CASE REPORT

The effect of bumetanide treatment on the sensory behaviours of a young girl with Asperger syndrome

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SUMMARY

Sensory behaviours were not considered as core features of autism spectrum disorders until recently. However, they constitute an important part of the observed symptoms that result in social maladjustment and are currently quite difficult to treat. One promising strategy for the treatment of these behaviours is the use of bumetanide, which was previously shown to reduce the severity of autism spectrum disorders. In this study, we proposed to evaluate sensory behaviours using Dunn's Sensory Profile after 18 months of bumetanide treatment in a 10-year-old girl with Asperger syndrome. Reported improvements covered a large range of sensory behaviours, including auditory, vestibular, tactile, multisensory and oral sensory processing. Although our results were limited to a single case report, we believe that our clinical observations warrant clinical trials to test the long-term efficacy of bumetanide to manage the sensory behaviours of people with autism spectrum disorders.

BACKGROUND

Impairments in social development associated with communication deficits, restricted interests and repetitive behaviours constitute the triad of autistic spectrum disorders (ASDs).[1 2] ASDs are associated with a failure to organise affective relationships[3] and a differential response to sensory experiences when compared with their peers without disabilities.[4] Individuals with ASD sometimes appear to avoid or seek ordinary tactile, visual, auditory and oral stimuli,[5 6] and the scientific and clinical literature,[7–10] together with the personal statements of individuals with ASD[11] yield a large range of examples. These sensory behaviours are classified into three categories, under-responsivity, over-responsivity and sensation seeking, and the same behaviours are often displayed successively by individuals with ASD.[5]

There are currently different types of support and treatment that alleviate the presentation of ASD to different extents.[12] With respect to the potential treatments for sensory dysregulation in ASD, there has been more interest in sensory-based therapies, including occupational therapy. With respect to pharmacotherapy, aripiprazole and risperidone are currently approved by the US Food and Drug Administration. Risperidone offers an emerging treatment for the irritability associated with ASD in children and adolescents.[13] Aripiprazole, which is generally used for the treatment of schizophrenia in adults and is not indicated to manage the core signs of ASD, has some side effects.[14 15] Recently, a novel therapeutic strategy has been proposed based on the use of bumetanide, a diuretic and chloride cotransporter antagonist.[16 17] This molecule reduces intracellular chloride, eliminating the aberrant excitatory actions of γ-aminobutyric acid (GABA). In ASD, GABA-ergic signalling is noted to be aberrant, with an imbalance between excitation and inhibition.[18 19] In this context, the intracellular concentration of chloride $[Cl-]_i$ is an important parameter. In adult neurones, the levels of $[Cl-]_i$ are kept low and the inhibitory transmitter GABA inhibits neurones. In contrast, for immature neurones, $[Cl-]_i$ levels are higher and GABA excites immature neurones, an action that highlights the wide range of actions in which GABA is engaged during brain maturation.[20] A persistent increase in $[Cl-]_i$ has been observed following a wide range of insults and in a variety of disorders, including ASD.[21–24] Moreover, GABAergic neurones are instrumental in sensory binding and higher cognitive functions.[25–27]

In a pilot study, bumetanide was used as a treatment for five children with ASD.[16] Data from this study showed improvements in the behavioural aspects of ASD. A double-blind randomised controlled trial of bumetanide was then performed, in which half of the children with ASD received bumetanide and the other half received placebo.[17] In this study, ASD symptoms were significantly ameliorated in 27 children [3–11 years) who were treated daily with bumetanide (1 mg) over the course of 3 months with no or few adverse events (eg, hypokalaemia). Improvements were noted on the Childhood Autism Rating Scale (CARS[28]), the Clinical Global Impression Scale (CGI[29]) and the Autism Diagnostic Observation Schedule (ADOS[30]) values for the most severe cases. Some patients were then maintained in open treatment. One of them presented with an interesting development of sensory behaviours, which are not yet part of the diagnostic criteria. Thus, we present here the clinical case of a young girl who had been treated with bumetanide for 18 months.

CASE PRESENTATION

We present a case of a female patient born in February 2002. She was the non-consanguineous couple's eldest child. She had a younger brother who was without health problems and was born in 2004. Her mother had a normal pregnancy and gave birth to this girl without any problems. At birth, she weighed 3250 g, was 50 cm long and had a head circumference of 35 cm. She was breastfed for 2 months. The neonatal period was not typical, as she had recurrent otitis and lactose intolerance.

