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QUANTITATIVE EVALUATION OF THE CLINICAL EFFECTS OF *S*-ADENOSYLMETHIONINE ON MOOD AND BEHAVIOR IN LESCH-NYHAN PATIENTS

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□ **Background, rationale, and methods**. *Lesch-Nyhan disease is a rare, X-linked disorder due to hypoxanthine phosphoribosyltransferase deficiency. To evaluate reported benefit on mood and behavior obtained by the administration of* S*-adenosyl-*L*-methionine in this condition, we developed 2 quantitative evaluation tools, and used them to assess the effects of the drug in our population: the weekly questionnaire and the resistance to self-injurious behavior test. We performed an open-label, dose-escalation trial of the drug on 14 patients.*

Results. *Four patients tolerated the drug and reported beneficial effects. The majority experienced worsened behavior. The 2 assessment tools demonstrated effectiveness in quantitatively evaluating the self-injurious behavior.*

Keywords: *S*-adenosylmethionine; Lesch-Nyhan disease; weekly questionnaire; resistance to self-injurious behavior test; resistance to heteroinjurious behavior test

INTRODUCTION

Lesch-Nyhan disease (LND; OMIM 300322) is a rare, X-linked inborn disease caused by mutation in the hypoxanthine phosphoribosyltransferase

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1 (HPRT1) gene.[1,2] It leads not only to hyperuricemia, gout, tophi, and renal calculi, but also to a complex neurological picture, manifest in a severe movement disorder, variable cognitive impairment, and, absolutely pathognomonic in the classical presentation, self-injurious behavior (SIB).[3–5] Milder forms, generally associated with a greater HPRT residual activity, are characterized by the absence of the behavioral abnormalities, and a lighter motor impairment (Lesch-Nyhan variants, LNV).[6]

In 2006, Glick reported a dramatic effect of *S*-adenosyl-L-methionine in a patient with LND. Progressive improvement of both mood and SIB was reported.[7]

SAMe is a physiological intermediate in methylation and trans-sulfu ration.

It has been used extensively as a coadjuvant antidepressant in the treatment of depression, bipolar disorder, and schizophrenia.[8–12] In Glick's patient, it was given to treat transaminase elevation resulting from an adverse effect to fentanyl.

The common tools available for the evaluation of aggressive behavior,[13–15] Modified Overt Aggressive Scale, the Behavior Problems Inventory and the Vineland Adaptive Behavior Scale, were tested by us. They were not ideal for the current study, neither seemed so the customized evaluation tool for the evaluation of LND mood proposed by Glick, expressed as good temper percentage. Accordingly, we have developed quantitative, analytic tools applicable to a patient population broadly scattered throughout the country. The assessment tools consisted of a questionnaire, to be filled-in by care-givers once a week, and an objective test, evaluating the resistance time to self-injurious (RSB) or heteroinjurious behavior (RHB). In the present report, we have evaluated the effects of SAMe in the Italian LND patient cohort.

METHODS

1. Design of the Trial

Our study was structured as an open-label, dose-escalation trial, lasting 12 months, in which subjects were regularly evaluated and observed. The enrolled patients were observed for the first 6 months, and then treated with SAMe for the following 6 months: SAMe was gradually added, reaching a steady-state dose in 2 months. Patients did not modify other current therapy. They could rarely move from their home to our Institute and were widespread over the Italian countryside. Therefore, they were visited if possible by our team every 3 months; they were always visited at least at the beginning of the trial, at the passage from the observational to the treatment period, and at the end. Complete blood count, transaminases and uric acid in blood and spot urine were obtained quarterly by local physicians. We

could not obtain a 24-hours urine assessment. The clinical trial protocol was approved by the Institutional Ethics Committee, and an informed written consent was obtained for each participant.

2. Patients

We initially enrolled 30 patients, most of them recently reviewed.[16]

Fourteen patients were entered into the administration phase and followed the protocol; others were excluded because of lack of compliance (v.i.) Patients studied ranged in ages from 18 to 49 years; only one was underage, 11 years old, but parents were strongly motivated to try the drug: we accepted him after acceptance of a stricter control schedule, by phone and email. After thorough explanation of the trial, they all signed the informed consent.

