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The relationship between balance and urinary cortisol and neopterin in autistic children

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ABSTRACT

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by stereotyped behavior, restricted interests and social/communicative deficits. The physiological etiology of ASD is not currently understood, however recent research has implicated dysregulation of the immune system as a central feature. The interplay between the stress systems, the immune system and the brain has been well-documented and implicated in other psychiatric and neurological disorders. This interplay suggests a role for the hypothalamic-pituitary-adrenal (HPA) axis in the etiology of ASD. We assessed levels of urinary cortisol and neopterin as markers of immune function and HPA activation in a cohort of 50 children from the central Johannesburg region. Additionally, we used the Autism Treatment Evaluation Checklist to assess autistic symptomatology and the Bruininks-Oseretsky Motor Proficiency Test (Second Edition) (BOT-2) to assess motor skills. No relationships were found between cortisol and autistic symptomatology. No relationships were found between neopterin and any of the other measures. However, a relationship was observed between urinary cortisol and performance on balance-related tasks from the BOT-2 ($P < 0.05$). Our findings support a theory of neurological interconnectedness between postural modulation and activation of the stress system, which has not previously been documented in children with ASD.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition without a clearly elucidated biological basis. However, recent evidence indicates a crucial role for dysregulation of the immune system in ASD [1]. In addition to the social, communicative, and behavioural aspects of ASD, motor impairments such as abnormalities in gait, postural control and praxis in ASD have also been documented [2–4].

Croonenberghs et al. [5] argue that products of the inflammatory response system may be associated with some of the behavioral symptoms of ASD, such as social withdrawal, resistance to novelty and sleep disorders. Increasing evidence for an immune dysregulation component of ASD has been accumulating [6]. Relationships between the brain and immune system are well-documented, with pro-inflammatory markers showing associations with sickness behaviors [7]. The brain and immune system are known to modulate one another, primarily via the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis [8].

Therefore, this study investigated relationships between ASD symptoms and markers of immune function and HPA activation. Data was collected from children diagnosed with ASD in the Johannesburg area (South Africa) looking at autistic characteristics, motor skills, socio-economic status and biomarkers of inflammation and the brain-immune axis. Two biomarkers were chosen for assessment, namely neopterin and cortisol, as both substances are physiologically involved with the brain-immune axis and have shown dysregulation in ASD previously [9–11].

2. Methods

2.1. Ethics and informed consent

The experimental protocol for this study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (clearance number M180767). Informed consent was obtained from the parents or legal guardians of all participants. Assent was additionally

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obtained from each child participating in the study. If a child expressed (at any point during the study) that they did not wish to complete a certain data collection activity, this was respected. Due to participants not completing every aspect of data collection, there are differences in the sample sizes of the various measurements.

2.2. Participants

Children who had been previously diagnosed with ASD were recruited through the Centre for Autism Research and Education (CARE) and the Fight with Insight clinic at the Children's Memorial Institute (CMI). A diagnosis of ASD by a primary healthcare provider is a requirement for the enrollment of a child into CARE or CMI. Participants were not excluded for any health reason, but all participants were of medium-to low-support needs, as these participants were better able to understand and complete the motor skills assessment.

2.3. Experimental protocol

Subjective ASD characteristics and motor skills were assessed in each participant. Urine samples were collected to assess levels of cortisol and neopterin via enzyme-linked immunosorbent assay (ELISA). The details of each assessment are provided in the sub-sections below. This was a cross-sectional study and all assessments and samples for each participant were collected within a month of each other.

2.3.1. Urine samples

Urine samples were collected by participants at home with the aid of their parent/caregiver. Parents/caregivers were asked to collect the samples from their child in the morning before 7 a.m. to obtain the morning void sample for each participant. Specific gravity of each urine sample was assessed using a portable refractometer (ATC, reference number 312), previously calibrated with distilled water, to correct ELISA results according to overall concentration of the urine. The chosen analytes, neopterin and cortisol, are both easily measured in the urine using ELISAs, only requiring correction by specific gravity to account for how hydration status may affect concentrations [12].