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The patient had spoken her first words at 9–10 months of age and the first sentence at 16–18 months of age. Although the patient's language development appeared normal after this period, the parents reported a high frequency of stereotyped sentences. Autonomous walking occurred at 18 months of age and the child achieved daytime and night-time control at 30 months of age.

When the girl was 2 years, her parents first became worried about her social difficulties, for example, initiating contact with other children at the childcare centre. At the age of three, patient's difficulties worsened and she was then consulted with the school psychologist. At the age of 4 years and 4 months, she attended the French day care centre, CMP, where she received two psychotherapy sessions per week. At this time, she was diagnosed with ASD.

A complete diagnosis was made at the Centre de Ressources de Bretagne (CRA) in April 2010 when she was 8 years. Based on these direct clinical observations, a diagnosis of Asperger syndrome was made based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[1] and the International Classification of Diseases, 10th Revision (ICD-10)[31] criteria and was confirmed using the ADI-R (Autism Diagnostic Interview-Revised[32]) and the ADOS[30]) ratings. The ADI-R assesses the following domains: reciprocal social interaction, verbal communication, stereotypies and prior to 3 years of age anomalies. The patient received a score of 15 for reciprocal social interaction (B, 15 items, threshold of 10), 13 for verbal communication (Cv, 13 items, threshold of 8), 2 for stereotypies (D, 8 items, threshold of 3) and 2 for prior to 3 years of age anomalies (5 items, threshold of 1). The patient's ADOS scores for the domains of communication and social interaction were 6 (threshold of 3) and 8 (threshold of 6), respectively; the total score was 14 (threshold of 10).

TREATMENT

Beginning in January 2011, the patient began receiving 2 mg of bumetanide divided by three daily doses. The patient had received the treatment for 18 months at the time of our evaluation in June 2012. Biological tests were carried out at baseline, 7 days after the first bumetanide dose and each month after the treatment was initiated, and these included assessment for orthostatic hypotension, allergy, cramps, asthenia, diarrhoea, myalgia, arthralgia, vertigo and nausea. Blood tests included γ-glutamyl transferase, transaminases, alkaline phosphatases, glycaemia, uric acid and creatinine, in addition to blood Na^+ and K^+. After 18 months of treatment, a child psychiatrist rated the CGI improvement, a scale that was used to evaluate changes over time and the efficacy of the medication.

The completed diagnosis in 2010 also revealed numerous peculiarities in sensory behaviours that seemed to change after treatment. Thus, they were precisely examined by our paediatrician in 2012 at two different time points, prior to bumetanide treatment and after 18 months of treatment. Measurement was conducted using the Sensory Profile, a 125-item parent report questionnaire that describes responses to sensory events in daily life, evaluates sensory abnormalities and compares such abnormalities to the available normative data.[33] The Sensory Profile measures the degree to which children exhibit problems in the three following categories: sensory processing, modulation and behavioural and emotional responses. Each category contains subcategories that allowed for more detailed analyses (n=14; table 1). For this scale, the parent uses a five-point Likert scale to report how frequently the child uses a certain response to particular sensory events (ie, always, frequently, occasionally, seldom or never). Lower scores reflect poorer performance. Thus, for each subcategory, we had a total score and a performance category (category 1 is typical performance, category 2 is probable difference and category 3 is real difference). Here, we compared the change in performance category before and after treatment.

Of note, the patient did not receive concurrent therapy during this time period.

OUTCOME AND FOLLOW-UP

Before treatment

Table 1 presents the scores and performance categories for the Sensory Profile before and after 18 months of treatment with bumetanide.

The parental report revealed that the patient had typical performance in the following five subdivision areas: visual processing, modulation of movement affecting activity level and the three subcategories of behavioural and emotional responses: emotional and social responses, behavioural outcomes of sensory processing and items indicating thresholds for response. However, her sensory behaviours were different from the typical performance (ie, 4 with probable difference and 5 with real difference).

One of the patient's major difficulties was her sensory hypersensitivity. She was very sensitive to loud noises (eg, fireworks, hand clapping and jackhammers). Consequently, she had physical reactions with motor inhibition, dilated pupils and a need to urinate. In the presence of less intense noises (eg, vacuum cleaner, strong voice, etc), she would put her fingers in her ears and isolate herself. Her touch processing also showed differences from typical performance. For example, she could not wear thick or rough clothing. Tactile contact was so difficult that she wiped her skin whenever it came into contact with other people. Moreover, her sense of smell was very sensitive, as she could detect subtle odours without being bothered by them. These particular sensory behaviours led to disordered eating behaviour. She was very selective and did not try unknown types of food. She was very attentive to the type of food and did not mix two different types of food. She frequently had nausea during mealtimes and sometimes even vomited. Finally, she was unable to display pain and tolerated it without any problem, even with important nociceptive stimuli (eg, burn).