Of the 14 patients, 11 had the classical clinical phenotype and 3 were attenuated variants (Table 1).

Patients with the classical disease displayed severe self-aggressive behavior during infancy, and all required restraints. The eldest patient, Pt #11, had the typical behavior when younger; at the time the study was, he no longer displayed SIB, but shouted for several hours each day, in the absence of an apparent reason. We considered this shouting as an expression of the LND behavior. Pt #1, #2, and #3 had attenuated variants of LND. They did not display SIB. All had a degree of anxiety.

TABLE 1 Patients' features

ID patients	Clinical form	Mut type	HPRT1 mut	Bioch activity [nmol/mg Hb /h] (blood)	Self-inj. behavior	DOB, age
Pt #1	Attenuated	Missense	c.143G>A	Absent	Absent	1973, 37
Pt #2	Attenuated	Missense	c.440T>C	Absent	Absent	1986, 24
Pt #3	Attenuated	Splicing	c.485+2T>C	0–0.1	Absent	1976, 34
Pt #4	Classical (mild)	Splicing	c.485+2T>C	0–0.1	Inconstant	1974, 36
Pt #5	Classical	Deletion	del E4	Not known	Present	1988, 22
Pt #6	Classical	Splicing?	exclusion E4	Absent	Present	1986, 24
Pt #7	Classical	Splicing	c.610-1G>A	Absent	Present	1975, 35
Pt #8	Classical	Missense	c.208G>T	4.1	Present	1993, 18
Pt #9	Classical	Duplication	c.212dupG	Absent	Present	1980, 30
Pt #10	Classical	Nonsense	c.508C>T	Absent	Present	1990, 20
Pt #11	Classical	Deletion	del E2-9	Not known	Present	1961, 49
Pt #12	Classical	Deletion	del E1-3	Absent	Present	1977, 33
Pt #13	Classical	Deletion	del E1	Not known	Present	1989, 21
Pt #14	Classical	Missense	c.145C>T	1.9	Present	1999, 11

HPRT biochemical activity, as measured in blood cells, was expressed as nmol/mg of hemoglobin/hour. These data were not always available.

3. Current Therapy and the Addition of SAMe

All patients were treated with allopurinol, in dose sufficient to maintain blood uric acid at lowest levels of the normal range. Gabapentin or pregabalin was received by 9 patients, and 4 received carbamazepine or valproate. None of them received neuroleptic drugs.

S-adenosyl-L-methionine (SAMe, Samyr) was kindly provided by Abbott – in 200 and 400 mg gastroresistant tablets. We employed the doses used in the initial publication[7] 400–1600 mg/day, up to 80 mg/kg, depending on body weight and renal function. The steady-state dose was reached in 8 weeks. Caregivers were instructed to give the drug distant from meals, as advised by the producer.

4. Patient Evaluation

Clinical History Surveillance: The Weekly Questionnaire

The clinical history was carefully recorded at every visit, and general conditions were evaluated. The behavior, mood, and movement disorder were thoroughly described and often videotaped. The visit was concluded by the compilation of a Weekly Questionnaire (WQ), together with the caregiver. Explanations of the questionnaire items and the first visit served as training for the completion of the WQ at home. The full report of the visit, containing both the complete description of the clinical condition and the relative WQ, and a WQ form were always given to the caregivers. Our initial written description and WQ constituted the baseline of reference for the next week's WQ – completed by the caregivers – and subsequently each WQ was compared with the immediately previous one. We asked caregivers to fill it in preferably in the same day of the week (generally Sunday was preferred), and by the same caregiver. The very first WQs filled in by caregivers were sent to us by email and discussed by telephone, as advised in the instruction sheet attached to them.

