

A clinical trial of combined anti-androgen and anti-heavy metal therapy in autistic disorders

David A. GEIER¹ & Mark R. GEIER²

1. Vice-President of the Institute of Chronic Illnesses, Silver Spring, MD, USA.
2. President, The Genetic Centers of America, USA

Correspondence to: Mark R. Geier, MD., PhD.
14 Redgate Ct., Silver Spring, MD 20905, USA
PHONE: +1-(301)989-0548
FAX: +1-(301)989-1543
EMAIL: mgeier@comcast.net

Submitted: June 19, 2006

Accepted: October 17, 2006

Key words: **autistic; DMSA; heavy metal; testosterone**

Neuroendocrinol Lett 2006; 27(6):833–838 PMID: 17187010 NEL270606A17 © Neuroendocrinology Letters www.nel.edu

Abstract

BACKGROUND: A medical hypothesis has suggested that some autism spectrum disorders (ASDs) may result from interactions between the methionine cycle-transsulfuration and androgen pathways following exposure to mercury.

METHODS: The IRB of the Institute for Chronic Illnesses approved the present study. A novel treatment was utilized combining LUPRON® (leuprolide acetate, TAP Pharmaceuticals, Inc.) and CHEMET® (meso-2, 3-dimercaptosuccinic acid – DMSA, McNeil Consumer Products Company) on 11 consecutive children with ASDs.

RESULTS: A significant ($p < 0.01$) overall improvement from the 70–79th percentile of severity (median baseline score=87) at baseline to the 40–49th percentile of severity (median end of study period score=63) at the end of the study was observed for patients treated for a median of approximately 4 months. Significant improvements in sociability, cognitive awareness, behavior, and clinical symptoms/behaviors of hyperandrogenemia were also observed. Significant decreases in blood androgens and increases in urinary heavy metal concentrations were observed. Minimal drug adverse effects were found.

CONCLUSION: This study provides the first clinical evidence for the benefit that combined anti-androgen and anti-heavy metal therapy may have on some children with ASDs. Additional studies should examine androgen and heavy metal mechanisms of action in ASDs, and future ASD treatment protocols should consider androgens and heavy metals.

Conflict of interests: David Geier has been a consultant in cases before the no-fault National Vaccine Injury Compensation Program and civil litigation regarding vaccines/biologics. Dr. Mark Geier has been a consultant and expert witness in cases before the no-fault National Vaccine Injury Compensation Program and civil litigation regarding vaccines/biologics. David Geier and Dr. Mark Geier have a patent pending for the treatment of autistic disorders.

Introduction

Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by impairments in social relatedness and communication, repetitive behaviors, abnormal movement patterns, and sensory dysfunction that can manifest between 12 and 24 months of age [7,9]. In addition to behavioral impairment, autistic persons have a high prevalence of gastrointestinal disease and dysbiosis [20], autoimmune disease [15], mental retardation [5], and premature puberty [1,9,18]. Autistic disorders also affect many more males than females, occurring at a ratio of at least 4:1.

While genetic factors are recognized as being important in the pathogenesis of ASDs, researchers have reported that exposure to mercury can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autistic disorders, and that these similarities extend to neuroanatomy, neurotransmitters, and biochemistry [2–4,14]. It has been reported, "...mercury can alter cell number and cell division; these impacts have been postulated as modes of action for the observed effects in neuronal development, and as a result the potential implications of such observations are evident when evaluated in context with research showing that altered cell proliferation and focal neuropathologic effects have been linked to specific behavioral deficits (e.g. autism)" [8]. A recent review has suggested that autistic children have been found to have significantly higher exposure to mercury than controls, and autistic children had significantly increased body-burdens of mercury resulting from biochemical and genomic susceptibilities within detoxification pathways [13]. Additionally, biochemical examinations of children with autistic disorders have suggested that they have significantly increased levels of androgens relative to controls [1,9,18].

It has previously been suggested as a medical hypothesis that some ASDs may result from interactions between the methionine cycle-transsulfuration and androgen pathways following exposure to mercury [10]. It was suggested that children experiencing such a condition would have an elevated body-burden of heavy metals and have increased androgens. Based upon this knowledge, treatment modalities were suggested to attempt to dually lower the body-burden of heavy metals and decrease androgen levels in children with ASDs, in the hopes that addressing the steroid hormone pathways, in addition to treatments that successfully lower heavy metal body-burdens, would work synergistically to improve clinical outcomes [10].