2.3.2. Cortisol and neopterin ELISAs

Concentrations of cortisol and neopterin in each urine sample were assessed using ELISA protocols. Concentrations of cortisol in the urine were assessed using an ELISA kit from Elabscience Biotechnology, Wuhan, China (Lot no. TKDP1LUSZU). Concentrations of neopterin in the urine were assessed using an ELISA kit from Wuhan Fine Biotech Co., Ltd., Wuhan, China (Lot no. H3413G062 Y).

ELISA results were obtained as absorbance values, from which concentration values were interpolated using the standard curve. Specific gravity of each sample was used to correct concentrations of neopterin and cortisol to a reference specific gravity of 1.030 (the mean specific gravity of the sample) according to the Levine-Fahy equation (where SG refers to specific gravity):

$$\text{Concentration}_{\text{SG normalized}} = \text{Concentration}_{\text{specimen}} \cdot (\text{SG}_{\text{reference}} - 1/(\text{SG}_{\text{specimen}} - 1)$$

2.3.3. The Autism Treatment Evaluation Checklist (ATEC)

A caregiver (parent, guardian, or teacher) of each participant completed an ATEC form assessing the participant. The ATEC scores autistic symptom severity in four different domains, namely: (1) Speech/Language/Communication, (2) Sociability, (3) Sensory/Cognitive Awareness and (4) Health/Physical/Behaviour. Each domain consists of between 14 and 25 items that are each scored on a Likert-type scale. Scores for each domain in addition to an overall score were obtained for each participant by numerically rating the possible answers. A lower score in each domain indicates greater severity, with the maximum scores for each domain being 28, 40, 36 and 75 respectively. The maximum possible score for the ATEC overall is therefore 179. The ATEC is freely available to download from https://www.aitinstitute.org/AIT_FORMS/ATEC.pdf and does not require training to administer. The ATEC has been found to be consistent and reliable in measuring autism symptoms, although it may be less sensitive in assessing autism trait severity at the extreme ends of the autism spectrum, i.e. individuals with very high or very low support needs [13]. Scoring on the ATEC has shown to correlate strongly with scores on the Childhood Autism Rating Scale, and the ATEC has been found to have high test-retest reliability and high concurrent validity [14].

2.3.4. The Bruininks-Oseretsky Motor Proficiency Test (BOT-2)

The lead researcher (a physiological scientist) assessed each participant individually using the BOT-2 motor assessment kit. No specific professional training is required to conduct the assessment, as the process follows rules laid out in the manual and training video. The BOT-2 was developed in the United States based on standards from normally-developing children [15] and has been used previously to quantify motor improvements in ASD children [16,17]. The BOT-2 has been found to be a reliable and internally consistent motor skills measurement tool [18], and has shown high test-retest reliability with an intra-class correlation coefficient of 0.80 for time reliability [19]. The BOT-2 assesses motor proficiency in four different domains, as shown in Table 1. Each domain is scored on two sub-domains and each sub-domain consists of between 5 and 8 motor activities completed by the participant. Performance in each domain and sub-domain was scored by the lead researcher according to rules laid out by the BOT-2 manual, where a higher score indicates a higher proficiency in that domain. A composite score for overall motor proficiency was obtained from all four domains following the process laid out in the BOT-2 manual. The raw scores for performance in each domain and sub-domain were converted to an age-appropriate score using tables provided in the BOT-2 manual. The maximum score for each domain (and the composite score) is 80 points, while the maximum score for each subdomain is 35 points.

