RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

An Open-Label Pilot Study of *N*-Acetylcysteine for Skin-Picking in Prader–Willi Syndrome

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Manuscript Received: 1 February 2013; Manuscript Accepted: 26 September 2013

Prader–Willi syndrome (PWS) is a complex neurodevelopmental disorder caused by an abnormality on the long arm of chromosome 15 (q11-q13) that results in a host of behavioral characteristics including excessive interest in food, skin picking, difficulty with a change in routine, and obsessive and compulsive behaviors. Skin-picking can result in serious and potentially life-threatening infections. Recent evidence suggests that the excitatory neurotransmitter glutamate is dysregulated in obsessive-compulsive behaviors, and modulation of the glutaminergic pathway may decrease compulsive behaviors, such as recurrent hair pulling or skin-picking behaviors. *N*-acetylcysteine (NAC), a derivative of the amino acid cysteine, is thought to act either via modulation of NMDA glutamate receptors or by increasing glutathione in pilot studies. Thirty-five individuals with confirmed PWS (ages 5–39 years, 23 females/12 males) and skin-picking behavior for more than 1 year were treated with *N*-acetylcysteine (Pharma-NAC®) at a dose of 450–1,200 mg/day. Skin-picking symptoms and open lesions were assessed after 12 weeks of treatment by counting and measuring lesions before and after the medication. All 35 individuals had improvement in skin-picking behaviors. Ten (29%) individuals (six males and four females) did not have complete resolution of skin-picking behavior, but had significant reduction in the number of active lesions. Longer-term, placebo-controlled trials are needed to further assess the potential benefit of this treatment.

Key words: Prader–Willi syndrome; skin-picking; *N*-acetylcysteine

How to Cite this Article:
Miller JL, Angulo M. 2013. An open-label pilot study of *N*-acetylcysteine for skin-picking in Prader–Willi syndrome.
Am J Med Genet Part A 9999:1–4.

INTRODUCTION

Prader–Willi syndrome (PWS) is a complex genetic disorder caused by the absence of normally active paternally expressed genes from the chromosome 15q11-q13 region. PWS is an imprinted condition with approximately 70% of the cases due to a de novo deletion in the paternally inherited chromosome 15 q11-q13 region, 25% from a maternal uniparental disomy of chromosome 15 (UPD), and the remaining 5% from either microdeletions or epimutations of the imprinting center in the 15q11-q13 region (i.e., imprinting defects; ID) [Butler et al., 2008; Cassidy and Driscoll, 2009]. Features of PWS include poor feeding in infancy often associated with failure to thrive, obesity beginning around age 2, hyperphagia, hypotonia, developmental and cognitive delay, behavioral problems, sleep abnormalities, and neuroendocrine abnormalities [Butler et al., 2008; Cassidy and Driscoll, 2009].

Self-mutilation behaviors such as skin-picking and severe nail biting are common in PWS. These behaviors can result in severe infections and can be highly-stressful for both children and their parents. Skin picking occurs in 80–95% of individuals with PWS [Morgan et al., 2010; Banga and Connor, 2012]. Obsessive-compulsive behaviors are considered part of the behavioral phenotype in PWS, and skin-picking is deemed to be a compulsive behavior [Dykens et al., 1996; Cassidy and Driscoll, 2009; Morgan et al., 2010]. The areas of the body most commonly involved are the face, hands, and legs [Symons et al., 1999; Morgan et al., 2010]. While many individuals pick at scabs, bites, or eczematous areas of the skin, some pick at healthy skin as well [Morgan et al., 2010]. Skin-picking behaviors often occur during times of relative inactivity, such as during school, watching television, riding in the car, lying in bed, or waiting for something [Dykens et al., 1996; Morgan et al., 2010]. Skin-picking behaviors can result in serious, life-threatening infections, social embarrassment, and significant scarring. Many interventions have been attempted to target skin-picking with limited success [Shapira et al., 2002; Morgan et al., 2010]. As animal models indicate that glutamate transmission may play an important role in the pathology of

Conflict of interest: none.
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Article first published online in Wiley Online Library (wileyonlinelibrary.com): 00 Month 2013
DOI 10.1002/ajmg.a.36306

obsessive-compulsive behaviors, targeting glutamate neurotransmission may offer novel treatments for this serious condition in PWS [Hoffman, 2011].