After 18 months of treatment

After 18 months of treatment, CGI improvement on global functioning received a score of two, which corresponded to a much improved clinical situation (not limited to sensory symptoms). Moreover, improvements in sensory behaviours, measured using the Sensory Profile, were reported. Of the 14 subcategories, changes were observed for 10 of them. Nine subcategories were noted to improve, which are as follows: auditory, vestibular, touch, multisensory and oral sensory processing as well as sensory processing related to endurance/tone, modulation related to body position and movement, modulation of sensory input and visual input affecting emotional responses and activity level. For example, the girl's parents reported that the patient no longer had a physical reaction to loud noises and could remain in a noisy room. Tactile contact with others was also no longer a problem. For example, she would allow an

Table 1 Scores and performance categories of the Sensory Profile[33] before and after 18 months of treatment with bumetanide

	Before		After		
	Score	Performance category	Score	Performance category	Change
Sensory processing					
Auditory processing	17/40	3	33/40	1	++
Visual processing	36/45	1	30/45	2	–
Vestibular processing	37/55	2	45/55	1	+
Tactile processing	52/90	3	76/90	1	++
Multisensory processing	20/35	3	30/35	1	++
Oral sensory processing	42/60	2	57/60	1	+
Sensory modulation					
Sensory processing related to endurance/tone	18/45	3	32/45	2	+
Modulation related to body position and movement	32/50	3	39/50	2	+
Modulation of movement affecting activity level	19/35	1	19/35	1	=
Modulation of sensory input affecting emotional responses and activity level	11/20	2	16/20	1	+
Modulation of visual input affecting emotional responses and activity level	12/20	2	16/20	1	+
Behavioural and emotional responses					
Emotional/social responses	61/85	1	72/85	1	=
Behavioural outcomes of sensory processing	22/30	1	29/30	1	=
Items indicating thresholds for response	15/15	1	15/15	1	=

Lower scores reflected poorer performance. Three performance categories were established, which are as follows: category 1 as typical performance, category 2 as probable difference and category 3 as real difference. The change was defined in the following way: improvement (+), stability (=) or decrease (–) of the performance studied.

unknown person to make up her face for a dance show. In addition, she was able to diversify the types of food she ate during her meals and no longer had nausea or vomiting with meals. Her nociceptive threshold continued to be higher than the norm; however, she could now name her pain (eg, when she was ill). Finally, we noticed decreases in performance for the subcategory of visual processing. This could be partially explained by parental report: the patient was currently in a research of visual aesthetics in which she expressed what she liked and disliked.

DISCUSSION

In this report, we described improvements in the sensory behaviours of a young girl with Asperger syndrome after 18 months of treatment with bumetanide. Improvements were not limited to one sensory modality and covered a large range of sensory behaviours (ie, auditory, vestibular, tactile, multisensory and oral sensory processing). This resulted in an improved quality of life for this young girl and her family. The improvements noted in this case expand data showing improvements after 3 months of treatment with bumetanide.[16 17] Thus, if previous literature showed that bumetanide could have a short-term impact on social interactions displayed by children with ASD, the present case study supports a possible long-term effect of this medication on sensory behaviours.

Treatment with another drug, aripiprazole, has been shown to be useful for treating sensory difficulties.[34] In their retrospective review, Fung *et al*[34] showed improvement in auditory processing and the modulation of visual input, which subsequently affected the emotional responses and activity level of 13 individuals with ASD after 24 weeks. However, aripiprazole is not recommended for use prior to the age of six. This is not the case for bumetanide, which may be prescribed from birth. Risperidone also had an impact on repetitive behaviours and especially on different sensory behaviours.[35] However, this medication has notable side effects, including, for example, weight gain, fatigue, drowsiness and drooling.[36]

Reducing impairment related to sensory behaviours constitutes a significant challenge for several reasons. Sensory behaviours have previously been observed in other people with Asperger syndrome and are generally reported in 30–100% of people with ASD.[5 37–41] Even if difficulties in sensory behaviours are not yet considered as core features of ASD (ie, deficits in social interaction, communication and stereotyped and restrictive behaviours), they reflect abnormal sensory integration and modulation in the central nervous system, resulting in maladaptive emotional and physical responses to environmental stimuli.[42] They are an important predictor of social maladjustment and are a source of aggression and behaviour problems, especially for people of low intellectual level.[41] The new DSM-V criteria incorporate sensory abnormalities into the restricted and repetitive behaviours cluster and are defined as hyper-reactivity or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment.[43]