2.4. Data analysis and statistical testing

Each data set was tested for normality using the Shapiro-Wilk test. The relationships between urinary cortisol, urinary neopterin, ATEC and BOT-2 score (domain scores as well as composite scores) for each participant were assessed using correlation analysis. Pearson's correlation was used for normally-distributed variables, while Spearman's correlation was used for variables that were not normally-distributed. All statistical tests were performed using the core package and the plyr and tidyr packages in R statistical software (R Core Team, 2016;

Table 1
Domains and sub-domains of the Bruininks-Oseretsky Motor Proficiency Test (Second Edition).

Domains	Sub-domains
Fine manual Control	Fine Motor Precision
	Fine Motor Integration
Manual Co-ordination	Manual Dexterity
	Upper-limb Co-ordination
Body Co-ordination	Bilateral Co-ordination
	Balance
Strength & Agility	Running Speed & Agility
	Strength

Wickham, 2011, 2017) and significance was set at P = 0.05.

3. Results

3.1. Sample characteristics

Data were collected from 50 participants in total, and the mean age of the sample was 13.38 ± 2.51 years. The sample was 92 % male (n = 46) and 8 % female (n = 4), which was reflective of the sex proportions observed in the schools from which the sample was drawn. The race of the sample was 84 % Black (n = 42), 8 % White (n = 4) and 8 % Indian (n = 4). Not all measures were collected for all 50 participants, as some refused to participate in certain procedures or provide certain information, and some of the processes were impacted by COVID-19 shutdowns. Table 2 provides summary statistics for the levels of cortisol and neopterin found in the urine of the cohort, as well as the specific gravity. The levels of cortisol and neopterin found in the cohort were similar to levels found previously in healthy subjects [20,21].

3.2. Correlations between autistic characteristics, motor skills and urinary measures of cortisol and neopterin

No significant relationships were found between any of the ATEC scores and any of the urinary measures (Table 3, n = 30). Scores for Balance and Running Speed & Agility were found to negatively correlate with urinary cortisol concentrations (Table 4, n = 19). There were no other significant relationships between urinary measurements and BOT-2 scores (Table 4, n = 19). No corrections for multiple correlations were run, as the sub-domains of the BOT-2 are each designed to measure independent and distinct constructs, and so the risk of Type I errors occurring is therefore expected to be minimal.

Table 2
Summary statistics for urinary cortisol, neopterin and specific gravity in a sample of autistic children (n = 40).

	Summary statistics
Urine Specific Gravity	1.03 ± 0.01
Urinary cortisol concentration (ng/ml)	38 (17.1–65.4)
Urinary neopterin concentration (ng/ml)	2.8 (1.9–4.8)
Corrected* urinary cortisol (ng/ml)	39.1 (23.6–68)
Corrected* urinary neopterin (ng/ml)	4.2 ± 2.1

Corrected to a reference specific gravity of 1.03 using the Levine-Fahy equation. Normally distributed variables are presented as mean ± standard deviation, while non-normally distributed variables are presented as median (interquartile range).

Table 3
Summary statistics for relationships between ATEC scores and urinary measures of cortisol and neopterin (after correction to a standard specific gravity of 1.030) for an autistic sample (n = 30).

	Urinary Cortisol		Urinary Neopterin	
	Correlation co-efficient (95 % CI)	p-value	Correlation coefficient (95 % CI)	p-value
Speech/Language/ Communication	0.089 (−0.322 – 0.386)	0.634	0.261 (−0.088 – 0.573)	0.157
Sociability	−0.179 (−0.517 – 0.167)	0.336	0.072 (−0.350 – 0.359)	0.699
Sensory/Cognitive Awareness	−0.026 (−0.300 – 0.407)	0.890	0.192 (−0.049 – 0.599)	0.300
Health/Physical/ Behaviour	0.100 (−0.247 – 0.453)	0.591	0.219 (−0.384 – 0.323)	0.237
ATEC Composite	−0.063 (−0.330–0.378)	0.737	0.128 (−0.256 – 0.445)	0.492

ATEC = Autism Treatment Evaluation Checklist, CI = confidence interval. Significance was set at p < 0.05.

