CLINICAL STUDY

Bio-behavioral model of aggression in autism spectrum disorders-pilot study

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ABSTRACT

Children with autism spectrum disorders (ASD) have a high rate of irritability and aggressive symptoms which have significant impact on their lives, families and society. The etiology of aggression in humans is likely complex and includes both biological and behavioral causes. Biological approaches have focused on hormones and neurotransmitters that are hypothesized to contribute to the etiology and clinical manifestation of aggressive behavior in humans. Testosterone is a male sex hormone and some studies suggest that it can play a role in the complex etiology of aggressive behavior. Two specific subtypes of aggression have been identified: explosive and non-explosive. Explosive aggression is accompanied by a raged affect and is usually more dangerous and not immediately responsive to behavioral treatment. We propose that individuals with ASD and explosive aggression will have higher androgen activity and higher arousal than neurotypical children and children with ASD without explosive aggression. We employed a unique method for aggression assessment- functional behavioral analysis- to obtain objective and quantitative measures of aggression and arousal signs. In our pilot study, we proposed to determine bio-behavioral model of explosive aggression in children with ASD which will predict which children will be most responsive to antiandrogen therapy and behavioral therapy *(Tab. 1, Fig. 1, Ref. 31)*. Text in PDF *www.elis.sk.*
KEY WORDS: autism spectrum disorders, aggression, testosterone, functional behavioral analysis.

Introduction

Autism spectrum disorders (ASD) are a set of heterogeneous neurodevelopmental conditions, characterized by early-onset difficulties in social communication and unusually restricted, repetitive behavior and interests. The worldwide population prevalence is about 1 % (1). Aggressive behavior is commonly reported in individuals with ASD and other intellectual development disabilities. A recent large-scale study found that prevalence of aggression in children with ASD was 68 % of parents reporting and 49 % of non-caregivers (2). These behavior disorders often place children at risk of harming themselves and others and are the single most cited reason for costly inpatient hospitalization, long-term residential placement, and restrictive living and treatment environments. Moreover all these factors lead to psychological disturbances in families along with social and economic costs to society (3).

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Clinical research, influenced by the work of Feshbach and others has frequently referred to two forms of aggression in humans (4–6). The first form is called *affective, reactive, defensive, impulsive, or hot-blooded aggression.* This type of aggression is defined as a violent response to physical or verbal aggression initiated by others that is relatively uncontrolled and emotionally charged. In contrast, the second form of aggression is referred to as *predatory, instrumental, proactive, or cold-blooded aggression.* This type of aggression is characterized as controlled, purposeful aggression lacking emotions that is used to achieve a desired goal, including escape of aversive events, access to positive reinforcing events, and the domination and control of others. For purposes of this paper, we will use the terms *explosive aggression* to refer to aggression accompanied by high arousal and rageful affect and *non-explosive aggression* to refer to aggression in the absence of high arousal and rageful affect.

Aggression in humans is a function of a complex interplay between biological (neurochemical imbalance in the brain) and behavioral (operant reinforcement contingency that maintains the behavior) causes. Diagnosis and treatment of aggression and other problems of behavior in ASD should include bio-behavioral approaches and involve inter-professional cooperation between physicians/psychiatrists and psychologists. This model takes into consideration the multi-faceted nature of the origins of aggression rather than relying on one model (7, 8).

Biological approaches have focused on hormones and neurotransmitters that are hypothesized to contribute to the etiology

and clinical manifestation of aggressive behavior in humans. This research has led to specific pharmacotherapeutic approaches to address neurochemical imbalances in the brain. For example, dopamine blockers such as antipsychotics (e.g. risperidone) have been observed to be effective in treating some aspects of autism (9), specifically hyperactivity, stereotypies, aggression, and self-injury (10). Some studies have shown that levels of dopamine metabolites in cerebrospinal fluid (11) are significantly elevated in individuals with autism. Risperidone blocks dopamine receptors in some areas of the brain (12) and may result in decreased dopamine effect which may lead to decreased aggression in individuals with autism. The literature also suggests that testosterone may be involved in the etiology of aggression in humans as another contributing biological factor. Testosterone is a male sex hormone, but in fact, it regulates sexual arousal and many other processes in both genders (13). Several studies have examined the relationship between salivary/plasmatic testosterone levels and aggression in various populations with mixed results. Some of them describe no clear relationship between the plasma/salivary testosterone levels and aggressive behavior in populations of pre-pubertal children (14), in male undergraduates (15) and in healthy male adults (16). However, there are studies showing strong positive correlations between testosterone (and testosterone precursor) levels in plasma/saliva and aggression (e.g., in populations of male children with conduct disorders, male/female adolescents and adults, and male prisoners (17–23).