Glutamate (glutamic acid) is the most prominent neurotransmitter in the body, and it is the main excitatory neurotransmitter [Simpson et al., 2012]. *N*-acetylcysteine (NAC) supports the body's antioxidant and nitric oxide systems during stress, infections, toxic assault, and inflammatory conditions [Uraz et al., 2013]. It is thought to act via modulation of NMDA glutamate receptors or by increasing glutathione [Amrouche-Mekkioui and Djerdjouri, 2012]. Pilot studies suggest potential efficacy in cocaine craving, smoking, and obsessive-compulsive symptoms [Schmaal et al., 2012; Ramirez-Niño et al., 2013]. It was also found to improve trichotillomania—a condition that causes compulsive hair pulling and nail biting [Grant et al., 2009; Rodrigues-Barata et al., 2012]. We conducted this open-label pilot study to determine if NAC would be effective for treating the skin-picking and nail biting behaviors in individuals with PWS.

METHODS

Thirty-five individuals with confirmed PWS ages 5–39 years (23 females/12 males; 24 with deletion, 11 with UPD) and persistent skin-picking behavior for more than 1 year were enrolled in the study. Patients were given 450–1,200 mg of NAC orally once daily. The skin-picked lesions were counted before and after the medication and parents were asked about the frequency and severity of skin picking and nail biting/picking before and after 12 weeks of

TABLE I. Number of Skin-Picked Lesions Before and After NAC Treatment

Patient	Sex	Age	Genetics	Other meds	Lesions (#) before	Lesions (#) after
1	F	5	Deletion	GH, THY	12	0
2	M	22	UPD	GH, THY, TES, FXT	8	0
3	F	10	Deletion	GH	15	4
4	F	17	UPD	GH, THY, MEF, FXT	3	0
5	M	8	Deletion	GH	1[a]	0
6	F	10	UPD	GH, MEF	3	0
7	M	7	Deletion	GH, THY, PRV	2	0
8	M	5	Deletion	GH, PRV	3	0
9	M	8	UPD	GH, PRV	6	2
10	F	5	Deletion	GH	2	0
11	F	18	UPD	GH, PRV	>20[b]	0
12	F	21	Deletion	GH, THY	3	0
13	M	7	Deletion	GH	2	0
14	F	5	UPD	GH	1[a]	0
15	F	30	UPD	GH	5	1
16	F	5.1	Deletion	GH	3	0
17	M	6	Deletion	GH	5	0
18	M	7	Deletion	GH	3	0
19	F	8.9	Deletion	GH	3	0
20	F	10.7	Deletion	GH, THY	2	0
21	F	10.8	Deletion	GH	3	1
22	F	11.4	Deletion	GH	4	0
23	F	13.2	Deletion	GH, SPR, THY	2	0
24	M	13.7	UPD	GH, QPE, RSP	3	1
25	F	14.7	Deletion	GH	4	1
26	F	15.3	UPD	GH	4	0
27	F	15	Deletion	MEF, SPR	4	0
28	F	17.5	Deletion	GH, MEF, SPR, THY	5	0
29	F	21	UPD	GH, MEF, THY	3	0
30	F	23	UPD	RSP, FXT	26	0
31	F	25	Deletion	MEF, DKT	6	0
32	F	29	Deletion	GH, MEF, SPR	3	0
33	M	29	Deletion	GH, THY	6	2
34	M	31	Deletion	GH, THY	4	0
35	M	39	Deletion	GH, TES	5	2

DKT, valproic Ac; GH, growth hormone; MEF, metformin; QPE, quetiapine; RSP, risperdone; SPR, spironolactone; TES, testosterone; THY, levothyroxine; FXT, fluoxetine; PRV, modafinil.
[a]Lesions present for over 90 days prior to treatment.
[b]Patient had in addition trichotillomania, which resolved with treatment.

treatment. Lesions were counted by two providers and were measured for diameter. Lesions were documented as improving if they were not open and were scabbed over. Lesions were considered completely healed if they were scarred over. Investigators recorded resolution of skin-picking behaviors when all lesions were scabbed or scarred over with no open lesions. Nail biting and picking were assessed by visual inspection of the nails and nail beds by two providers.

Liver enzymes were monitored before and after NAC treatment in those patients on psychotropic medication. Plasma ammonia levels in addition to liver enzymes were monitored in all patients on Valproic acid, regardless NAC treatment. The investigators recorded adverse events, side effects, and intolerance of the medication.