A critical point of our report was the retrospective exploration of sensory behaviour change after 18 months of treatment. The parental report may have been distorted by the personal expectations of the parents. However, the large range of improvements and the numerous examples reported support the fact that bumetanide may have a long-term impact on sensory behaviours in ASD. One could argue that the improvements reported correspond to ordinary development, as sensory difficulties decrease with age.[44] However, they remain present despite maturation in ASD.[45] Finally, one could argue that a similar design could be applied to the 26 other children who were included in the randomised controlled trial; however, the situation is not so simple. For example, some patients were lost to follow-up, some had treatments that may have influenced sensory behaviours, etc. The remaining patients had different durations of treatment, which was dependent on the date that they enrolled in the initial study. Thus, we were not able to compare patients. Although our results were limited to a single case report, we believe that the finding of our report warrants clinical trials to test the long-term efficacy of bumetanide for sensory behaviours among people with ASD.

Learning points

- Sensory behaviours constitute an important part of the observed symptoms of autism spectrum disorders that are currently quite difficult to treat.
- Bumetanide was previously shown to reduce the severity of autism spectrum disorders.
- Improvements after treatment with bumetanide covered a large range of sensory behaviours after 18 months.

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REFERENCES

1 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 1994.
2 Wing L, Gould J. Severe impairments of social interaction and associated abnormalities in children: epidemiology and classification. *J Autism Dev Disord* 1979;9:11–29.
3 Rutgers AH, Bakermans-Kranenburg MJ, van Ijzendoorn MH, *et al*. Autism and attachment: a meta-analytic review. *J Child Psychol Psychiatry* 2004;45:1123–34.
4 Suarez MA. Sensory processing in children with autism spectrum disorders and impact on functioning. *Pediatr Clin N Am* 2012;59:203–14.
5 Ben-Sasson A, Hen L, Fluss R, *et al*. A metaanalysis of sensory modulation symptoms in individuals with autism spectrum disorders. *J Autism Dev Disord* 2009;39:1–11.
6 Rogers SJ, Ozonoff S. Annotation: what do we know about sensory dysfunction in autism? A critical review of the empirical evidence. *J Child Psychol Psychiatry* 2005;46:1255–68.
7 Kientz MA, Dunn W. A comparison of the performance of children with and without autism on the sensory profile. *Am J Occup Ther* 1996;51:530–7.
8 Ornitz EM, Lane SJ, Sugiyama T, *et al*. Startle modulation studies in autism. *J Autism Dev Disord* 1993;23:619–37.
9 Ornitz EM. Autism at the interface between sensory and information processing. In: Dawson G. ed. *Autism: nature, diagnosis and treatment*. New York: Guilford, 1989:174–207.
10 Watling RL, Deitz J, White O. Comparison of sensory profile scores of young children with and without autism spectrum disorders. *Am J Occup Ther* 2001;55:416–23.
11 Grandin T. An inside view of autism. In: Schopler E, Mesibov G. eds. *High-functioning individuals with autism*. New-York: Plenum Press, 1992.
12 Howlin P, Magiati I, Charman T. Systematic review of early intensive behavioral interventions for children with autism. *Am J Intellect Dev Disabil* 2009;114:23–41.
13 Scott LJ, Dhillon S. Risperidone: a review of its use in the treatment of irritability associated with autistic disorder in children and adolescents. *Paediatr Drugs* 2007;9:343–54.
14 Kirino E. Efficacy and safety of aripiprazole in child and adolescent patients. *Eur Child Adolesc Psychiatry* 2012;21:361–8.
15 Croxtall JD. Aripiprazole. *CNS Drugs* 2012;26:155–83.
16 Lemonnier E, Ben-Ari Y. The diuretic bumetanide decreases autistic behaviour in five infants treated during 3 months with no side effects. *Acta Paediatr* 2010;99:1885–8.
17 Lemonnier E, Degrez C, Phelep M, *et al*. A randomised controlled trial of bumetanide in the treatment of autism in children. *Transl Psychiatry* 2012;2:e202.