There are several studies investigating the relationship between testosterone and symptoms of ASD. However, we have found only one study showing an association between testosterone and aggression in these individuals. Tordjman et al. measured plasma testosterone in nine patients with ASD compared to a group of neurotypical children. The nine adolescent children with ASD were divided into three groups comprised of (1) those aggressive against others, (2) those who are self-mutilating, and (3) a group that had the withdrawal characteristic of ASD. The group that exhibited aggression against others had higher testosterone levels than any of the comparison subjects. However, the other autistic patients showed normal adrenal androgen levels (24).

We conducted a preliminary test of bio-behavioral model of explosive aggression in children with ASD. Our primary hypothesis was that individuals with ASD and explosive aggression will have higher androgen activity and higher arousal than neurotypical children and children with ASD without explosive aggression. We used a unique method for aggression assessment- functional behavioral analysis to obtain objective, quantitative measures of aggressive behavior that are reflective of explosive and non-explosive aggression. The case studies presented here replicate the essential findings from Tordjman et al. that suggest testosterone may play explosive role in aggression in ASD patients (24).

Methods

Participants

Participants were three pre-pubertal male patients from Slovakia with aggressive behavior, tantrum-like behaviors, noncompli-

ance, flopping, and disrobing/wetting. The parent of one patients reported that behavior problems were accompanied by rageful affect (see Tordjman et al.'s reference to explosive aggression) (24).The study inclusion criteria were defined according to the ICD 10 F84.1 Child autism reported by parents or care givers. Exclusion criteria were comorbid psychiatric diagnoses and endocrine diseases.

Peter (5 year-old boy) engaged in: (a) Type 1 Aggression (aggression without rage) – open hand hits and kicking. This type of aggression also occurred with a sad affect and crying; (b) Type 2 Aggression (aggression with rage) – open hand hits with his hands, kicking, head butts, and bites that break the skin. This type of aggression was of high intensity, explosive and co-occurred with a raged affect; and (c) Tantrums–screams, loud cries, and throwing objects and property destruction. His tantrums co-occurred with aggressive behavior and an angry/rageful affect. Marek (3 year-old) engaged in (a) Type 1 Aggression – open hand hits with one or two hands, and (b) Tantrums–crying, falling to the floor, kicking objects, loud cries, and whining. Tantrums co-occurred with aggressive behavior, and throwing objects and property destruction. Andrej (8 year-old) who engaged in (a) Type 1 Aggression (aggression without rage) – open hand hits with both hands, biting, pinching, and hair pulling. Biting often broke the skin; and (b) Tantrums – whining, loud vocalizations, and disruptive behavior. All participants had mild cognitive delays, spoke using one to four words and lived with their parents.

The control group consisted of 9 typically developing pre-pubertal male participants from the pediatric unit of Children's faculty hospital in Bratislava, Slovakia, matched by gender and age.

Aggression assessment

All three ASD patients received a behavioral mental health assessment using three methodologies: (a) Structured functional assessment interview with parents. This interview solicits information about a wide range of problem behaviors and concentrates the discussion on the environmental events surrounding the two or three behaviors of greatest concern to parents (25); (b) Reinforcer assessment interview was conducted via telephone prior to the initial visit with each family (i.e., the Reinforcer Assessment for Individuals with Severe Disabilities (26); and (c) Parent-run functional analysis (see below). Indicators of high autonomic involvement (explosive aggression) included raged facial expressions, extreme motor agitation, and screaming observed during parent-run functional analyses.

One parent of each patient conducted a *parent-run functional analysis* in the presence of the senior behavioral psychologist who guided the assessment procedures. Parents were trained individually to present a pre-determined set of motivating conditions to each child in sessions that lasted 5 to 10 min. Sessions alternated in a quasi-random order to provide within-subject experimental control for the assessment (27). All sessions were conducted with the patient, his mother and one or two behavior therapists in a 3 x 4 m room with an adjacent observation room with one-way observation window.

