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Treating Fragile X syndrome with the diuretic bumetanide: a case report

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ABSTRACT

We report that daily administration of the diuretic NKCC1 chloride co-transporter, bumetanide, reduces the severity of autism in a 10-year-old *Fragile X* boy using CARS, ADOS, ABC, RDEG and RRB before and after treatment. In keeping with extensive clinical use of this diuretic, the only side effect was a small hypokalaemia. A double-blind clinical trial is warranted to test the efficacy of bumetanide in FRX.

Conclusion: This single case report showed an improvement of the scores of each test used after 3 months of treatment. Double-blind clinical trials are warranted to test the efficacy of bumetanide in FRX.

INTRODUCTION

Fragile X syndrome (FRX) is caused by the presence of more than 200 CGG repeats in the 5′ un-translated region of the FMR1 gene located at Xq27.3 (1). FRX is the most common monogenic cause of intellectual disability and autism spectrum disorders (ASD) (2). FRX is identified in approximately 2% of ASD cases (3,4), whereas 40–60% of FRX patients meet the criteria for ASD (5–7). The morphological, behavioural, neurological and cognitive manifestations of FRX are highly variable (8,9). Behavioural and cognitive symptoms include hyperactivity, hypersensitivity to sensory stimuli, anxiety, mood disorders, disrupted sleep patterns (10) and cognitive impairments, ranging from severe intellectual disability to mild defects in cognitive learning and memory consolidation (11). Elevated electroencephalogram activity is frequent: around 20% of FRX patients have epileptic seizures (11). Relying on the Fragile X knockout mouse (11), a wide range of therapeutic strategies have been tested to reduce the severity of autistic traits, including drugs acting on glutamate e.g. (12), GABAergic receptors e.g. (13,14) and antagonists of glutamate metabotropic receptors e.g. (10).

Experimental studies suggest that GABAergic signalling may be deficient in both ASD and FRX, thereby shifting the excitation/inhibition balance (11,15–18). However, elevated intracellular chloride levels that shift the polarity of GABA actions from inhibition to excitation are observed in many pathological disorders (19–21). In these conditions, the GABA-acting benzodiazepines produce paradoxical effects, aggravating seizures and agitation (19,20). As benzodiazepines produce paradoxical effects in ASD patients (22), we have recently tested the hypothesis that chronic treatment with the diuretic NKCC1 chloride importer antagonist bumetanide, which reduces intracellular chloride, also decreases the severity of ASD. We reported significant amelioration of social communication in a double-blind randomized study on 57 children (13,14). We now report that bumetanide also reduces the severity of the syndrome in an adolescent with a typical FRX deletion.

CASE STUDY

AA is a bilingual boy, who was born in October 2002 to a Ukrainian mother and French father. He is the couple's eldest child and has a younger sister. His mother had a normal pregnancy. At birth, he weighed 3.335 kg, was 50.5 cm long and had a head circumference of 36 cm. His transfontanel cranial ultrasound examination was normal. His mother breastfed him for the first 3 months; he sat at 10 months, walked at 19 months and achieved daytime bladder control at 29 months and night-time control at 36 months. He had surgical treatment for a right-side inguinal hernia when he was 10 months old, and a slope in his right foot was treated by physiotherapy. During the spring of 2004, AA experienced a malaise when swimming with his father, which took the form of sudden generalized tension, followed by a brief, spontaneous episode of hypotonia and empty gaze that lasted a few seconds. Normal EEG was observed during wakefulness.

AA's parents first became concerned when he was 2 years old, because he had not started talking. He was frequently excited, seemed very anxious, scratched, felt and smelled objects and refused physical contact and hugs. Staff at the day care centre he attended also noticed that he did not interact with the other children. He was then admitted to a daily child and adolescent psychiatry service in May 2005, which he attended for three half-days a week until September 2010. Speech rehabilitation was initiated in May 2007. AA was admitted to kindergarten in September 2005, repeated a year in 2008 and was then accompanied by a

special needs assistant before being admitted to a specialized institution.

In February 2008, AA was diagnosed with pervasive development disorder. An EEG test in March 2008 revealed no abnormality. He slept readily, but woke frequently at night. Melatonin treatment (2 mg at night) ameliorated his sleep cycles and reduced night-time awakenings. Communication became essentially echolalic. Genetic exploration with karyotype and specific research of FRX was made in May 2008 with an insertion in the locus FRAXA of 1,200 base pairs corresponding to 400 CGG repeats.

