URINARY AND BOWEL DISFUNCTION IN AUTISM SPECTRUM DISORDER: A PROSPECTIVE, OBSERVATIONAL STUDY

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SUMMARY
Background: Vesico-sphincter and bowel dysfunction have been frequently detected in Autism spectrum disorder (ASD) patients, but to date no consistent information exist on adults affected by the disease. We evaluated the prevalence and types of bladder and bowel dysfunction (BBD) in young and adult patients affected by ASD.

Subjects and methods: Twenty-seven adults and 20 children/teens with ASD and a matched group of typically developing subjects were enrolled. Daily pads use and episodes of urinary incontinence (UI) were recorded in a 3-day voiding diary. Patients underwent also the measurement of post-void urinary residual volume and 3-day bowel diary. In addition, type and duration of the pharmacological agents assumed by the patients were accurately recorded.

Results: Any type of UI was observed in 85.1% of adults and in 90% of children/teens. In adults, nocturnal enuresis (NE, 62.9%) and diurnal intermittent UI (37%) were the most frequently observed bladder dysfunction while in children/teens were NE (75%) and diurnal continuous UI (40%). In all patients was demonstrated a significant relationship between urinary symptoms and pharmacological agents, particularly NE and clozapine (p<0.004) and periciazine (p<0.008).

Conclusions: Young and adult patients with ASD present with a high prevalence of BBD and concomitant antipsychotic medications could to play a contribution in induction and/or maintaining of BBD.

Key words: Autism spectrum disorders - bladder and bowel dysfunction - antipsychotic medication

INTRODUCTION
Autism spectrum disorders (ASDs) are multifactorial neurodevelopmental conditions, which include impairments in social communication and interaction, and restricted, repetitive patterns of behaviour, interests, or activities (American Psychiatric Association 2013). Comorbid psychiatric and medical morbidities are frequently observed, including social anxiety disorder, attention-deficit/hyperactivity disorder, and intellectual disability (Simonoff et al. 2008, Mannion & Leader 2016, Matson & Shoemaker 2009). The most frequently reported medical conditions are immune system abnormalities, gastrointestinal disorder, mitochondrial dysfunction, sleep disorders, and epilepsy (Mannion & Leader 2016). Although the prevalence of ASD has been more frequently described in children, as being 1 out of 68 children worldwide (Lee et al. 2017), few data exist on epidemiologic data of ASD in the adult age, which would be an important information considering that the disorder is a long-lasting condition which can persevere throughout life. One important clinical aspect, more often under-diagnosed and under-reported is represented by the presence of vesico-sphincter and bowel dysfunction in the affected subjects. Some previous reports described the presence of urinary incontinence, faecal incontinence and constipation in subjects in the paediatric age (Niemczyce et al. 2018), but to date no consistent information exist on adults affected by the disease. We evaluated bladder and bowel dysfunction in a group of subjects affected by ASD in order to clearly identify their urologic and gastro-intestinal status. A comparison with typically developing (TD) subjects was also performed.

SUBJECTS AND METHODS
A prospective, observational study was conducted at the Serafico Institute of Assisi, “InVita” Research Centre. The experimental procedures were performed according to the Declaration of Helsinki and approved by the local Ethics Committee (CEAS No. 3308/18). Included patients were 27 adults (aged ≥ 18 years) and 20 children/teens (aged from 5 to 17 years), all with confirmed ASD according to DSM-V (American Psychiatric Association 2013) and International Classification of Diseases-10 (ICD-10) criteria (Cambridge: New York Cambridge University Press). Patients’ families/caregivers and control subjects provided written informed consent. The study included also a control group consisting of TD subjects, which were matched to patients for sex and age. Exclusion criteria for both patients and TD subjects were neurological diseases, congenital lower urinary tract diseases, previous surgical intervention in the pelvis and lower urinary tract, any previous pharmacological treatment for urinary disturbances during the last 3 months. BBD were evaluated according to the standards of the International Continence Children Society (Austin et al. 2013) and the Inter-
Urinary incontinence (UI) was classified as: diurnal, continuous, or intermittent UI. Nocturnal enuresis (NE) in patients aged ≥ 18 years, and 20 aged from 5 to 17 years (mean age ± SD was 25.3±10 years). Overall, 41/47 (87.2%) patients presented with any type of incontinence, which was detected in 23 adults (85.1%) and in 18 children (90%). In adults, NE and diurnal intermittent UI were the most frequently observed bladder dysfunction, identified in 17 (62.9%) and 10 (37%) patients, respectively. In children/teens, any type of UI was detected in 18/20 (90%) cases, with primary NE being observed in 15 (75%), and diurnal continuous UI in 8 (40%). Voiding disturbances, such as delaying, interrupted stream and abdominal straining during voiding were observed in 4 (14.8%) adult males and in only 1 (5%) children, who also showed a confirmed high PVR (300 ml). FI was detected in 9/27 (33.3%) adults and 8/20 (40%) children/teens; constipation was observed in 19/27 (70.3%) adults and in 13/20 (65%) children/teens (Table 1).