The WQ asks the caregiver to observe and judge (1) Lesch-Nyhan behavior including all the pleomorphic expressions of the characteristic aggressive behaviors of the disease (2) mood; and (3) the movement disorder, as these aspects were displayed during each 7 day period. Behavior was itemized in several specific categories of behavior: SIB, oppositional behavior (purposeful interference with daily activities such as dressing, bathing, feeding, or transport), aggressive behavior toward objects, verbal aggressive behavior, and aggressive behavior toward others. Each week each of the categories was judged as unchanged, slightly or definitely improved; or slightly or definitely worsened.

To permit the transformation to numeric values, therefore, the statistical analysis of data and a plot of clinical course, our initial evaluations were described in details. For WQs filled in at home, the following week, slight

improvement was, as compared with the initial evaluation, given +1 point, and definite improvement was given +2 points. In contrast −1 and −2 points were recorded for worsened behavior, mood or movement disorder. The WQ was not designed for variant (LNV) patients, which lack of the distinctive SIB. We considered the issue of how to evaluate an effect of SAMe in patients with attenuated disease (Pt #1, #2, and #3). We elected to evaluate motor deficit, and to assess other effects of SAMe. The speech of all the LNV participants was carefully evaluated.

Objective Assessment: The Resistance Time to Self-Injurious and to Hetero-Injurious Behavior

RSB was assessed as follows: under the strict control of the assistant and of one of the caregivers, and after thoroughly explaining the procedure and obtaining the patient's consent, restraints were removed, one by one. The same sequence was maintained at every assessment. Time – expressed in seconds – the patient refrained from SIB was recorded. The test was stopped after 9 minutes (540 seconds).

The RHB test has never been explained to the patient, but only to the caregivers. A plastic glass filled with water was placed at patient's hand-distance near a desk border avoiding his attention, and the time elapsed between his finding it and his hitting it was recorded.

5. Statistical Analysis

Numerical data were gathered as described above on mood, SIB, oppositional movements, involuntary movements, and night awakenings. They were analyzed using multivariate nonparametric permutation tests by the software NPC Test 2.0, useful to draw statistical significance even on small sample sizes.[17] RSB data were also evaluated with the same program. It is worth noting that such methods are the most powerful tools available at the moment in the case of small sample size and a large number of endpoints.[18]

RESULTS

1. Observation Period

No seasonal variability in LND has been reported in the past and none emerged from the WQs. A few patients experienced an important improvement during holidays, and a worsening during even minor illnesses (see Figure 1) – e.g. Herpes Zoster. The data are summarized in a column of Table 2 as the average value ±SD. Prior to the administration of SAMe, the RHB always approximated 0, indicating that the plastic glass of water was hit as soon as it was discovered at hand-distance. The RSB was always measurable, but varied from seconds to minutes and from patient to patient.

