin from tarantula venom compound ProTx-II,[25-27] huwentoxin-IV, a product of "comprehensive engineering" of the tarantula venom peptide,[28-30] pyridyl urea quinolinone sulfonamide inhibitors, [31] compound C65780 that stabilizes voltage gated sodium channels[32] a novel NaVs antagonist, 2-(2-(diethylamino) gene NaV1.9 activity,[33] the anti-diabetic drug metformin,[34] pyridyl urea,[35] bis-guanidinium analogue 25 of saxitoxin [36], gene therapy delivery of a Na_V1.7-interacting cytosolic collapsin response mediator protein 2 (CRMP2),[37] targeting a small ubiquitin-like modifier (SUMO) 194 on the NaV1.7-interacting cytosolic collapsin response mediator protein 2 (CRMP2),[38] a venom peptide inhibitor Ta3a, from the African ant species, Tetramorium africanum,[39] 3-hydroxyindole backbone modulators,[40] 3-hydroxyinaphthylisoquinoline alkaloids (NIQs) from Ancistrocladus tectorius,[41,42] Bulley-aconitine A,[43] NAN-190, a 5-HT_{1A} antagonist, isoquinoline alkaloid HJ-69 isolated from Zanthoxylum bungeanum,[44] 3'-O-Methylorobol,[45] Oyada channel blocker ANP-230, [46,47] sodium channel blocker, XEN402,[48] 20S-Ginsenoside Rh2, bioactive saponin from Panax notoginseng flowers, [49] novel cyclopentane carboxylic acids,[50,51] lamotrigine,[52] AM404, a metabolite of paracetamol,[53] compound 194 inhibition of collapsin response mediator protein 2-SUMOylation,[54] novel compound, 5-chloro-N-(cyclopropylsulfonyl) -2- fluoro-4-(2-(8-(furan-2-ylmethyl)-8-azaspiro [4.5] decan-2-yl) ethoxy) benzamide (QLS-278),[55] synthetic peptide difopein, a 14-3-3 inhibitor known to functionally uncouple dimers which "restores the phenotype of a pain-linked Nav 1.7 channel mutation,"[56] Also, μ-Conotoxin KIIIA, [57] *N*-Aryl Indoles, [58] and GX-936 and related inhibitors that "bind to the activate state of voltage-sensor domain IV (VSD4), where their anionic aryl sulfonamide warhead engages the fourth arginine gating charge on the S4 helix" and "inhibit Nav1.7 through a voltage-sensor trapping mechanism, likely by stabilizing inactivated states of the channel" and "oppose VSD4 deactivation," [60] and α-Adrenoreceptor blocker phen8olamine which is mostly used to reverse local anesthesia.[59] If that were not enough, we have a "novel antigen strategy" with and antigen/antibody approach,[61] and Schisandrin B, the dried, ripe fruit from the magnolia tree. [62] And then there is the antifungal drug amorolfine [63] and the intrathecal administration of inhibitor IPF-0508977 which was successful in a mouse model.[64] Recently there have been "antisense transcripts" [65] and "efficiency based selective inhibitors [66] and "engineered zinc finger repressors.[67] that gives hope just as old studies of this kind of directed research gave hope in the past.[68] Although multiple direct and indirect approaches/drugs/extracts/ venoms/micro-poisons and diverse substances and materials detailed above have shown some effectiveness in treating Na_V 1.7 sodium channel dysfunction in the laboratory, and normalizing or minimizing sodium channel irregularities *in vitro*, with the potential to generate a positive clinical

effect in patients *in vivo*, no drug or chemical approach has emerged from clinical trials to successfully treat pain in patients with hyperactive Na_V 1.7 channel disorders. [69-71]

Separate measures to alleviate pain include artisanal and commercial CBD-dominant hemp-based products,[72] annabidiol and marijuana products. [73, 74]

Conclusion:

The administration of iron therapy to a patient with iron deficiency anemia and a NaV1.7 sodium channel A1632E mutation in our patient led to severe adverse consequences. With the mutation related negatively charged glutamic acid at the active site of sodium exchange, now bound to a positively charged Fe^{+++} molecule, the complex initiated a prolonged activated state of the $Na_V1.7$ channel and secondary aggravated pain from the altered $Na_V1.7$ primary pain channel. Alternative iron therapy was used, and the patient recovered to her usual state of health

Oral iron therapy should not be used to treat patients with hyperactive A1632E mutations of the *SCN9A* gene and iron deficiency anemia. Blood transfusion and iron patches can be used if this complication occurs. Iron therapy is potentially toxic with any gene mutation that generates a carboxy group at the active site of the gene. With so much attention, effort and money directed at examining blockers/substances that affect the NaV1.7 sodium channel recited above, and apparently negative practical utilizable clinical results, it remains positive in the short term that still such high attention is being paid to aid the management of these seriously impacted affected patients and their families. As a practical matter, this gene as a source of pain mechanism appears to play a role in common conditions like joint pain.[75] Recent clinical FDA approval has been obtained for Suzetrigine, a specific inhibitor of NaV1.9 channelopathy disorders [76] and that is encouraging. It is not known if approval of one or another drug is yet in the offing for patients with $Na_V1.7$ channelopathy disorders. Such approval could have large practical impact, since recent work suggests that potential NaV1.7 drugs could be a "therapeutic target for arthritis.[77] Until better and more specific treatment becomes available, we show that ice cold water showers and pool immersion, and cannabis can be small, well tolerated and mild to moderately impactful measures to help but not solve the painful episodes of patients with hyperactive NaV1.7 channelopathy disorders.

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