Furthermore, the underpinnings of this previous medical hypothesis have been clinically evaluated in children with ASDs [9]. It has been observed in a consecutive series of children with ASDs that they had significantly increased androgen metabolites and significantly decreased methionine cycle-transsulfuration metabolites relative to controls. These same ASD children were also found to have a significant increase in potentially hyper-

androgen-related behaviors. It was suggested substances that significantly lower glutathione levels (i.e. mercury) may establish a multiplier loop of interaction between the methionine cycle-transsulfuration and androgen pathways, and may result in increased androgen metabolites and decreased methionine cycle-transsulfuration metabolites.

The purpose of the present clinical trial was to employ a combined anti-androgen and anti-heavy metal treatment in consecutive series of children with ASDs that presented to the Genetic Centers of America, and to evaluate its effect on clinical behaviors.

Materials and Methods

The Institutional Review Board (IRB) of the Institute for Chronic Illnesses (Office for Human Research Protections, US Department of Health and Human Services IRB number: IRB00005375) approved the present experimental study, and informed consent was obtained from each patient. In the present study, an open-label clinical trial was conducted on 11 consecutive children with previously diagnosed (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) regressive ASDs (Autism or Pervasive Developmental Delay – Not Otherwise Specified) [19] that presented to the Genetic Centers of America from November 2004 through January 2006 (two children were excluded from the present study that deviated from the treatment protocol). Table 1 summarizes the study profile of the children treated in the present study.

The criteria for entry into the present study was that the children had to have exposure to mercury in their medical history, and evidence of elevated serum testosterone, serum/plasma DHEA, or serum androstenedione (LabCorp, Inc.). Additionally, these children were negative for Rett's Syndrome, Angelman/Prader Willi Syndrome, Fragile-X Syndrome, chromosomal abnormalities, chromosomal sub-telomere abnormalities, inherited metabolic abnormalities, polychlorinated biphenyls/chlorinated pesticide exposure, kidney function abnormalities, thyroid function abnormalities, liver function abnormalities (LabCorp, Inc.), brain structural abnormalities (CT or MRI head scan), and adrenal abnormalities (abdominal ultrasound).

The treatment protocol employed in the present study consisted of administering each child a 0.2 mL test-dose of subcutaneous injected daily LUPRON® (leuprolide acetate, TAP Pharmaceuticals). Each child was carefully observed for three days to exclude any possible adverse events. The children were then administered an intramuscular injection of LUPRON DEPOT® (28 day – 15 mg, TAP Pharmaceuticals, Inc.). Children also were supplemented with subcutaneously injected daily LUPRON® dosing, so that overall children were started on a dose of 50 µg of Lupron/kg bodyweight/day. This level was selected based as compatible with that observed by Tanaka et al. as a dose of LUPRON® that would significantly reduce androgen levels [16]. Three days following starting of the

Table 1. Study profile of children with autism spectrum disorders that presented for outpatient care to the Genetic Centers of America from November 2004 through January 2005 and were treated in the present study

	Regressive autism spectrum disorder group
Autistic Disorder (n)	82% (9)
Pervasive Developmental Delay – Not Otherwise Specified (n)	18% (2)
Number of males/females (ratio)	10/1 (10:1)
Race	
Caucasian	91%
Minority	9%
Median age in years (range)	9 (6–14)
Median year of birth (range)	1996 (1991–1999)
Median Number of Days Enrolled in the Study (range)	111 (60–196)
Residence^a	
Northeast	27%
Midwest	9%
Mountain/Plains/South Central	9%
Southeast	46%
West	9%

^aMidwest: IN. Mountain/Plains/South Central: KS. Northeast: MA, NJ. Southeast: DE, MD, VA. West: CA.

Table 2. An evaluation of the effects of treatment on skills in the study group of children with autism spectrum disorders using the Autism Treatment Evaluation Checklist (ATEC)¹

	Median Overall Score	Median Communication Score	Median Sociability Score	Median Cognitive Awareness Score	Median Behavior Score
Baseline [Percentile]	87 [70–79]	10 [30–39]	18 [60–69]	18 [60–69]	35 [80–89]
End of Study Period [Percentile]	63 [40–49]	11 [40–49]	12 [40–49]	14 [40–49]	22 [50–59]
p-value²	<0.01	NS	<0.05	<0.005	<0.05

¹Autism Research Institute, San Diego, CA

²The non-parametric Mann-Whitney U test statistic was employed to determine statistical significance.

