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RESEARCH ARTICLE

Neuropsychological manifestations in children with Sydenham's chorea after adjunct intravenous immunoglobulin and standard treatment

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Abstract This was an exploratory study comparing neuropsychological manifestations of Sydenham's chorea (SC), 6 months after initiation of treatment, in children who had received intravenous immunoglobulins as an adjunct to standard treatment, with those who had received standard treatment. We included a non-SC control group for comparison. We hypothesized that compared to controls, children with SC who had received prior intravenous immunoglobulins would demonstrate less pronounced impairments compared to those who had received standard care. We conducted a cross-sectional analysis of 17 children with −SC who had received treatment 6 months previously (9 treated with standard of care and 8 augmented with intravenous immunoglobulins) and 17 non-SC, medically well controls. The standard treatment group (n=9) exhibited significant behavioral difficulties, including significantly poorer co-operation (p= 0.009) compared with the other augmented immunoglobulins and non-SC control groups, and increased impulsivity (p= 0.016) compared with non-SC controls. The standard treatment group scored significantly lower than the other two groups on a measure of executive functioning (p= 0.03). Children with SC may be more at risk for neuropsychological difficulties than non-SC, medically well children. Intravenous immunoglobulins may mitigate some of these impairments.

Keywords Sydenham's chorea · Intravenous immunoglobulins · Neuropsychiatric · Neuropsychological · Treatment

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Introduction

Sydenham's chorea is the neurological manifestation of rheumatic fever, usually following a group A beta-hemolytic streptococcus (GABS) pharyngitis (Perlmutter et al. 1999). The typical age of onset of Sydenham's chorea (SC) is 8–9 years (Cardoso 2011). It usually manifests as involuntary, purposeless movements and may include speech abnormalities (Cardoso 2011; Aron et al. 1965; Bonthius and Karacay 2003; Dale 2005). The psychiatric manifestations of SC include emotional lability (such as tearfulness and irritability), obsessions and compulsions, attention problems, depression and separation anxiety (Bonthius and Karacay 2003; Ben-Pazi et al. 2011; Swedo et al. 1993; Van Toorn et al. 2004). Neurological and psychiatric symptoms generally resolve spontaneously within 3 to 6 months, but reports indicate that it can remit and relapse for up to 2 years or it may evolve into a persistent chronic disorder (Cardoso et al. 1999; Walker et al. 2005). The occurrence of SC in childhood or adolescence may lead to a predisposition to psychiatric sequelae in adulthood (Bonthius and Karacay 2003; Chapman et al. 1958; Hounie et al. 2004). Studies have established a link between SC and obsessive compulsive symptomatology and attention deficit hyperactivity disorder (ADHD), with rates of between 70 and 81 % reported for obsessive-compulsive symptoms and

rates of 17 to 38 % for obsessive-compulsive disorder (OCD) (Swedo et al. 1993; Hounie et al. 2004; Maia et al. 2005; Asbahr et al. 1998, 2005a). Some authors have proposed a possible inherited predisposition to the development of SC following streptococcal pharyngitis and suggest that ADHD and anxiety disorders may be considered predictive risk factors for the development of SC which manifests with neuropsychiatric sequelae rather than resolution within 3 to 6 months (Hounie et al. 2007; Ridel et al. 2010). A less robust association between SC and other psychiatric disorders such as depression has been reported (Ridel et al. 2010).