Table 4
Summary statistics for relationships between BOT-2 scores and urinary measures of cortisol and neopterin (after correction to a standard specific gravity of 1.030) for an autistic sample (n = 19).

	Urinary Cortisol		Urinary Neopterin	
	Correlation co-efficient (95 % CI)	p-value	Correlation co-efficient (95 % CI)	p-value
Fine Motor Precision	−0.244 (−0.215–0.642)	0.314	0.208 (−0.272–0.605)	0.392
Fine Motor Integration	−0.442 (−0.714–0.081)	0.058	−0.152 (−0.567–0.325)	0.534
Fine Manual Control	−0.388 (−0.594–0.288)	0.101	−0.090 (−0.523–0.380)	0.714
Manual Dexterity	−0.067 (−0.650–0.201)	0.786	−0.291 (−0.658–0.188)	0.226
Upper-limb Co-ordination	0.008 (−0.424–0.483)	0.974	0.098 (−0.373–0.528)	0.691
Manual Co-ordination	−0.067 (−0.500–0.405)	0.786	−0.028 (−0.476–0.432)	0.909
Bilateral Co-ordination	−0.295 (−0.659–0.187)	0.220	−0.017 (−0.484–0.423)	0.946
Balance	**−0.466 (-0.694–0.124)***	**0.044***	−0.106 (−0.528–0.374)	0.666
Body Co-ordination	−0.453 (−0.712–0.088)	0.051	−0.102 (−0.531–0.369)	0.678
Running Speed & Agility	**−0.483 (-0.735–0.040)***	**0.036***	−0.098 (−0.481–0.426)	0.688
Strength	−0.342 (−0.670–0.167)	0.152	−0.177 (−0.584–0.301)	0.468
Strength & Agility	−0.447 (−0.716–0.081)	0.055	−0.104 (−0.533–0.367)	0.671
BOT-2 Composite	−0.342 (−0.670–0.167)	0.152	−0.108 (−0.536–0.364)	0.660

BOT-2 = Bruininks-Oseretsky Motor Proficiency Test Second Edition. Significant relationships are given in bold and marked with an asterisk (*). Significance was set at p < 0.05.

4. Discussion

In this study we assessed levels of urinary cortisol and neopterin in a cohort of children diagnosed with ASD in the Johannesburg area. We did not find evidence for increased levels of urinary cortisol or neopterin in this sample. Additionally, we looked at relationships between urinary cortisol and neopterin, and motor impairment and ASD characteristics. No relationships were found between urinary cortisol or neopterin and ASD characteristics. We found evidence for a relationship between higher cortisol concentration in the urine and decreased performance on balance tasks and agility.

The average level of urinary neopterin in the sample is comparable to that found previously in healthy subjects [20], which suggests that the neopterin levels are not abnormal in this cohort of ASD children. Previously, neopterin has been found to be increased in ASD subjects [9,10,22], but our findings do not agree with this observation. Neopterin is closely associated with activation of cellular immunity, as macrophages release neopterin in response to stimulation by T-cell-derived IFN-γ [23]. Neopterin is also a marker of oxidative stress [24]. Our data suggest that oxidative stress and activation of cellular immunity are not significantly increased in this cohort, and therefore are unlikely to be integral to the physiological etiology underlying the symptoms of autism. However, it must be noted that further study with a matched non-ASD control group from the same region would strengthen this finding.

There is very little existing data on levels of urinary cortisol in ASD as cortisol is more commonly assessed either by blood draw or in saliva. However, previous research has found that salivary and urinary cortisol levels of children with ASD measured by ELISA do not differ significantly [21]. Importantly, evidence of a dysregulated rhythm has been reported in most studies looking at the circadian variation of cortisol in ASD [11].