LUPRON DEPOT® and the subcutaneous daily LUPRON®, children were begun on an oral dose of CHEMET® 100 mg capsules (CHEMET® (*meso*-2, 3-dimercaptosuccinic acid – DMSA, McNeil Consumer Products Company) at 10 mg/kg bodyweight. This dose was administered three times per day in the morning, mid-day, and night and repeated every other day throughout the treatment period. This level was selected to be similar to that observed by Bradstreet et al. as a dose of DMSA that would significantly increase urinary heavy metal excretion [6]. If severe gastrointestinal disturbances (i.e. severe diarrhea or severe constipation) were observed following oral CHEMET®, trans-dermal DMSA was to be administered according to the same treatment schedule as the oral CHEMET®. On the alternate days when the children were not receiving CHEMET®, vitamin and mineral supplementation was administered. On day 28 children were administered their second intramuscular injection of LUPRON DEPOT® (28 day – 15 mg), and the children continued to be administered additional

intramuscular injections of LUPRON DEPOT® every 28 days. Patients were monitored as successive doses of LUPRON DEPOT® were administered for persistent clinical/laboratory signs of increased androgens, and patients were supplemented with subcutaneous injections of LUPRON® dosing and/or oral ANDROCUR® 100 mg capsules (cyproterone acetate, Schering AG) as clinically necessary.

Patients assessed in the present study were on the therapy for a minimum of 2 months and a maximum of 7 months. Laboratory testing was conducted on each patient at baseline and at approximately 3 months of treatment to assess first voided morning urine heavy metal levels (including: arsenic, lead, and mercury), serum testosterone levels, essential mineral levels and thyroid, kidney, and liver testing (LabCorp, Inc.). The tests collected on each patient at baseline and at approximately 3 months into the therapy were collected in the morning.

Table 3. An evaluation of the effects of treatment on essential minerals levels in the study group of children with autism spectrum disorders

	Serum Potassium [mmol/L]	Serum Calcium [mg/dL]	Serum Iron [µg/dL]	Serum Magnesium [mg/dL]	Serum Copper [µg/dL]	Serum Zinc [µg/dL]
Baseline [range]	4.1 [3.6–4.4]	10 [9.7–10.3]	67 [60–94]	2.05 [2–2.1]	95 [73–106]	102 [84–270]
~3 Months [range]	3.9 [3.5–4.8]	9.9 [9.6–11]	82 [32–102]	2.05 [2–2.5]	106 [81–124]	103 [101–216]
p-value¹	NS	NS	NS	NS	NS	NS

¹The non-parametric Mann-Whitney U test statistic was employed to determine statistical significance.

A clinical examination was undertaken for each patient to evaluate clinical symptoms/behaviors of hyperandrogenemia such as early growth spurt, early secondary sexual changes, body and facial hair, and aggressive behaviors at baseline and at the end of the study period for each child. Autism Treatment Evaluation Checklist (ATEC) (Autism Research Institute, San Diego, CA) evaluations were conducted prior to beginning the protocol on each child and at the end of the study period for each child. The ATEC quantitatively evaluates (using a numeric scoring system) skills in a number of areas, including speech language/communication, sociability, sensory/cognitive awareness, and health/physical/behavior.

The results of testing in the present study were evaluated using the non-parametric Mann-Whitney U test statistic in StatsDirect (Version 2.4.2) and a p -value < 0.05 was considered significant.

Results

Table 2 summarizes the effects of the treatment protocol employed in the present study on skills in the study group of children with ASDs. It was observed among the children treated in the present study that there was

a significant overall improvement from the 70–79th percentile of severity (median baseline score=87) at baseline to the 40–49th percentile of severity (median end of study period score=63) at the end of the study. Additionally, it was observed in the specific areas of sociability, cognitive awareness, and behavior that there were significant improvements among treated children when evaluating baseline measurements in comparison to those obtained at the end of the study period. It was also observed for the clinical examinations undertaken for each patient in the present trial at baseline and at the end of the study period that there were significant reductions in their clinical symptoms/behaviors of hyperandrogenemia such as early growth spurt, early secondary sexual changes, body and facial hair, and aggressive behaviors.