TABLE 2 Outcomes

In-trial patients	Clinical form	Average score of the observational period	Score at the end of the administrational period	Main effect showed	Maximal dose reached	Participation to the trial
Pt #2	LNV	Never assessed	Never assessed	Legs weakness, anxiety	400 mg × 3 (22 mg/kg)	Discontinued after 7 weeks
Pt #3	LNV	Never assessed	Never assessed	Falling backward, anxiety	400 mg (5 mg/kg)	Discontinued after 2 weeks
Pt #4	Classical (very mild)	Mood: 10 (0.0) Behavior: 10 (0.0)	Mood: 10 Behavior: 9	SIB worsened	400 mg (7 mg/kg)	Discontinued after 3 weeks
Pt #5	Classical	Mood: 10.2 (0.2) Behavior: 10.2 (0.3)	Mood: 8 Behavior: 9	Sleep disturbed	400 mg twice (18 mg/kg)	Discontinued after 8 weeks
Pt #6	Classical	Mood: 10.1 (0.5) Behavior: 10.1 (0.5)	Mood: 8 Behavior: 8	SIB worsened	400 mg twice 16 mg/kg)	Discontinued after 4 weeks
Pt #7	Classical	Mood: 9.6 (0.5) Behavior: 9.6 (0.5)	Mood: 8 Behavior: 8	Sleep disturbed	200 mg twice (10 mg/kg)	Discontinued after 8 weeks
Pt #8	Classical	Mood: 11.4 (2.1) Behavior: 11 (1.3)	Mood: 7 Behavior: 8	Movement disorder and SIB worsened	400 mg × 3 (20 mg/kg)	Discontinued after 28 weeks
Pt #9	Classical	Mood: 9.9 (0.7) Behavior: 9.8 (0.7)	Mood: 4 Behavior: 4	Movement disorder and SIB worsened	400 mg twice (15 mg/kg)	Discontinued after 19 weeks
Pt #10	Classical	Mood: 9.5 (0.7) Behavior: 9.5 (0.7)	Mood: 8 Behavior: 8	SIB worsened (vomiting)	400 mg × 3 (39 mg/kg)	Discontinued after 8 weeks
Pt #11	Classical	Mood: 10 (0.0) Behavior: 10 (0.0)	Mood: 10 Behavior: 10	Unchanged or slightly worsened	400 mg (8 mg/kg)	Discontinued after 6 months
Pt #1	LNV	Never assessed	Never assessed	Speech and anxiety improved	800 mg twice (25 mg/kg)	Max dose tolerated
Pt #12	Classical	Mood: 10.1 (0.4) Behavior: 10.3 (0.5)	Mood: 14 Behavior: 13	SIB improved (1 year after > 30)	800 mg twice (43 mg/kg)	Max dose tolerated
Pt #13	Classical	Mood: 9.8. (1.5) Behavior: 10.3 (1.3)	Mood: 10.8 (0.9) Behavior: 10.3 (1.0)	Sleep improved	800 mg twice 40 mg/kg)	Max dose tolerated
Pt #14	Classical	Mood: 11.6 (1.7) Behavior: 11.4 (1.8)	Mood: 13 Behavior: 13	SIB improved (1 year after > 26)	800 mg twice (80 mg/kg)	Max dose tolerated

The 14 patients following the trial on SAMe; clinical form; average score on mood and behavior during the observation period (in parenthesis the standard deviation is reported); score on mood and behavior as assessed in the last filled in WQ; main effect observed (and specific score in SIB achieved 1 year after); maximal dosage reached, absolute and expressed in mg/kg (never more than 1600 mg/day, and than 80 mg/kg); duration of the participation to the trial.

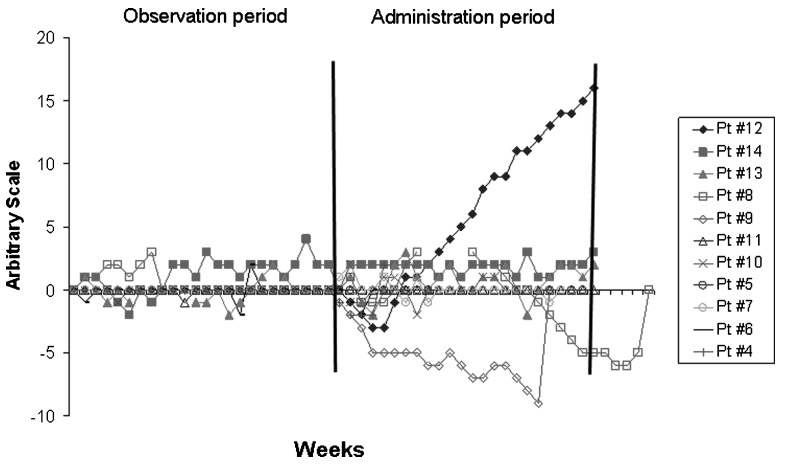

FIGURE 1 SIB of all patients initially participating to the trial, as assessed by the WQs. We report results of the 24 weeks of the observation period. Few patients went on taking SAMe until and beyond the 24 weeks of the administration phase. Among "nontolerating" patients, only Pt #8 kept on taking SAMe until week 28, hoping in an eventual positive shift. All of nontolerating patients promptly returned to the baseline within a week. Time – in weeks – in the *x*-axis, the arbitrary scale as described in the Methods section in the *y*-axis (Color figure available online).

2. Tolerability

Of the 30 patients enrolled, 16 LND/LNV patients who initially signed the informed consent later refused to enter the treatment period.