**Table 1. Bladder and Bowel Dysfunction in 27 adults and 20 children/teens affected by ASD, and in 47 typically developing (TD) subjects**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total (n=47)</th>
<th>Adults (n=27)</th>
<th>Children/Teens (n=20)</th>
<th>TD subjects (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any incontinence</td>
<td>41 (87.2%)</td>
<td>23 (85.1%)</td>
<td>18 (90%)</td>
<td>2 (4.2%)</td>
</tr>
<tr>
<td>Nocturnal enuresis n (%)</td>
<td>34 (72.3%)</td>
<td>17 (62.9%)</td>
<td>15 (75%)</td>
<td>0</td>
</tr>
<tr>
<td>Diurnal continuous incontinence n (%)</td>
<td>21 (44.6%)</td>
<td>6 (22.2%)</td>
<td>8 (40%)</td>
<td>0</td>
</tr>
<tr>
<td>Diurnal intermittent incontinence n (%)</td>
<td>13 (27.6%)</td>
<td>10 (37%)</td>
<td>1 (5)</td>
<td>2 (4.2%)</td>
</tr>
<tr>
<td>Faecal incontinence n (%)</td>
<td>18 (38.2%)</td>
<td>9 (33.3%)</td>
<td>8 (40%)</td>
<td>0</td>
</tr>
<tr>
<td>Voiding symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delaying n (%)</td>
<td>5 (10.6%)</td>
<td>4 (14.8%)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Interrupted stream n (%)</td>
<td>5 (10.6%)</td>
<td>4 (14.8%)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Straining n (%)</td>
<td>5 (10.6%)</td>
<td>4 (14.8%)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoactive bladder</td>
<td>2 (4.2%)</td>
<td>2 (7.4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation n (%)</td>
<td>30 (63.8%)</td>
<td>19 (70.3%)</td>
<td>13 (65%)</td>
<td>5 (10.6%)</td>
</tr>
</tbody>
</table>

The primary aim of the study was to evaluate prevalence and types of BBD in young and adult patients affected by ASD. Secondary aims were: to compare urinary and bowel dysfunction identified in ASD patients with those presented by TD subjects; to identify any possible relationship between urinary and bowel symptoms and the pharmacological treatment assumed by the patients.

**Statistical Analysis**

The Mann-Whitney U test was performed to compare continuous non-parametric variables. The associations between categorical variables were tested by $\chi^2$ test with Yates’ continuity correction or Fisher’s exact test. All values in the text and tables are expressed for facility as mean ± SD. All calculations were carried out with IBM-SPSS® version 25.0 (IBM Corp., Armonk, NY, USA, 2017). A two-sided P value of <0.05 was considered significant.