For the parent-run functional analysis, parents were instructed to introduce a single motivating condition during each session.

Parents responded to occurrences of problem behaviors in the way they would normally at home and no prescribed consequences for problem behavior were arranged (28, 29). Participants were individually exposed to the following functional behavioral assessment conditions: (a) *non-demand interaction* – the patient's mother interacted with him on a nearly continuous basis, allowed access to his preferred activities, and placed no performance demands on him; (b) *task demands* – The patient's mother provided both easy and difficult tasks to perform consisting of matching, sorting, simple counting, letter tracing and sequencing tasks while seated together at a table; (c) *restricted access to an iPad video* – the parent told the patient that video time was over after approximately 4 min of video access and removed the iPad; (d) *low adult attention* – the patient was allowed to have access to preferred activities while his mother either read a magazine or engaged in conversation with a therapist; and (e*) transitions* – one patient (Marek) reportedly engaged in problem behaviors during transitions from one preferred activity to another. In this condition, Marek's mother asked him to transition between two identical activities at two separate tables in the room after engaging in the activity for approximately 4 min. All assessment conditions simulated naturally occurring situations in the home as reported by all three patients' parents.

Data were collected on each child's target problem behaviors as operationally defined above. Indicators of high autonomic involvement (explosive aggression) included raged facial expressions, extreme motor agitation, and screaming which were observed only in Peter. One or two observers used a continuous count within 10-s interval recording procedure for Type 1 and Type 2 aggression and for Tantrums for Andrej. These data were then converted into a rate measure. Behaviors defined as tantrums that varied considerably in duration were recorded using a continuous 10-s partial-interval recording procedure, and converted into a percentage of 10-s intervals measure. Inter-observer agreement (IOA) was calculated for all behaviors measured a minimum of 45 % of the sessions for all patients. IOA was calculated on a point-by-point or interval-by-interval basis and averaged 93.5 % across all three patients.

Biochemical analyses

Blood drawing for testosterone was conducted in all patients (taken between 8:00- 10:00 am, in June/July 2013) according to standardized procedure and was obtained within one month of the behavioral mental health assessment for all ASD and control patients. Total testosterone levels were measured by ELISA kit. The ELISA kit was used according to manufacturer's instructions (DRG Instruments GmbH, Marburg, Germany). The intra-assay coefficient of variation was 3.3 % and inter-assay coefficient of variation was 6.2 %.

Results

Functional Analysis Findings

Figure 1 graphically depicts the results of the parent-run functional analyses. Quantitative levels of target behaviors are represented on the y-axes across assessment conditions located along the x-axes. Peter engaged in the highest levels of Type 1 Aggres-
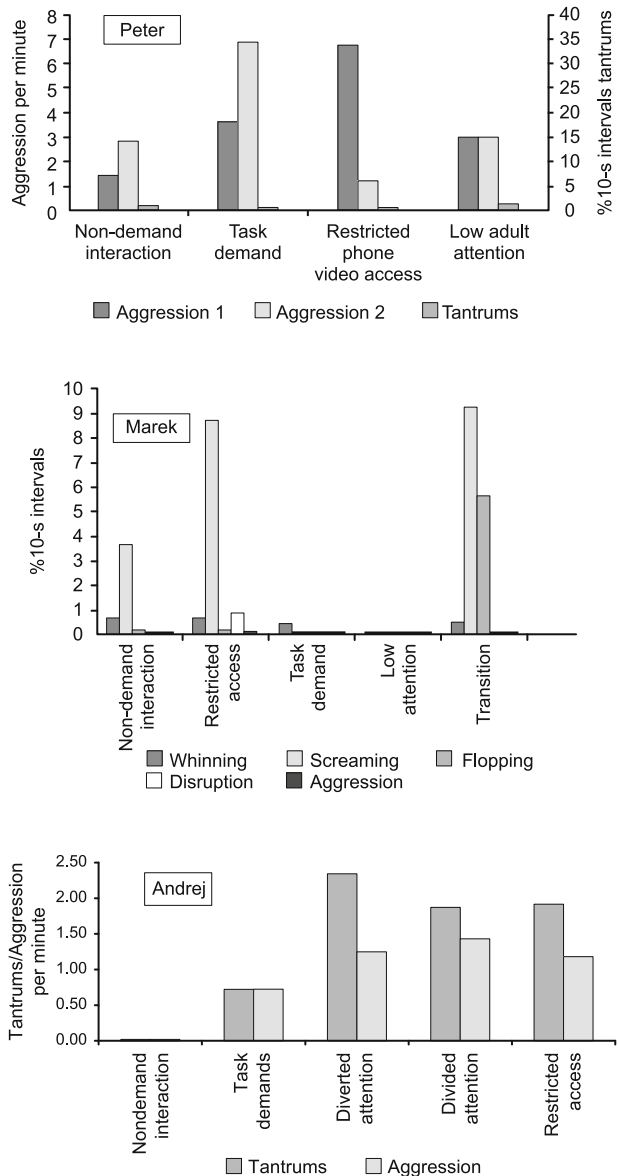