In the 14 remaining patients, the full dose was scheduled to be reached in 8 weeks. In many patients, it could not be reached because an excess of excitement experienced at lower dosage. The excess of excitement was often displayed as increase of temper tantrums, or oppositional behavior, or increase of awakenings in number and length, indicated in Table 2. These features excluded further increases in dose, and acted to discourage parents from continued administration. Patients were widely distributed over the country; only Pt #8 could be visited before the decision to stop the trial; in others the decision to withdraw SAMe was made after telephone consultation, so RSB before withdrawal could not be recorded.

Seven patients displayed an increase of anxiety during SAMe administration, and discontinued SAMe within 2 months (see table 2: Pt #2, #3, #4, #5, #6, #7, and #10).

Pt #2, a LNV, showed an increment of anxiety and weakness of the legs, which impaired his already precarious gait and ability to walk.

Pt #3, also a variant, usually walked without any aid, but following the early administration of SAMe, he developed anxiety and displayed a tendency to fall backward, never shown before. Both Pt #2 and #3 promptly recovered after discontinuation of SAMe.

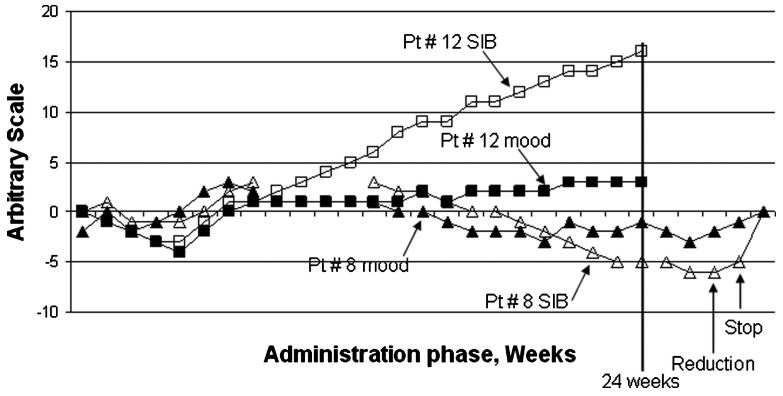

FIGURE 2 Isolation and enlargement of the SIB (empty symbols) and Mood (black symbols) displayed in the administration phase by Pt #12 (squares) – our best performer – and by #8 (triangles); Pt #8 took SAMe beyond the scheduled 24 weeks, hoping to repeat the outcomes the caregivers could observe during holidays, in which they did not completed the WQs (missing points 8–12). Week 1 represent the results after the first week of treatment. In the *x*-axis: time, in weeks; in the *y*-axis: arbitrary scale, as described in the Methods section.

Pt #4, who displayed a mild classical form of disease, had not displayed SIB for a long period of time. After the very first administration of SAMe, he began to bite his fingers.

Pt #5 was thought to have improvement of speech, but concomitant increase of excitement during the day, reduction of sleep time, and increased number and duration of awakenings led to discontinuation of treatment.

In Pt #10, adverse events leading to discontinuation of treatment were vomiting and worsening of SIB over a period of 2 months. Administration was discontinued. The following week, the caregiver reported a substantial improvement in behavior and vomiting.

In Pt #11, adverse events appeared on increasing the daily dose over 400 mg, as manifested by worsening of shouting. The SAMe administration was, therefore, maintained at 400 mg.

In Pt #8 and #9, the SAMe effects were well documented by the families who continued the administration and at-home completion of WQs up to 28 and 19 weeks, respectively, maintaining strict telephone contact with our team. The former thus maintained the administration well beyond the scheduled treatment period of 6 months. This was because, after a seeming initial improvement, followed by gradual worsening, parents thought the patient might be undergoing stabilization and asked to continue for some weeks more; worsening was documented and SAMe was withdrawn. Both patients displayed in summary a progressive worsening of Lesch-Nyhan behavior. Mood and behavior of Pt #8 are shown in Figure 2. A worsening of SIB emerged. Plotting of SIB and of oppositional movements indicated clearly the return to baseline following withdrawal at 28 weeks. It was elected