RESULTS

Prior to treatment, skin lesions were between 0.3×0.2 to $2.5 \times 3\,cm^2$ in size. Number of lesions per child ranged from one to as many as 25. After treatment, all 35 individuals had improvement in skin-picking behaviors. Twenty-five (71%) had complete resolution of their self-mutilation behaviors with NAC treatment and improvement of all lesions without open lesions. Most had some scabs remaining, but with no irritation or erythema seen around the area and no need for protective covering over the areas. Ten (29%) individuals (six males and four females) did not have complete resolution of skin-picking behavior, but had significant reduction in the number of active lesions (Table I). Those 10 who did not have complete resolution had scabbed over lesions and reduction in number of open lesions. After treatment, only one to two lesions remained in those who did not have complete resolution, and these were smaller in size than prior to treatment, all measuring less than $1 \times 1\,cm^2$ in diameter. Complete resolution was seen as fast as 2 weeks in a 5-year-old girl.

Only two patients experienced side effects of the medication, which were mild and included gastrointestinal upset with cramping, flatulence, and diarrhea. These effects improved over the first few weeks of therapy. There were no adverse events. All of the individuals in this study tolerated NAC and were able to continue taking it without having to discontinue it for any period of time due to side effects.

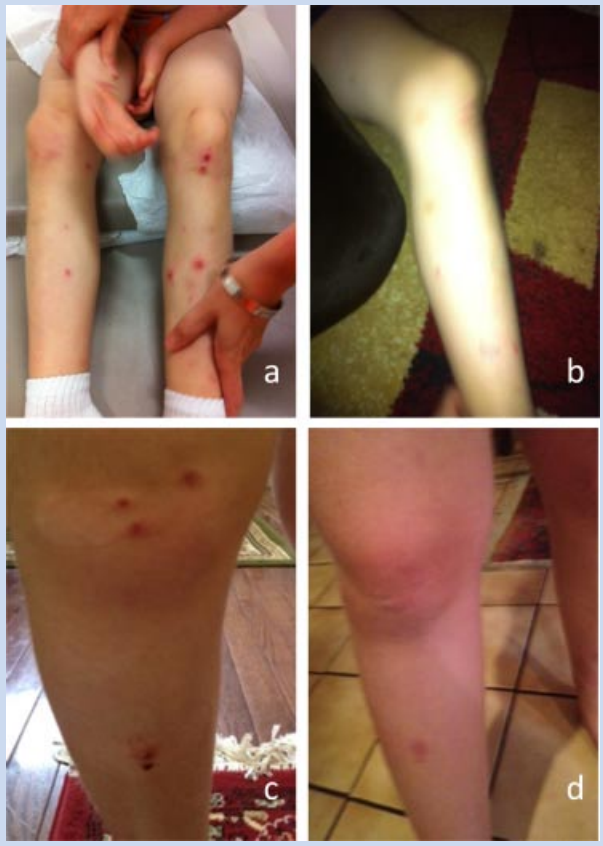

FIG. 1. Skin-picked lesions in PWS before and after 12 weeks of NAC treatment in 5-year-old male (a and b) and 10-year-old female (c and d).

DISCUSSION

Supplementation with NAC has been shown to increase levels of glutathione, the body's major anti-oxidant [Cao et al., 2012]. Glutathione is critically important for detoxifying an array of toxic substances, including xenobiotics (chemicals foreign to biologic systems), peroxide compounds, and other free radical–generating molecules [Srikanth et al., 2013]. NAC has been shown to inhibit OCD-type behaviors in mice [Egashira et al., 2012], as well as in limited studies in humans [Grant et al., 2007]. Additionally, it has been shown to improve irritability in children with autism [Hardan et al., 2012].

Thus far, no medication has been universally effective in treating skin picking in PWS. The results of this small pilot study suggest that NAC may be helpful for skin picking and nail biting behaviors in PWS. Additional placebo-controlled studies are needed in order to verify these results. Long-term follow-up will also be necessary to determine the persistence of improvement over time. If these results are confirmed, NAC could be a life-changing treatment for individuals with PWS because skin-picked lesions can become infected and be life threatening (Fig. 1).

NAC is thought to improve anti-oxidative capacity in neurons, which reverses the existing cognitive impairment in aging brains of mice, implying a potential role in cognitive improvement [Cao et al., 2012]. NAC has been found to be effective in treating Alzheimer's disease in mouse models by decreasing γ-secretase activity resulting in the attenuation of Aβ production and calpain activity [Robinson et al., 2011]. NAC has been shown to reduce the symptoms of both schizophrenia and bipolar disorder in early trials [Berk et al., 2011; Asevedo et al., 2012; Shungu, 2012]. As individuals with PWS have cognitive impairment and evidence of premature Alzheimer disease on autopsy, NAC may have other potential benefits in this population that should be investigated in future studies.

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