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Association of conduct problems and gastrointestinal symptoms in individuals with autism spectrum disorders

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Abstract

OBJECTIVES: A sizeable fraction of individuals with autism spectrum disorder (ASD) is affected by a variety of comorbid conditions including behavioural or psychiatric disorders, and medical problems. The evidence indicates that behavioural symptoms and gastrointestinal (GI) dysfunction are possibly interrelated phenomena in ASD, and it is hypothesized that they may have common underlying mechanisms. The aim of the study was to investigate associations between GI symptoms and conduct problems in individuals with ASD.

METHODS: The study involved 102 participants aged 3–18 years. Nisonger Child Behavior Rating Form was used for assessment of the conduct problems, and history of GI symptoms was obtained. Score of GI dysfunction and conduct problem score were calculated.

RESULTS: Only 8.7% of participants were free of GI symptoms, majority (56.3%) suffered from severe GI dysfunction. Of the individuals free of GI disorder 20% displayed conduct problems, the frequency increased to 41.9% in the subgroup with mild GI dysfunction, and to 67.9% in subjects with severe GI dysfunction, respectively (p=0.024). The severity of conduct problems significantly correlated with the severity of GI dysfunction (r=0.26; p=0.018).

CONCLUSION: Our results show association between GI symptoms and conduct problems. Conduct problems may have profound adverse consequences on the individuals. Many of the GI conditions occurring in ASD are treatable, and treatment of the physical problems might have positive effect also on behavioural presentation of autism. It may be possible that research into GI symptoms might elucidate aspects of the underlying neurobiological mechanisms associated with ASD.

Introduction

Autism spectrum disorders (ASD) are a group of lifelong neurodevelopmental disorders defined by a dyad of core symptoms: impairments of social interaction, verbal and non-verbal communication, and the presence of restricted and stereotyped behaviour and interests (American Psychiatric Association 2013).

There are a variety of other symptoms not considered as "core", which affect a sizeable fraction of individuals with ASD. These comorbid problems include an array of behavioural or psychiatric disorders, such

as ADHD, depression, anxiety, conduct disorder/challenging behaviours, poor attention, or intellectual disability. It is also a broad range of medical conditions that have been shown to be more prevalent in ASD than in neurotypical population, such as the gastrointestinal dysfunction, seizure disorders, poor sleep, motor deficits, sensory abnormalities, dysregulation of the immune functions, or metabolic abnormalities (Matson & Williams 2013). Due to many co-occurring medical, emotional and behavioural concerns ASD are increasingly being referred to as a "system disorder".

Gastrointestinal (GI) dysfunction is one of the most frequent comorbidities in ASD (McElhanon *et al* 2014). When compared with neurotypical children greater frequency of GI symptoms among children with ASD was found, with the prevalence ranging up to 91% (Coury *et al* 2012). Different GI symptoms have been observed; commonly reported problems include constipation, bloating, diarrhoea, vomiting, or gastroesophageal reflux. The evidence suggests that ASD patients do not always display characteristic GI symptoms as recognized in typically developing individuals, and the underlying GI disorders are presented as alterations of behaviour, such as aggression, self-injurious activity, or sleep problems, that are often attributed to be just "symptom of the autism" (McElhanon *et al* 2014).

Several studies have revealed association between a variety of behavioural problems and GI symptoms in individuals with ASD. It was observed that children with GI problems had significantly higher rates of anxiety and sensory over-responsivity, which both provided contributions to the prediction of chronic GI problems (Mazurek *et al* 2013a). In a sample of individuals with high functioning autism participants with GI problems had significantly higher levels of affective problems (Mazefsky *et al* 2014). GI disorders were also strongly correlated with the severity of ASD (Adams *et al* 2011). Thus, the evidence indicates that behavioural symptoms and GI problems are possibly interrelated phenomena in children with ASD, and it is hypothesized that they may have common underlying mechanisms (McElhanon *et al* 2014).

Children with ASD frequently present with symptoms of conduct problems, which is often reported in terms of challenging behaviour. Besides the aggressive behaviour, conduct problems include other oppositional behaviour, self-injury, bullying, disruptive behaviour, temper tantrums, etc., which may have profound adverse consequences on the individuals as well as their families and society. The aim of our pilot study was to investigate associations between gastrointestinal comorbidities and conduct problems in individuals with ASD.

Material and methods

The study involved 102 subjects with ASD, of that 92 (91.2%) boys, and 10 (8.9%) girls aged 3–18 years, mean age 7.2±3.4 years (mean ±standard deviation).

All participants underwent complex psychological assessment based on "golden standard" instruments for diagnosing ASD: the Autism Diagnostic Observation Schedule – second revision (ADOS-2) (Lord 1996) and the Autism Diagnostic Interview-Revised (ADI-R) (Lord *et al* 1994). All children met the criteria for ASD on both autism scales and underwent also clinical evaluation.