A completed diagnosis made at the Centre de Ressources de Bretagne (CRA) in June 2009 revealed an axial hypertonicity, hypermobility of the hands and feet, difficulty in appreciating height and depth, absence of lateralization, difficulties in equilibrium and inadequate tonicity. Semantic tests revealed a delay of 3 years, with important syntax troubles, isolated words and rare spontaneous sentences limited to various requests. AA was tested using the Wechsler scale (WPPSI III). Performance IQ was 50, and verbal IQ was 56. During the tests, AA explored the environment and objects with an emphasis on smell and hearing sensory modalities. There were clear social interaction deficits, for example, AA was unable to develop relations with his peers and to share pleasurable plans, presenting great difficulties with socio-emotive reciprocity.

A diagnosis of typical autism (F84.0) was made according to DSM IV (APA, 1994) and ICD-10 (WHO, 1994) and was confirmed by the ADI-R [Autism Diagnostic Interview-Revised, (23)] and ADOS [Autism Diagnosis Observation Schedule (24)] ratings. The ADI-R scores for each main domain were 14 for reciprocal social interaction (B, 15 items, threshold of 10), 13 for verbal communication (Cv, 13 items, threshold of 8), 5 for stereotypies (D, 8 items, threshold of 3) and 5 for anomalies before the age of 3 years (5 items, threshold of 1). The ADOS scores were 5 in communication (threshold of 3) and 7 in social interaction (threshold of 6), with a total score of 12 (threshold of 10).

AA starting receiving bumetanide twice a day from 5 January 2011 (0.5 mg morning and 0.5 mg evening), and the treatment lasted 3 months. Biological tests carried out at baseline (D_0) and 7 days (D_7), 1 month (M_1), 2 months (M_2) and 3 months (M_3) after the treatment started included orthostatic hypotension, allergy, cramps, asthenia, diarrhoea, myalgia, arthralgia, vertigo and nausea. Blood tests included γ-glutamyltransferase, transaminases, alkaline phosphatases, glycaemia, uric acid and creatine, in addition to blood Na^+ and K^+.

Five clinical tests were carried out at baseline (D_0) and after 3 months of treatment (M_3):

1 *The Childhood Autism Rating Scale* [CARS, (25,26)].
2 *The Autism Diagnostic Observation Schedule* (24).
3 *The Aberrant Behaviour Checklist* [ABC, (27)].
4 *The Regulation Disorders Evaluation Grid* (RDEG) is a French scale that enables doctors to detect the level of deregulation and how slowly children are responding (28).
5 *The Repetitive and Restricted Behaviour scale* [RRB, (29)] is a 35-item standardized checklist rating on a 5-point scale from 0 (the behaviour is never expressed by the person) to 5 (the behaviour is severely expressed and characteristic of the person). Factorial analysis produces four clinical meaningful factors: sensorimotor stereotypes (F1), reaction to change (F2), restricted behaviours (F3) and modulation insufficiency (F4).

RESULTS

Table S1 shows the results of the different scales before and after 3 months of treatment. The CARS, ADOS, ABC, RDEG and RRB scores improved. The CARS, total severity score fell by 6 points and 12 items that were equal, or above, three at baseline fell to 7. The ABC, RDEG and RRB scores were divided by 1.5 or 2 in 3 months, and the total ADOS score was reduced by 9 points, especially in sub-domains B (reciprocal social interactions) and C (play).

The clinical examination revealed no side effects (orthostatic hypotension, allergy, cramps, asthenia, diarrhoea, myalgia, arthralgia, vertigo and nausea). Conventional blood tests were also unaffected (γ-glutamyltransferase, transaminases, alkaline phosphatases, glycaemia, uric acid and creatine). Body weight was not altered and blood Na^+ remained stable (Table S2). As K^+ was reduced to the inferior limit (3.5 mmol/L), AA received potassium gluconate syrup 4 months after treatment, leading to recuperation of normal K^+ (3.71 mmol/L) 1 month later.

DISCUSSION

Single case reports like the present results must be confirmed by double-blind randomized trials as they are hampered by placebo effects and the intrinsic limitations of population size. Nevertheless, our results raise the possibility of treating FRX children with bumetanide with a good benefit/risk ratio. The amelioration observed in AA is in accordance with our recent observations of an efficient action of bumetanide on ASD (non-FRX children) (13,14). GABAergic signals are altered in Fragile X mice (15–18,30), and we have recently measured intracellular chloride levels in neurons of Fragile X mice from birth to adulthood and found elevated levels associated with excitatory actions of GABA and benzodiazepines (Tyzio et al., paper submitted). Therefore, double-blind clinical assays of FRX patients with, and without, autistic traits will confirm or infirm the usefulness of bumetanide in FRX.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Scores of different evaluation scales before, and three months after, treatment.
Table S2 Weight and blood ions during the three months of treatment.