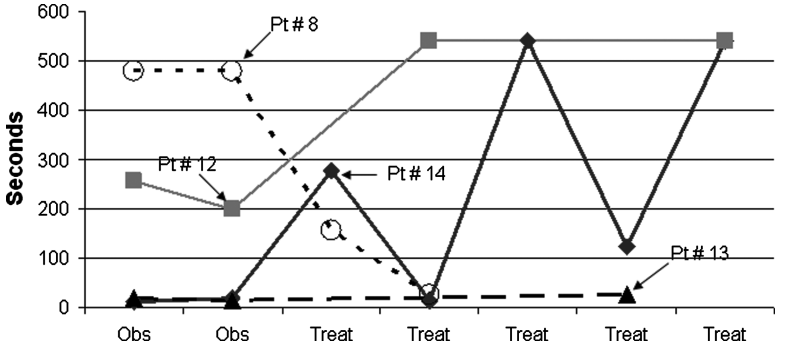

FIGURE 3 RSB. RSB of all LND patients who took SAMe at full dose for a prolonged period of the trial. Only 2 in-trial LND patients (Pt #8 and #14) regularly came to the Institute every 3 months during the trial. Pt #8 (dotted line, empty circles) and #14 (continuous line, diamonds) started from opposite baselines, showing opposite trends. Pt #14 displayed a very instable RSB performance, on average positive (in facts he continued taking SAMe, and he is currently taking it). Pt #12 (gray, thin line, squares), despite initial worsening, rapidly and steadily did not displayed any SIB all the test long. Pt #13 (dotted line, triangles) RSB was not substantially affected by SAMe. Pt #13's WQs confirm a positive effect on sleep quality only.

The test was stopped at 540 seconds, 9 minutes (Color figure available online).

after a visit and objective evaluation. The RSB of this patient is shown in Figure 3.

In both Pt #8 and #9 recovery to baseline was prompt and complete.

All patients who experienced worsening of behavior referred prompt return to baseline after withdrawal. In Pt #11, behavior was unchanged or slightly worsened.

3. Efficacy

Only 4 patients tolerated the full dose of SAMe. These were also the ones who displayed a benefit, as observed by the caregivers in WQs, and by us at visits and measured by the RSB, or assessed by speech evaluation.

Pt #12 (Figure 2a and b) displayed a biphasic response to treatment, showing an initial increase in excitement (mainly temper tantrums and oppositional behavior), but 1 month later improvement in behavior was apparent to the caregivers. This was documented in the WQs. The patient asked for removal of hand restrains for longer and longer periods of the day, passing from initial never, to 6–8 hours/day within the 6-months treatment period. Because of the benefit observed, the treatment was not discontinued; after 1 year of treatment, he was able to go the entire day without hand and arm restraints. This was evident in the WQs and in the RSB. Furthermore, there was a prolongation of RHB, from 0–1 to 3–4 seconds, the only modification observed with this test in our population.

Pt #13 displayed an important improvement only in the quality of sleep. He went from 5–10 awakenings/night to 1. There was no improvement in the SIB as documented by the WQs, RSB, and RHB.

Pt #14 attended high school for most of his day time. Substantial progressive improvement of SIB at home and in the school was reported in WQs by caregivers. This was confirmed by RSB testing (see Figure 3).

Pt #1 was an attenuated variant. He was married and employed. During treatment with SAMe, he reported improvement both of anxiety and speech. Objectively, his speech was evaluated and video recorded at the start and at the end of the study, and there appeared to be some improvement in the clarity of pronunciation.

In sum, there were 2 groups; 10 patients who displayed worsening, and 4 patients who displayed improvement and tolerated the full dose. The blood and urine content of uric acid appeared not to be modified by the drug administration.

4. Statistical Analysis

Only 1 patient of the first group concluded the trial taking a full dose of SAMe, and among the 4 displaying improvement, there was a LNV. Thus, data obtained from WQs and RSB did not achieve differences statistically significant between the 2 groups, both for each single end point and globally with respect to each variable analyzed. The unexpected split reaction to the drug made the sample size too little even if analyzed with powerful statistic tools, specific for small numbers.