Fig. 1. Levels of problem behavior across different conditions of the parent-run functional analysis for Peter , Marek and Andrej.

sion in the test conditions of task demands, restricted phone video access and low adult attention. Although levels of Type 2 Aggression were by comparison much lower, Peter engaged in high levels of tantrums across all assessment conditions and these tantrums reliably co-occurred with an angry/rageful affect that sometimes included aggression. Marek's aggressive behavior was categorized as Type 1 (without arousal or rage) but was only observed to occur once during the entire assessment. His parents did not describe Marek's aggression in terms consistent with Type 2 Aggression. By contrast, Marek engaged in high levels of tantrums (with absence of high arousal and rage) especially in the restricted access and transition conditions including the separate behaviors shown in the middle panel of Figure 1. Andrej also engaged in

Tab. 1. Plasmatic testosterone and observed indicators of rage, explosive aggression and increased autonomic arousal during the functional analysis by individual patient and ASD and Control group means, standard deviations and standard error of measurement.

Patient	Plasmatic testosterone nmol/l	Indicators of rage/autonomic arousal
Peter	0.88722098**	Yes
Marek	0.27986813	No
Andrej	0.65826892	No
Group	Autism Spectrum Disorders	Age & Gender Matched Control
Mean	0.60845267667	0.44183671500
SD	0.30672563420	0.21487841526**
SEM	0.17708812747	0.07162613842
N	3	9

** Peter's plasmatic testosterone in nmol/l was 2.07 SD above the Control Group mean

frequent rates of aggression and tantrum-like behaviors across all test conditions and nearly zero rates during the non-demand interaction condition which serves as a control for the other test conditions. The bottom panel of Figure 1 shows that Andrej was similarly sensitive to the diverted (mother reading a magazine) and divided attention (mother conversing with a therapist) conditions and restricted access to videos. Andrej was also more sensitive to difficult tasks than easy tasks.

Plasmatic Testosterone and Indicators of Rage/Arousal

Only one of the three children with ASD engaged in aggression that co-occurred with rageful affect and indicators of high arousal during episodes of problem behavior. Although Peter displayed low levels of Type 2 Aggression, they all occurred in combination with Tantrums that included rageful behavior. As shown in Table 1, Peter's plasmatic testosterone level was 2.07 standard deviations above the mean of the age and gender matched control group, indicating an abnormally high level of plasmatic testosterone (24).

The functional analysis results allowed us to design individualized behavioral treatments for all three children that were effective. However, given the focus of this article, detailed treatment protocols and results may be obtained from the first author upon request.

Discussion and conclusion

In our pilot study we replicated the findings of Tordjman et al (24). We found that only one of the three children with ASD engaged in aggression that co-occurred with rageful affect and indicators of high arousal during episodes of problem behavior and this child´s plasmatic testosterone level was 2.07 standard deviations above the mean of the age and gender matched control group, indicating an abnormally high level of plasmatic testosterone. However in future research it is necessary to increase the sample size and to study the relationship between testosterone and explosive aggression in more comprehensive way, taking into consideration complex androgen activity (30) not only total testosterone plasmatic levels (e.g. sensitivity of androgen receptor, activity of enzymes involved in testosterone metabolism). Moreover arousal associated with explosive aggression might be measured more exactly using heart rate variability/skin conduc-

tance measurements in probands, helping to distinguish between the aggression subtypes.