Additionally, evidence for a hypo-activation of the HPA axis in response to social threat and physiological manipulation, but a hyper-responsiveness to unpleasant physical stimuli has been noted in this population [11]. This is in alignment with other research that indicates that children with ASD have a heightened stress response with an increased secretion of cortisol when encountering a stressor [25]. Mean morning void urinary cortisol levels of children with ASD has been reported at 315.32 μg/dl [21], which is comparable to the mean obtained in the current study (~380 μg/dl). Spratt et al. [21] also found that the morning void urinary cortisol concentration in individuals with ASD is not significantly different to a group of non-ASD controls. It is likely then that our results, although a little increased compared to those of Spratt et al., do not represent an abnormally high level of cortisol in the urine. However, as with neopterin, further study comparing these results with a matched non-ASD cohort from the same region would bolster the strength of this finding.

In the current study, no relationships between neopterin and any of the ATEC or BOT-2 scores was found, which suggests that increased oxidative stress and activation of the cellular immune system (Th1-type response) are not closely associated with ASD severity or motor impairment. To our knowledge, no previous studies have assessed the relationships between urinary cortisol or neopterin and ASD symptoms and motor impairment. Furthermore, no relationships were found between any of the ATEC measures and urinary cortisol. This indicates that morning cortisol levels, and therefore, daily activation of the HPA axis, are unlikely to be related to the severity of autistic symptoms. The lack of relationships observed between urinary cortisol and neopterin and the ATEC scores could be due to the significant fluctuations occurring in both cortisol and neopterin over days and weeks.

However, urinary cortisol levels were found to associate with two of the BOT-2 scores, namely Balance and Running Speed & Agility. These were both negative relationships with scores on the Balance and Running Speed & Agility sub-domains decreasing with increasing levels of cortisol in the urine. Interestingly, many of the tasks comprising the Running Speed & Agility sub-domain of the BOT-2 involved balance (for example, hopping tasks). These results suggest that regulation of cortisol levels may be neurologically intertwined with the balance aspect of motor capability.

Balance is particularly complex as it requires a combination of exteroceptive (cues from the environment), proprioceptive (cues from the muscles and sensory organs) and interoceptive (cues from the viscera about the internal state of the body) input in order to function [26]. All of this somatosensory information is integrated through centers in the brain stem, the cerebellum and higher cortical structures that provide learned input to movement. Balance is not controlled by a single central system but rather through the complex interaction of various physiological mechanisms, including biomechanical variables, movement strategies, sensory input, dynamic control and cognitive processing [27]. Critically in ASD, the amount of cortical input required in the balance system is dependent on both the complexity of the task as well as the capability of the individual's balance-control system [27].

As discussed previously, there is a wide range of motor impairment observed in ASD. Balance is no different, with ASD children scoring lower on tests assessing balance than controls [2,4,28–30]. Vestibular processing has been found to be impaired in participants with ASD as compared with controls [31], and vestibular dysfunction has been suggested to play a role in the development of ASD [32]. Postural instability has been found to be increased in children with ASD when standing on one leg, as compared with controls [33]. Postural instability in response to changing the angle of the support surface [3] and closing eyes [34] has been found to worsen more in ASD individuals as compared with controls. Additionally, providing unreliable sensory information causes increased instability in individuals with ASD as compared with controls [35], and individuals with ASD exhibit greater postural benefit from touching a wall lightly than controls do [36]. These data all indicate that in ASD there may be a heightened reactivity to sensory disturbance in the control of balance. Additionally, postural asymmetry [33] and instability [37] in individuals with ASD has shown to be predictive of the presence and severity of repetitive behaviors, indicating a link between postural dysregulation and ASD symptoms. In a meta-analysis, dysregulation of sensory processing has been suggested to lie at the core of the postural deficits observed in ASD [38].