**RESULTS**

Thirty-eight males and 9 females affected by ASD were prospectively included in the study. Twenty-seven patients aged ≥ 18 years, and 20 aged from 5 to 17 years (mean age ± SD was 25.3±10 years). Overall, 41/47 (87.2%) patients presented with any type of incontinence, which was detected in 23 adults (85.1%) and in 18 children (90%). In adults, NE and diurnal intermittent UI were the most frequently observed bladder dysfunction, identified in 17 (62.9%) and 10 (37%) patients, respectively. In children/teens, any type of UI was detected in 18/20 (90%) cases, with primary NE being observed in 15 (75%), and diurnal continuous UI in 8 (40%). Voiding disturbances, such as delaying, interrupted stream and abdominal straining during voiding were observed in 4 (14.8%) adult males and in only 1 (5%) children, who also showed a confirmed high PVR (300 ml). FI was detected in 9/27 (33.3%) adults and 8/20 (40%) children/teens; constipation was observed in 19/27 (70.3%) adults and in 13/20 (65%) children/teens (Table 1).
The patients and voiding symptoms. No significant relationships were observed between periciazine with NE and intermittent UI in adults (p<0.04) and between clotiapine and FI (p<0.01), and between clotiapine and NE and intermittent urinary incontinence. In the present study, a significant association was found between clotiapine and FI, and between clotiapine and NE and intermittent urinary incontinence in adults. In addition, and a trend to a significant association between periciazine with intermittent UI and NE was identified in both adults and children/teens. Pharmacological agents that alter the normal circuits underlying urinary continence expose patients to the risk of urinary leakages. Actions of these drugs can be exerted at the level of the urinary system, particularly the autonomic nervous system and, as a consequence, in some cases urine output increases, in some others a physical or cognitive function can be affected. In a recent study, significant associations were identified between UI and selective serotonin reuptake inhibitors (SSRIs), and between UI and antipsychotics (Mauseth et al. 2018). Antipsychotics are dopamine receptor antagonists and can thereby lead to UI. On the other hand, antipsychotics could be hypothesized to reduce the risk of urinary incontinence due to their anticholinergic effect (Tsakiris et al. 2008). Thus the contribution of antipsychotics as drugs inducing urinary incontinence is not definitely elucidated. Another important point to take into account is the dose-effect relationship, which unfortunately in our study has not been investigated.

Finally, in our study voiding disturbances were detected in a small proportion of cases, specifically in 14.8% of adult males and in 1 (5%) children, and no case presented with a damage of the upper urinary tract. Whether voiding disturbances could be related to coexistent vesico-sphincter dysfunction, cognitive impairment or drugs’ intake needs to be fully investigated.

**CONCLUSIONS**

Young and adult patients affected by ASD present with high prevalence of bladder and bowel dysfunction, with UI as the most frequently observed dysfunction. Concomitant antipsychotic medications appear to play a great contribution in induction and/or maintaining of BBD in patients with ASD.

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**Table 2. Relationships between BBD and pharmacological agents in 27 adults and 20 children/teens affected by ASD**

<table>
<thead>
<tr>
<th></th>
<th>Adults (n=27)</th>
<th>p</th>
<th>Children/Teens (n=20)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent Urinary Incontinence</td>
<td>Clotiapine</td>
<td>0.03</td>
<td>Periciazine</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Periciazine</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturnal Enuresis</td>
<td>Clotiapine</td>
<td>0.04</td>
<td>Periciazine</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Periciazine</td>
<td>0.08</td>
<td>Clotiapine</td>
<td>0.07</td>
</tr>
<tr>
<td>Faecal Incontinence</td>
<td>Clotiapine</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

With regards to TD subjects, SCQ scores were within normal ranges in all cases. Only 2 (4.2%) woman complained of intermittent urge UI, and 5 (10.6%) patients presented with constipation (Table 1). No other BBD were detected.

Forty-two patients were under psychotropic pharmacological agents, which were assumed alone or in multidrug combination regimen. The number of the different drugs assumed ranged from 1 to 5. The most frequently adopted pharmacological agents were antipsychotics (APD) followed by mood stabilizers (MS) and benzodiazepines (BDZ).

A significant relationship was observed between the use of clotiapine and FI (p<0.01), and between clotiapine and NE and intermittent UI, in adults (p<0.04 and p<0.03, respectively). A trend to a significant association between periciazine with NE and intermittent UI in both adults and children/teens (p=0.08 and p=0.009, respectively) (Table 2). No significant relationships were identified between pharmacological agents assumed by the patients and voiding symptoms.
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Conflict of interest: None to declare.

Contribution of individual authors:
Marilena Gubbiotti & Antonella Giannantoni: contributed to conception and design, collected data, contributed to the analysis and interpretation of data, drafted the manuscript.
Chiara Bedetti & Moreno Marchiafava: collected and interpreted data.
Sandro Elisei: manuscript revision.

References

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