Children in our pilot study were ages 3 to 8. Although one child showed clear signs of rageful aggression and correlated tantrums, none of the children engaged in aggression that posed high-risk of injury to others. However, with older and larger children presenting with severe aggression accompanied by rage and high arousal, adjunctive anti-androgen therapy may prove especially useful.

Among the main limitations of most past studies conducted in order to determine the relationship between testosterone levels and aggression in humans are the methods of measurement of aggressive symptoms. These measurements are based on subjective evaluation in scales/inventories completed by tested individuals or on rankings provided by caregivers/parents (13–22). In our pilot study we used specific method for assessments of aggressive behavior- functional behavioral assessment based on principles of applied behavioral analysis (ABA) (31). During functional behavioral analysis we were directly able to observe aggressive behavior and signs of high arousal in real time helping to classify the possible aggression subtypes (e.g. explosive aggression).Assessment of aggressive behavior based on experimental design during functional behavioral analysis is useful in order to obtain objective and quantitative characteristics such as function, frequency, intensity, and duration of aggressive episodes (27). In our future studies, these characteristics could be correlated with plasmatic testosterone levels (and other components of androgen activity) and thus define more specifically the relationships between this hormone and behavior.

In summary, the presented pilot work introduces a bio-behavioral model for the diagnosis and treatment of aggression in ASD patients. We implemented objective methods of measurement of problem behavior and we observed signs of explosivity in children with aggression and ASD. Our findings are consistent with those of Tordjman (24) who found that only three of nine children with autism who engaged in explosive aggression had elevated levels of testosterone compared to their counterpart ASD patients who did not engage in aggression and neurotypical controls. Our study, although with only a single patient, showed the same results as Tordjman et al insofar as the only child with ASD who engaged in explosive aggression had abnormally high levels of testosterone. We believe these findings are sufficiently promising to warrant further pursuit of a bio-behavioral approach to the treatment of children with autism. In the future we would like to extend our study and enroll more probands, objectively measure arousal using heart rate variability measurement, and measure other components of androgen activity (activity of aromatase and 5 alpha reductase, androgen sensitivity etc.).

References

1. Lai MC, Lombardo MV, Baron-Cohen S. Autism. Lancet 2014; (383): 896–910.

2. Kanne SM, Mazurek MO. Aggression in children and adolescents with ASD: prevalence and risk factors. J Autism Dev Disord 2011; (41): 926–937.

3. Hartley SL, Barker ET, Seltzer MM et al. The relative risk and timing of divorce in families of children with an autism spectrum disorder. J Fam Psychol 2010; (24): 449–457.

4. Dodge KA. The structure and function of reactive and proactive aggression. In: D. Pepler and K. Rubin, Editors, The development and treatment for childhood aggression., Erlbaum, Hillsdale, NJ (1991).

5. Feshbach S. Dynamics and morality of violence and aggression: some psychological considerations. Am Psychol 1971; (26): 281–292.

6. Scarpa A, Raine A. Psychophysiology of anger and violent behavior. Psychiatr Clin North Am 1997; (20): 375–394.

7. Mace FC, Mauk JE. Bio-behavioral diagnosis and treatment of self-injury. Mental Retardation and Developmental Disabilities Research Reviews 1995; (1): 104–110.

8. Frazier TW, Youngstrom EA, Haycook T et al. Effectiveness of medication combined with intensive behavioral intervention for reducing aggression in youth with autism spectrum disorder. J Child Adolesc Psychopharmacol 2010; (20): 167–177.

9. Wink LK, Plawecki MH, Erickson CA, Stigler KA, McDougle CJ. Emerging drugs for the treatment of symptoms associated with autism spectrum disorders. Expert Opin Emerg Drugs 2010; (15): 481–494.

10. Young JG, Kavanagh ME, Anderson GM, Shaywitz BA ,Cohen DJ. Clinical neurochemistry of autism and associated disorders. J Autism Dev Disord 1982; (12): 147–165.

11. Gillberg C, Svennerholm L. CSF monoamines in autistic syndromes and other pervasive developmental disorders of early childhood. Br J Psychiatry 1987; (151): 89–94.