Balance is known to be affected by neuro-endocrine and psychological factors [26,39–42]. Anxiety in particular affects clinical outcomes of balance, however our understanding of the mechanisms behind this is limited [41]. Previous research has indicated that the ability to balance is linked to anxiety levels [26,39,42]. It has been theorized that anxiety may alter basic sensory processing and thereby affect balance [40]. Balaban & Thayer [26] propose that disconcerting input about our relationship with the environment induces panic cues to motivate a quick adjustment to the environmental change, which provides an evolutionary explanation for the neurological link between balance and anxiety. The parabrachial nucleus is a site of convergence for vestibular and visceral information and has been suggested as a circuit underpinning the relationship between balance and anxiety [26]. This theory is based on the neuroanatomical connections between the vestibular nuclei and the parabrachial nucleus [43,44], which provide a link between the vestibular system and the networks associated with fear and anxiety [45,46]. Pathways carrying visceral and vestibular information converge at the parabrachial nucleus, which then modulates the information sent onwards to the amygdala, hypothalamus, basal forebrain and cortical regions, also affecting autonomic output [26]. It is therefore possible that activation of the stress systems (i.e., activation of the SNS and HPA axis) may involve the parabrachial nucleus and therefore increased cortisol release would co-occur with modulation of the balance system. The relationship between cortisol as a marker of stress and performance on balance tasks has been assessed in only a handful of studies, and never in ASD to our knowledge. In a study on subjects with multiple sclerosis, no correlations were observed between hair cortisol levels and balance [47]. In opposition to our findings, increased cortisol has been found to associate with decreased postural sway in healthy young females [48]. However, an increased cortisol awakening response and increased stress levels have been observed to have a relationship with decreased balance performance in young males [49]. Additionally, increased cortisol levels have been found to relate to decreased balance scores in healthy young individuals [50], and increased cortisol levels have been found to associate with poorer postural control during menstruation [51]. Our findings of a relationship between increasing urinary cortisol and decreased balance performance therefore add to the evidence for a relationship between activation of the stress system and modulation of balance control. Furthermore, our results suggest a potential link between cortisol dysregulation and the development of balance impairments in ASD.

A limitation of this study is that we did not collect data on co-occurring diagnoses (such as attention-deficit hyperactivity disorder or epilepsy) in the cohort and as such could not control for those factors in the analysis. While we originally intended to collect data on a matched neurotypical sample as a control group, there were logistical difficulties in recruiting such a sample. Future research would benefit from including control groups such as those mentioned above to assess for differences in the relationship between cortisol and balance as it may occur in neurologically distinct populations. Additional limitations include the cross-sectional nature of the analysis and the relatively small sample size.

Future research looking at the relationship between ASD symptomatology and dysregulations of the brain-immune axis should consider additional physiological measurements. Variables such as heart rate variability, C-reactive protein levels and cytokine profiles may play a role in the development of ASD symptoms and may also therefore have relevance as early diagnostic biomarkers. Longitudinal assessments of immunological variables would also add greater strength and validity to the findings. Additionally, sensory data such as pain threshold measures

and psychological data such as a perceived stress scale, would also be useful to contextualize HPA axis results. Importantly, this research was conducted during the COVID-19 pandemic, and the disruption to routines that came with the pandemic may have affected stress levels in the children and therefore impacted our HPA axis results.

5. Conclusion

This study contributes to the body of research assessing the impact of the brain-immune axis on ASD. No relationships were found between autistic symptomatology and cortisol as a marker of HPA activation. Additionally, no relationships were found between autistic symptomatology and neopterin as a marker of cellular immunity and oxidative stress. However, a relationship was observed between increased levels of morning void urinary cortisol and decreased performance on balance-related tasks. This data supports previous research indicating that activation of the stress system may be neurologically interlinked with modulation of postural control, and provides the first evidence of this relationship occurring specifically in children with ASD.

Author contributions

SdL – conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, writing of original draft; CD – supervision, writing (review and editing); DM – supervision, writing (review and editing).

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Declaration of competing interest

The authors have no known conflicts of interest to declare.

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