5. The Weekly Questionnaire was Effective in Detecting Positive and Negative Effects on Behavior

The WQ is an observational questionnaire designed to evaluate Lesch-Nyhan behavior, movement disorder, and mood over time in patients with the classical form of LND. We found that the parents' training in completing the WQs was short, and at the next visit their last WQ was exactly as accurate as ours. They distinguished between oppositional behavior and movement disorder as well as the investigators. Compliant caregivers related that completion of the WQ initially required about 15 minutes and this was reduced to 3–5 minutes after some weeks.

The instrument permitted the delineation of both positive and negative responses to the administration of the drug. Changes in mood and behavior followed the same patterns. In the case of Pt #8 and #9, despite a negative drug effect, families continued administering SAMe up to 19 and 28 weeks.

6. The Resistance Time to Self-Injurious Behavior Objectively Measures the Main Feature of the Disease

RSB was designed to measure the pathognomonic sign of the classical form of LND, SIB. Pt #8 and #14 started from opposite baselines. This permitted the graph in Figure 3, highlighting of the opposite responses to SAMe. The first 2 tests were performed in the pretreatment phase: Pt #8 who was 18 years of age appeared quite calm at the beginning; he resisted self-injurious so long the test was stopped at 9 minutes. Pt #14 on the other hand started quite prone to SIB. Further assessments were done every 3 months. Pt #8 promptly displayed worsening of SIB – leading to cessation of the administration after 29 weeks, when he violently hit his teacher on the face. In contrast Pt #14 displayed a progressive improvement, even though affected by seasonal illnesses-related worsening (see 4th and 6th evaluations). The RSB in our experience always perfectly matched the results of the WQs. The RHB gave always the same results: the plastic glass was always hit as soon as it became reachable at a hand-distance. Only one patient (Pt #12), far the best responder, displayed some hesitation at the end of the administration period.

DISCUSSION

SAMe is a well-known compound, widely employed for positive effects on mood and for hepatic injury. This study of HPRT deficiency was unique in that the same compound produced unequivocally opposite effects on patients with the same disease; it clearly identified 2 distinct groups, a smaller one responding and the other worsening. We believe the reason high rate of drop out (16 of 30) is mostly due to the fact that caregiver-to-caregiver communication is common in our population of families, and information patient-to-patient on negative effects was quickly communicated. It was highly unexpected by both patients and us, and difficult to explain. The assessment tools were designed to evaluate patients with the classic form of disease, but opposite clinical changes were also observed in the few patients with attenuated variants.

In the nonresponding group many maneuvers were made in order to avoid the negative effects. It was not possible to find administration conditions that affected drug effect. A major adverse effect in the nontolerating group appeared to be an increase in level of excitement, variously expressed as increase of awakenings at night, irritability, and temper tantrums; the most impressive change was the increase in SIB. In each patient, withdrawal of drug was followed by prompt and complete return to baseline within a week, even after an administration lasting 20 weeks or more. Positive effect observed in 4 patients is consistent with effects of SAMe on mood and monoamine metabolism.[19] SAMe efficacy/intolerance did not appear to

relate to mutation type, age, or residual HPRT biochemical activity. The immediate negative effects, even at low doses, the prompt return in each to baseline after suspension, as well as the opposite important positive effects in other, are not of easy interpretation.

In a recent double blind, randomized clinical trial on schizophrenic patients,[12] treated with SAMe, an improvement of aggressive behavior and quality of life was observed, but an opposite effect was displayed by 2 patients out of 18. This creates a precedent with this drug in a different disease, in which anxiety plays a crucial role too.

Another precedent for largely inexplicable different responses to the same drug in LND has been reported in the 1970s in case of 5-hydroxytryptophan (5-HT) along with carbidopa and imipramine.[20–22] This indicates that results very different than expected, even if not opposite, can be found with the same drug in different diseases (SAMe in schizophrenia), as well as with different drugs in the same disease (5HT in LND).