18 Chao HT, Chen H, Samaco RC, *et al*. Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. *Nature* 2010;468:263–9.
19 Pizzarelli R, Cherubini E. Alterations of gabaergic signaling in autism spectrum disorders. *Neural Plast* 2011;297:1–12.
20 Ben-Ari Y, Gaiarsa JL, Tyzio R, *et al*. GABA: a pioneer transmitter that excites immature neurons and generates primitive oscillations. *Physiol Rev* 2007;87:1215–84.
21 Blaesse P, Airaksinen MS, Rivera C, *et al*. Cation-chloride cotransporters and neuronal function. *Neuron* 2009;61:820–38.
22 Nardou R, Yamamoto S, Chazal G, *et al*. Neuronal chloride accumulation and excitatory GABA underlie aggravation of neonatal epileptiform activities by phenobarbital. *Brain* 2011;134:987–1002.
23 Boulenguez P, Liabeuf S, Bos R, *et al*. Down-regulation of the potassium-chloride cotransporter KCC2 contributes to spasticity after spinal cord injury. *Nat Med* 2010;16:302–7.
24 Simard JM, Kahle KT, Gerzanich V. Molecular mechanisms of microvascular failure in central nervous system injury—synergistic roles of NKCC1 and SUR1/TRPM4. *J Neurosurg* 2010;113:622–9.
25 Singer W. Synchronization of cortical activity and its putative role in information-processing and learning. *Annu Rev Physiol* 1993;55:349–74.
26 Lisman JE, Idiart MAP. Storage of 7+/-2 short-term memories in oscillatory subcycles1. *Science* 1995;267:1512–15.
27 Murthy VN, Fetz EE. Coherent 25-Hz to 35-Hz oscillations in the sensorimotor cortex of awake behaving monkeys. *Proc Natl Acad Sci USA* 1992;89:5670–4.
28 Schopler E, Reichler RJ, Devellis RF, *et al*. Toward objective classification of childhood autism—Childhood Autism Rating-Scale (CARS). *J Autism Dev Disord* 1980;10:91–103.
29 Busner J, Targum SD. The Clinical Global Impressions Scale: applying a research tool in clinical practice. *Psychiatry* 2007;4:28–37.
30 Lord C, Risi S, Lambrecht L, *et al*. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord* 2000;30:205–23.
31 World Health Organization. *The composite international diagnostic interview, Version 1.1*. Geneva: Researcher's Manual, 1994.
32 Lord C, Rutter M, Le Couteur A. Autism diagnostic interview-revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* 1994;24:659–85.
33 Dunn W. *The sensory profile: user's manual*. San Antonio, TX: Psychological Corporation, 1999.
34 Fung LK, Chahal L, Libove RA, *et al*. A retrospective review of the effectiveness of aripiprazole in the treatment of sensory abnormalities in autism. *J Child Adolesc Psychopharmacol* 2012;22:245–8.
35 McDougle CJ, Scahill L, Aman MG, *et al*. Risperidone for the core symptom domains of autism: results from the study by the Autism Network of the Research Units on Pediatric Psychopharmacology. *Am J Psychiatry* 2005;162:1142–8.
36 Anagnostou E, Hollander E. Four drugs can improve autism's repetitive behaviors. *Curr Psychiatry* 2006;5:55–64.
37 O'Neill M, Jones RS. Sensory-perceptual abnormalities in autism: a case for more research? *J Autism Dev Disord* 1997;27:283–93.
38 Dawson G, Watling R. Interventions to facilitate auditory, visual, and motor integration in autism: a review of the evidence. *J Autism Dev Disord* 2000;30:415–21.
39 Baker AE, Lane A, Angley A, *et al*. The relationship between sensory processing patterns and behavioural responsiveness in autistic disorder: a pilot study. *J Autism Dev Disord* 2008;38:867–75.
40 Rapin I, Tuchman RF. Autism: definition, neurobiology, screening, diagnosis. *Pediatr Clin N Am* 2008;55:1129–46.
41 Hilton CL, Harper JD, Kueker RH, *et al*. Sensory responsiveness as a predictor of social severity in children with height functioning autism spectrum disorders. *J Autism Dev Disord* 2010;40:937–45.
42 Iarocci G, McDonald J. Sensory integration and the perceptual experience of persons with autism. *J Autism Dev Disord* 2006;36:77–90.
43 APA. *Diagnostic and statistical manual of mental disorders*.5th edn. American Psychiatric Publishing, 2013.
44 Phoebe PP, Siu AM. A comparison of patterns of sensory processing in children with and without developmental disabilities. *Res Dev Disab* 2009;30:1468–80.
45 Leekam SR, Nieto C, Libby SJ, *et al*. Describing the sensory abnormalities of children and adults with autism. *J Autism Dev Disord* 2007;37:894–910.