Parents of the children with ASD completed the Nisonger Child Behavior Rating Form (NCBRF) version for parents. NCBRF is a behaviour rating scale with good psychometric properties designed for children and adolescents with intellectual disabilities (Aman *et al* 1996). NCBRF is a 66 items rating scale including 6 subscales for assessment of behavioural problems: conduct problems, insecure/anxious, self-injury/stereotypic, self-isolated/ritualistic, overly sensitive and hyperactive behaviour. The conduct problem subscale was used for assessment of conduct problems in our study. The problem behaviour items are rated on a four-point Likert scale with ratings varying from "did not occur" or "was not a problem" (0) to "occurred a lot" or "was a serious problem". Conduct problem subscale score was calculated as the sum of the subscale items score.

Frequency of the GI problems in recent three months (abdominal pain, constipation, bloating, loose stools, pain in stooling, hard consistency of faeces, voluminous stools) was rated on a five point Likert scale (0-free of the disorder, 1-one to three times per month, 2-once a week, 3-several times per week, 4-daily). A score of GI dysfunction was calculated for each participant as a sum of individual scores for all GI problems. Scores 1–4 were considered as a mild GI dysfunction, scores over 5 were regarded as a severe GI disorder.

Software GraphPad Prism 6 was used for the data analysis. The Chi-square test for trend was performed, and Spearman correlation coefficient was calculated to test the correlation between score of gastrointestinal dysfunction and score of challenging behaviour. Values $p<0.05$ were considered statistically significant.

The study protocol was approved by the Ethics Committee of the Comenius University Faculty of Medicine.

Results

High frequency of GI problems was observed in the sample both in boys and girls with ASD, no correlation with age was observed. Only 8.7% of participants were free of any GI symptoms (score of GI dysfunction=0), 35% displayed mild GI problems, majority (56.3%) suffered from severe GI dysfunction. The most prevalent GI disorders included hard or voluminous stools (58.9%) and constipation (35.6%). Conduct problems, i.e. presence of at least one type of problem behaviour, were observed in 54.9% of the individuals .

In subgroup of subjects free of GI disorders conduct behaviour was observed in 20% of individuals, the

frequency of conduct problems increased to 41.9% in the subgroup with mild GI dysfunction, and to 67.9% in subjects with severe GI dysfunction, respectively (Figure 1; χ^2 for trend =7.42; p=0.024). A significant correlation (r=0.26; p=0.018) was found between the conduct problem score and the score of GI dysfunction (Figure 2), i.e. severity of conduct problems correlated with the severity of GI dysfunction.

Discussion

In individuals with ASD, aggressive behaviour is very often part of the wider conduct problems (Mazurek *et al* 2013b). Besides the aggressive behaviour, conduct problems may include other oppositional behaviour, argumentative or disruptive behaviour, temper tantrums, etc. These behaviour 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. At the same time, they are a serious obstacle for interventions and education of children with ASD (Jang *et al* 2011). In correspondence with our study, several other studies have revealed association between problem behaviour and GI symptoms. It has been shown that children with ASD who suffered from frequent abdominal pain, gaseousness, diarrhoea, constipation or pain on stooling scored worse on irritability, social withdrawal, stereotypy, and hyperactivity compared with children having no frequent GI symptoms (Chaidez *et al* 2014). Children with aggressive behaviour had significantly greater difficulties with GI problems than those without aggression (Mazurek *et al* 2013b). In contrast, another study failed to show the association of maladaptive behaviour in ASD children with GI symptoms, still, important enterocyte damage in ASD children with severe maladaptive behaviour was found (Pusponegoro *et al* 2015).

Many questions concerning the connection between GI dysfunction and conduct problems or behavioural symptoms in autism remain to be answered. The aetiology and pathomechanisms of ASD are still poorly understood, and it is also not known, yet, what connects the core symptoms of ASD with the associated comorbidities. Evidence indicates that the common link may lie in dysregulation of the immune system and chronic low grade inflammation. Not only signs of neuroinflammation were reported in ASD, there is evidence indicating that immune responses in the periphery, including the gut, are also dysfunctional (Onore *et al* 2012).

Communication between the gut and the brain, referred to as the gut–brain axis, is a bidirectional neurohumoral communication system. It is increasingly recognized as playing an important role in neurodevelopment and also has the ability to modify behaviour. Growing evidence has shown that the microbiota residing in the gut can modulate brain development and produce behavioural phenotypes via the gut–brain axis. The metabolites that are derived from the microbiota can be absorbed and transported by blood before crossing the blood–brain barrier to modulate brain function. When compared to neurotypical subjects in children with ASD abnormalities in gut microbiota were found (Li & Zhou 2016). It is hypothesized that abnormal gut micriobiota, in combination with chronic low grade inflammation and higher intestinal permeability, possibly together with some food components influence via neurohumoral pathway the processes in brain and may be the cause of behavioural symptoms of autism (Hsiao 2014).