Most patients displayed important effects on anxiety and/or sleep, and this often represented the main reason for discontinuation of drug or maintenance (see Table 2). On the other hand, only Pt # 12 and #14 continued taking SAMe because of perceived improvement in SIB, while in Pt #4, #6, #8, #9, and #10 SAMe provoked clear worsening, as distinctly detected by WQs and RSB. No significant data about blood pressure and pulse were collected from nontolerant patients. However, it is well known by both caregivers and experts, that excitement – associated with either positive or negative experiences – tends to worsen SIB. In the HPRT deficient mouse,[23] SIB appears only when amphetamine, a psychostimulant, is administered.

In our study, prior therapy was not discontinued, and this limits the speculations on interaction between medications. However, we could find the very same drug association in both groups, and we could not establish any link with the responsible genetic mutation or residual biochemical activity. We have concluded that the effects of this drug in LND are currently unpredictable. The clearly distinct 2 classes of LND patients could be related to a greater sensitivity than other patients to excitation as a side effect of SAMe, which in LND can possibly result in a variable combination of symptoms as described above.

The rationale that we initially believed to be driving the described SAMe's efficacy in LND,[7] was that the drug looked able to replace adenosine depletion provoked by the HPRT deficiency. We are now persuaded that this appealing a theory could not represent more than a valid concurring cause. SAMe is known to be a pleiotrophic molecule,[8] influencing neurotransmitters' synthesis and metabolism[24] (e.g., both norepinephrine and serotonine). Recent reports have outlined a new role of the adenosine's pool in the pathogenesis of schizophrenia.[25,26] In vitro experimentation should be performed to test the contribution of the "adenosine balancing theory" to other SAMe effects, i.e., on neurotransmitters' metabolism. Elucidation

mechanisms connecting adenosine pool and neurotransmitters might come from recent advances in the comprehension of the role of HPRT in neurogenesis.[27,28]

To investigate the reasons why so often LND patients show intolerance or a paradoxical effect to SAMe, it would be interesting to check if the SAMe response bears any relation with the recently published imbalance of neurotransmitter receptor expression in lymphocytes.[29]

Clinically, in view of the very good response in a very small number of patients, SAMe appears worth a try in a classic patient. It can be avoided in a patient without SIB.

A major result of our research was the development of 2 evaluation tools, allowing quantitative assessment of effects on LND aggressive behavior. The first one was based on caregivers' observation: the WQ, evaluating mood, and the variety of Lesch-Nyhan behaviors. Changes in self-injurious and oppositional behavior always went in the same direction, either positive or negative. The WQ considered the LND motor dysfunction too, ranging from dystonia to a ballistic disorder.[30] In our view, the WQ represents a valuable tool for the assessment of improvement or worsening in Lesch-Nyhan behavior.

The second evaluation tool was an objective test assessing the LND aggressive behavior through the measurement of the time elapsed before an aggressive action takes place (or time of resistance). Patients were often reliable in assessing the severity of their own SIB, when they refused to undergo the RSB test, because they felt that their SIB was particularly uncontrollable. Patients are known to be able to anticipate their aggressive behavior, and ask for preventive reinforcement of physical restraints.[31] In the few patients that completed the trial, the WQs and RSB always gave results consistent each other, and with our written clinical description. Dependency upon restraints, manifesting as a RSB worsening was never inconsistent with the results of WQs.

The resistance test to RHB, proved less useful, possibly because it substituted an inanimate object for a real person.

A major accomplishment of this study was the development of assessment tools which proved sensitive enough to detect even slight worsening or improvement. Clear effects of the drug were observed in both positive and negative behavioral changes. It convinced us that SAMe, even if in one case of ours only, can display a great impact in quality of life, confirming Glick's report. Therefore, we believe its administration is worth to be attempted, very carefully monitoring its effects over a 2 months period. If tolerated, positive outcomes, even if generally less noteworthy, were always observed.

The validation of the proposed tools – WQs and RSB – would require a randomized clinical trial and an evaluation of the sample size along with the study of possible confounding factors.

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