Among collected first voided morning urine samples tested for heavy metals (including arsenic, lead, and mercury) a significant ($p < 0.05$) increase from a baseline median=0 ug/L (range=0–15) to an approximately 3 month median=2.5 ug/L (range=0–112) in heavy metal concentrations was observed. It was observed that serum testosterone levels showed a significant ($p < 0.05$) decrease from a baseline median=1.96 multiples of the mean (age- and sex-adjusted reference values) to an approximately

Figure 1. A summary of disruption and opposition behaviors at school¹ from January 19, 2006 through March 31, 2006 by one the patients examined in the present study while being on the protocol²
¹The school was unaware that medical treatment had been initiated on the patient.
²The patient began the protocol starting on January 10, 2006.

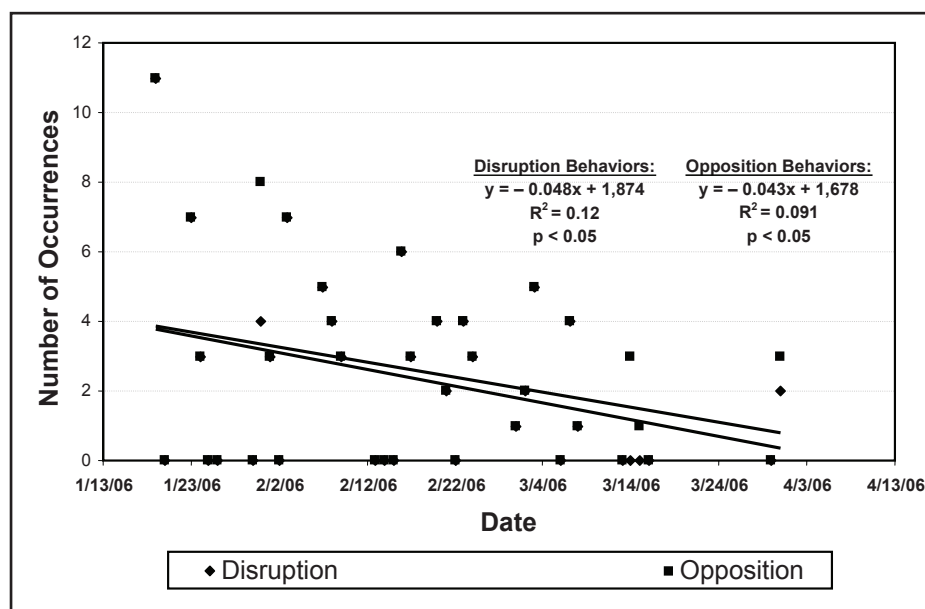


Table 4. A summary of skills mastered at school¹ by one the patients examined in the present study while being on the protocol

Reporting Quarter	Skills Mastered
4 th Reporting Quarter 2003–2004 School Year	0 Skills Mastered
Treatment Initiated	
2 nd Reporting Quarter 2004–2005 School Year	21 Skills Mastered Uses eating utensils appropriately, Washes hands independently, Takes care of own toileting, Observes likenesses and differences in objects, Observes likenesses and differences in pictures, Classifies objects according to color, Classifies objects according to shape, Has left/right orientation, Follows oral directions, Cooperates in group activities, Accepts adult guidance, Accepts consequences of own behavior, Demonstrates adequate self-control, Follow school rules, Respects rights and property of others, Demonstrates good manners, Traces simple lines, Runs, Jumps, Hops, and Throws a ball
4 th Reporting Quarter 2004–2005 School Year	40 Skills Mastered ² Off/on outer garments, Recognizes and names body parts, Recognizes name in print, Writes name from memory, Classifies objects by size, States full name, Initiates greetings and farewells, Responds to greetings and farewells, Speaks in short phrases, Uses simple sentences, Attends to the speaker, Attempts new tasks in a positive manner, Traces name, Copies name, Catches a ball, Participates in group singing, Responds to rhythms and music, Participates in art activities, and Participates in good preparation activities

¹The school was unaware that medical treatment had been initiated on the patient.

²All of the skills mastered during the 2nd Reporting Quarter continued to be mastered during the 4th Reporting Quarter. These are the new skills mastered as of the end of the 4th Reporting Quarter.

3 months median=1.16 multiples of the mean (age- and sex-adjusted reference values).

Table 3 summarizes the effects of the treatment employed on essential minerals levels among the children treated in the present study. It was observed that the treatment protocol employed in the present study did not result in significant differences in serum potassium, calcium, iron, magnesium, copper, or zinc when comparing baseline measurements with those obtained at approximately 3 months into the treatment protocol. It was found among the patients treated in the present study that the treatment protocol employed did not significantly affect kidney, thyroid or liver function tests.