Limitation of our study is a small sample size, and the fact that our GI data were based on parent report

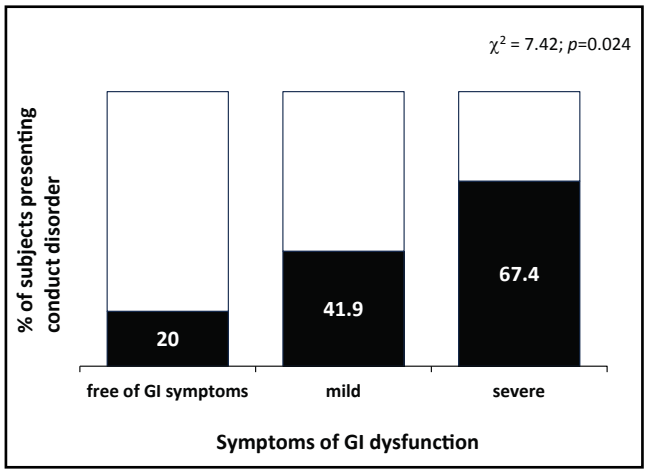

Fig. 1. The prevalence rates (%) of conduct disorder in subgroup of individuals free of GI symptoms, and subjects with mild and severe gastrointestinal dysfunction (χ^2=7.42; p=0.024)

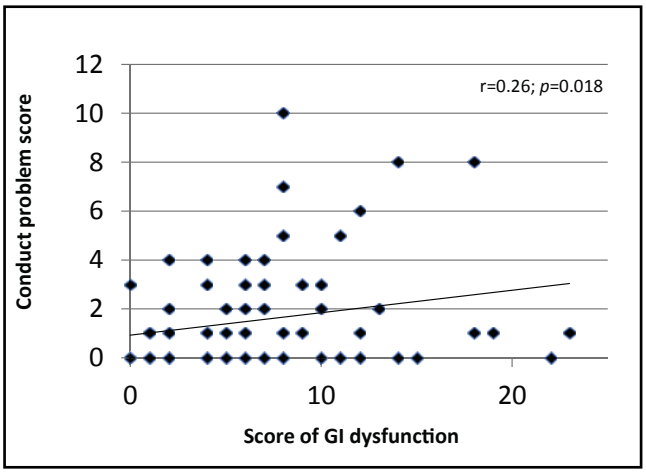

Fig. 2. Correlation between score of GI dysfunction and conduct problem score in a sample of children with autism spectrum disorder (r=0.26; p=0.018)

without any support of biological markers, so there is a level of subjectivity. On the other hand the sample is well-defined, and for children in this age range parents are likely best suited to follow the symptoms. Also, more detailed analysis of associations between individual GI symptoms (constipation, diarrhoea, etc.) and conduct disorders should be performed in order to bring more light into the topic.

Many of the GI conditions occurring in ASD are treatable. Since they may present as behavioural change, they are often overlooked. As a result, the patients are commonly referred for behavioural management and/or psychopharmacological intervention because of failure to interpret these behaviours as indicators of an underlying medical condition. At the same time, intervention studies indicate that treatment of the physical problems has a positive effect also on behavioural presentation of autism (Bauman 2010). It can be assumed that identification and treatment of GI symptoms will result in an improved sense of well-being of children with ASD, more effective participation in educational and therapeutic programs, and improved quality of life. At present time there are no empirically supported assessment or therapeutic approaches to GI problems specific for ASD population (Buie *et al* 2010). Therefore clinical practice guidelines available for the general population should be used (Mannion & Leader 2014).

The problem of comorbidity in individuals with ASD is a relatively new concept, and relationships between ASD and comorbid disorders have become an increasingly studied area. Revealing the links between symptoms of ASD and comorbid problems may be important in furthering our understanding of the causes of the ASD. Although ASD are behaviorally defined disorders, current evidence suggests multiple "autisms" with varying biological backgrounds (Coury 2012). Identification of medical disorders involving specific organ systems may help to identify phenotypic and genetic clusters of ASD persons, thus possibly defining meaningful subtypes that may result in a better understanding of subsets of causative and biological mechanisms (Bauman 2010; Matson & Goldin 2013). Further research should be directed at detection of biological markers that could help to distinguish groups of children with different symptoms of ASD, in order to answer the question if it is possible to specify a typical profile within subtypes of children with ASD.

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