12. Kozielska M, Johnson M, Pilla Reddy V et al. Pharmacokinetic-pharmacodynamic modeling of the D(2) and 5-HT (2A) receptor occupancy of risperidone and paliperidone in rats. Pharm Res 2012; (29): 1932–1948.

13. Zatko T, Matejovicova B, Boledovicova M, Vondrakova M, Bezakova A, Sirotkin AV. Growth and obesity and its association with plasma level of steroid hormones and insulin-like growth factor-I (IGF-I) in Slovak female students. Bratisl Lek Listy 2013; (114): 573–580.

14. Constantino JN, Grosz D, Saenger P, Chandler DW, Nandi R, Earls FJ. Testosterone and aggression in children. J Am Acad Child Adolesc Psychiatry 1993; (32): 1217–1222.

15. Campbell A, Muncer S, Odber J. Aggression and testosterone: Testing a bio-social model. Aggressive Behavior 1997; (23): 229–238.

16. Anderson RA, Bancroft J, Wu FC. The effects of exogenous testosterone on sexuality and mood of normal men. J Clin Endocrinol Metab 1992; (75): 1503–1507.

17. Barzman DH, Mossman D, Appel K et al. The Association Between Salivary Hormone Levels and Children's Inpatient Aggression: A Pilot Study. Psychiatr Q 2013.

18. Dabbs JM Jr, Frady RL, Carr TS, Besch NF. Saliva testosterone and criminal violence in young adult prison inmates. Psychosom Med 1987; (49): 174–182.

19. Dmitrieva TN, Oades RD, Hauffa BP, Eggers C. Dehydroepiandrosterone sulphate and corticotropin levels are high in young male patients with conduct disorder: comparisons for growth factors, thyroid and gonadal hormones. Neuropsychobiology 2001; (43): 134–140.

20. Golubchik P, Mozes T, Maayan R, Weizman A. Neurosteroid blood levels in delinquent adolescent boys with conduct disorder. Eur. Neuropsychopharmacol. 2009; (19): 49–52.

21. Scerbo AS, Kolko DJ. Salivary testosterone and cortisol in disruptive children: relationship to aggressive, hyperactive, and internalizing behaviors. J Am Acad Child Adolesc Psychiatry 1994; (33): 1174–1184.

22. van Goozen SH, Matthys W, Cohen-Kettenis PT, Thijssen JH, van Engeland H. Adrenal androgens and aggression in conduct disorder prepubertal boys and normal controls. Biol Psychiatry 1998; (43): 156–158.

23. Yu YZ, Shi JX. Relationship between Levels of Testosterone and Cortisol in Saliva and Aggressive Behaviors of Adolescents. Biomed. Environ. Sci. 2009; (22): 44–49.

24. Tordjman S, Ferrari P, Sulmont V, Duyme M, Roubertoux P. Androgenic activity in autism. Am. J. Psychiatry 1997; (154): 1626–1627.

25. Steege MW, Watson TS, Gresham FM (Eds). Conducting School-Based Functional Behavioral Assessments, Second Edition: A Practitioner's Guide (2nd ed.), Guilford Press, New York (2009).

26. Fisher WW, Piazza CC, Bowman LG, Amari A. Integrating caregiver report with systematic choice assessment to enhance reinforcer identification. Am J Ment Retard 1996; (101): 15-25.

27. Iwata BA, Dorsey MF, Slifer KJ, Bauman KE, Richman GS. Toward a functional analysis of self-injury. J Appl Behav Anal 1994; (27): 197–209.

28. Carr EG, Durand VM. Reducing behavior problems through functional communication training. J. Appl. Behav. Anal. 1985; (18): 111–126.

29. Cooper LJ, Wacker DP, Sasso GM, Reimers TM, Donn LK. Using parents as therapists to evaluate appropriate behavior of their children: application to a tertiary diagnostic clinic. J. Appl. Behav. Anal. 1990; (23): 285–296.

30. Durdiakova J, Ostatnikova D, Celec P. Testosterone and its metabolites-modulators of brain functions. Acta Neurobiol Exp (Wars) 2011; (71): 434–454.

31. Fisher WW, Piazza CC, Roane HS. Handbook of applied behavior analysis. Guilford Press. New York (2011).