Discussion

In the present study, a novel treatment protocol was employed in children with ASDs. It consisted of significantly lowering androgen levels by using LURPON[®], while also chelating by using CHEMET[®] to remove potentially increased body-burdens of heavy metals.

It was observed that the treatment protocol employed in the present study resulted in significant quantitative improvements in the children participating in the trial using the ATEC scoring system. It was found that there were specific significant improvements in overall, sociability, cognitive awareness, and behavior scores at the end of the treatment relative to baseline. The parents of all eleven children undergoing the treatment protocol reported what they considered to be significant improvements in socialization, cognition, and behaviors of their children. Additionally, it was observed for

specific patients that had independent assessments by school evaluators, who were not aware that the children were receiving treatment, that there were significant improvements in general school skills mastered and in disruptive/oppositional behavior at the end of the treatment period relative to baseline as summarized for two patient examples in Table 4 and Figure 1.

It was also observed that the treatment protocol employed in the present study resulted in minimal significant adverse health effects. It was found that essential minerals, kidney function tests, thyroid function tests, and liver function tests revealed no significant abnormalities among the ASD children receiving the protocol in the present study. The patients' parents also reported no significant adverse health effects of the treatment protocol employed. Furthermore, while long-term follow-up is not presently available for the patients treated in the present study for effects on reproductive function, it has been previously reported that long-term LUPRON[®] treatment of children with premature puberty had no adverse effects on future reproductive function [17].

In evaluating the effects of the drugs employed in the present study, it was observed that they produced a significant impact on the laboratory measures employed to evaluate urinary heavy metal and testosterone levels. The impact observed was consistent with their described pharmacological activity. It was found that LUPRON[®] administration resulted in a significant approximately 2-fold drop in serum testosterone levels over the course of an approximately 3 months period among the children with ASDs treated in the present study relative to pretreatment levels. This type of significant decrease in

serum testosterone levels is consistent with observations made in children with premature puberty following LURPON® administration [16]. The present study also showed that administration of CHEMET® significantly increased urinary levels of heavy metals in comparison to pretreatment levels. This type of significant increase in urinary heavy metal levels is consistent with previous observations made in ASD children following DMSA therapy [6].

In considering the observed significant improvement in clinical presentation of the patients treated in the present study, it is important to understand beyond the previously reported improvements observed in children with ASDs following chelation therapy [12], the potential effects that androgens may have on behavior in ASDs. Baron-Cohen et al. have evaluated the potential neurological effects androgens may have on behavior, and have observed that androgens are capable of producing similar behavioral traits as those observed in autistic children [1]. Furthermore, in recent studies of other genetic disorders that result in increased androgen levels (i.e. congenital adrenal hyperplasia), it has been observed that these children had significantly increased autistic-like behaviors relative to controls [11].

As a result, since the present study employed therapeutic agents that were designed to lower androgen levels, and significant decreases in androgen levels were observed, the present treatment protocol presents a novel method for helping to significantly reduce autistic-like behaviors. It was observed that in some of the patients examined in the present study significant autistic behavior improvements were observed to occur within days of the administration of the LUPRON® (i.e. better sleep patterns, improvement in attention and hyperactivity, and increased socialization) prior to the administration of chelation therapy. Additionally, it is also clear that the LUPRON® therapy may have significantly helped to ameliorate clinical symptoms/behaviors of hyperandrogenemia such as early growth spurt, early secondary sexual changes, body and facial hair, and aggressive behaviors that may be observed among some children with ASDs.

Conclusion

This study provides the first clinical evidence for the benefit that combined anti-androgen and anti-heavy metal therapy may have for some children with ASDs. In light of the fact that both androgens and heavy metals appear to be significantly involved in the clinical presentation of some children with ASDs, additional studies should be conducted to evaluate their impact on ASDs, and potential treatments should consider addressing these two aspects of ASDs.

Study Funding: This study was funded in part by the non-profit Institute of Chronic Illnesses (Silver Spring, MD) through a grant from the Brenen Hornstein Autism

Research & Education (BHARE) Foundation (Elk Grove, IL).

REFERENCES

- 1 Baron-Cohen S, Knickmeyer RC, Belmonte MK. Sex differences in the brain: implications for explaining autism. *Science*. 2005; **310**: 819–23.
- 2 Bernard S, Enayati A, Redwood L, Roger H, Binstock T. Autism: a novel form of mercury poisoning. *Med Hypotheses*. 2001; **56**: 462–71.
- 3 Bernard S, Enayati A, Roger H, Binstock T, Redwood L. The role of mercury in the pathogenesis of autism. *Mol Psychiatry*. 2002; **7** Suppl 2: S42–3.
- 4 Blaxill MF, Redwood L, Bernard S. Thimerosal and autism? A plausible hypothesis that should not be dismissed. *Med Hypotheses*. 2004; **62**(5): 788–94.
- 5 Bolte S, Poustka F. The relation between general cognitive level and adaptive behavior domains in individuals with autism with and without comorbid mental retardation. *Child Psychiatry Hum Dev*. 2002; **33**: 165–72.
- 6 Bradstreet J, Geier DA, Kartzinell JJ, Adams JB, Geier MR. A case-control study of mercury burden in children with autistic spectrum disorders. *J Am Phys Surg*. 2003; **8**: 76–9.
- 7 Eigsti IM, Shapiro T. A systems neuroscience approach to autism: biological, cognitive, and clinical perspectives. *Ment Retard Dev Disabil Res Rev*. 2003; **9**: 205–15.
- 8 Faustman EM, Silbernagel SM, Fenske RA, Burbacher TM, Ponce RA. Mechanisms underlying Children's susceptibility to environmental toxicants. *Environ Health Perspect*. 2000 Mar; **108** Suppl 1: 13–21.
- 9 Geier DA, Geier MR. A clinical and laboratory evaluation of methionine cycle-transsulfuration and androgen pathway markers in children with autistic disorders. *Horm Res*. (in press).
- 10 Geier MR, Geier DA. The potential importance of steroids in the treatment of autistic spectrum disorders and other disorders involving mercury toxicity. *Med Hypotheses*. 2005; **64**: 946–54.
- 11 Knickmeyer R, Baron-Cohen S, Fane BA, Wheelwright S, Mathews GA, Conway GS, Brook CG, Hines M. Androgens and autistic traits: a study of individuals with congenital adrenal hyperplasia. *Horm Behav*. 2006; **50**: 148–53.
- 12 Lonsdale D, Shamberger RJ, Audhya T. Treatment of autism spectrum children with thiamine tetrahydrofuryl disulfide: a pilot study. *Neuro Endocrinol Lett*. 2002; **23**: 303–8.
- 13 Mutter J, Naumann J, Schneider R, Walach H, Haley B. Mercury and autism: accelerating evidence? *Neuro Endocrinol Lett*. 2005; **26**: 439–46.
- 14 Redwood L, Bernard S, Brown D. Predicted mercury concentrations in hair from infant immunizations: cause for concern. *Neurotoxicology*. 2001; **22**: 691–7.
- 15 Sweeten TL, Bowyer SL, Posey DJ, Halberstadt GM, McDougale CJ. Increased prevalence of familial autoimmunity in probands with pervasive developmental disorders. *Pediatrics*. 2003; **112**: E420–4.
- 16 Tanaka T, Hibi I, Kato K, Saito S, Shimizu N, Suwa S, Nakahima H. A dose finding study of a super long-acting luteinizing hormone-releasing hormone analog (leuprolide acetate depot, TAP-144-SR) in the treatment of central precocious puberty. The TAP-144-SR CPP Study Group. *Endocrinol Jpn*. 1991; **38**: 369–76.
- 17 Tanaka T, Niimi H, Matsuo N, Fujieda K, Tachibana K, Ohyama K, Satoh M, Kugu K. Results of long-term follow-up after treatment of central precocious puberty with leuprorelin acetate: evaluation of effectiveness of treatment and recovery of gonadal function. The TAP-144-SR Japanese Study Group on Central Precocious Puberty. *J Clin Endocrinol Metab*. 2005; **90**: 1371–6.
- 18 Tordjman S, Ferrari P, Sulmont V, Duyme M, Roubertoux P. Androgenic activity in autism. *Am J Psychiatry*. 1997; **154**: 1626–7.
- 19 Werner E, Dawson G. Validation of the phenomenon of autistic regression using home videotapes. *Arch Gen Psychiatry*. 2005; **62**: 889–95.
- 20 White JF. Intestinal pathology in autism. *Exp Biol Med* (Maywood). 2003; **228**: 639–49.