To date, there are few studies which examine the neuropsychological sequelae of SC (Swedo et al. 1993; Casey et al. 1994a, b). Some of these report deficits in aspects of executive functioning. For example, Casey et al., in a group of 7–15 year old SC patients (n=10), reported difficulties on tasks which require the maintenance and sequencing of spatially controlled motor moves, with subsequent impairment on the Tower of London task but not on the Wisconsin Card Sorting Test (Casey et al. 1994b). In the same sample, deficits were also seen in *divided* attention when 2 (or more) tasks are performed at the same time and attention is required for the performance of both (all) tasks as well as with response inhibition (Casey et al. 1994a). In a retrospective study, weaker performance on neuropsychological tasks which measure executive functioning, working memory, timed information processing and attention was reported in a group of adults with a history of SC (n=20) compared with a group of adults with a history of rheumatic fever without SC (n=23) and a control group (n=19) (Cavalcanti et al. 2010). In another study, poorer performance on the coding subtest of the WISC-R which measures memory, processing speed and paired associate learning was reported in a group of SC patients (n=7) compared with an age- and sex-matched control group (Swedo et al. 1993). Reduced phonemic verbal fluency was also found in a group of subjects with SC (n=20) compared with a matched control group (n=40) (Cunningham et al. 2006). Mathematics skills and handwriting are also reported to be compromised in a group of 50 children diagnosed with Paediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS) (Swedo et al. 1998).

Treatment for SC aims to control the chorea, the associated behavioural problems and to provide prophylaxis for the prevention of streptococcus infection (Cardoso 2011). In addition to the administration of penicillin, neuroleptics (such as risperidone and haloperidol) or sodium valproate are used to correct neurochemical imbalances in the basal ganglia (Cardoso 2011; Bonthius and Karacay 2003; Davutoglu et al. 2004; Walker and Wilmshurst 2010). Immunomodulatory therapies, including corticosteroids, plasma exchange (PE) and intravenous immunoglobulins (IVIG), have also been effectively used to treat PANDAS and SC (Van Toorn et al. 2004; Cardoso et al. 2003; Garvey et al. 2005; Van Immerzeel et al. 2010; Walker et al. 2012). However, there is a paucity of controlled studies measuring the efficacy of these various treatments (Cardoso 2011; Bonthius and Karacay 2003; Walker and Wilmshurst 2010). Recommendations for treatment are mostly "off label"; i.e., there are no guidelines indicating the optimal duration of treatment. Moreover, side-effects to current SC treatments are common (Cardoso 2010; Teixeira 2003).

In a randomized study published recently, the efficacy of intravenous immunoglobulins as an adjunct to standard treatment (i.e., haloperidol and penicillin) was assessed for the treatment of neurological symptoms such as hypotonia, abnormal movements and emotional lability. Using a chorea rating scale (i.e., the Walker, Wilmshurst, Wendy Clinical Rating Scale for Sydenham chorea) (Walker et al. 2012) as well as SPECT data and examining symptomatic treatment duration, the authors compared the outcomes of 10 children who received standard treatment to 10 children who received IVIG in addition to the standard treatment regimen (IVIG+STDT) (Walker et al. 2012). The IVIG+STDT group demonstrated statistically significant improvements on the Clinical Rating Scale at 1, 3 and 6 months, and there was evidence of improved outcomes in this group on both SPECT scans and length of time on haloperidol compared with patients in the standard treatment group (Walker et al. 2012). Specifically, the IVIG+STDT group had a mean of 51 days on haloperidol (SD=44.27) for symptomatic treatment compared with a mean of 137 days (SD=55.85) in the standard treatment group. Furthermore, poor outcomes were reported for six patients in the standard treatment group, including continued learning difficulties, as indicated by patients' school reports; ADHD and behavior difficulties (Walker et al. 2012). The current study is an add-on investigation to the study by Walker and her colleagues, and used participants drawn from the same sample (Walker et al. 2012).

The primary objective of this study was to compare long term neuropsychological/psychiatric outcomes to two different treatment modalities in children with SC who had been treated 6 months previously. We included a non-SC control group for comparison. Similar to results reported by Walker et al. (Walker and Wilmshurst 2010), we hypothesized that children with SC who had received IV immunoglobulins in addition to the standard treatment (IVIG+STDT) would demonstrate less pronounced impairments 6 months after initiating treatment compared with children who received standard treatment alone.

Methods

Sample

The sample consisted of 34 participants (17 SC patients aged 5 to 13 years and 17 gender-, age and education matched non-

SC controls). Patients were recruited from Red Cross War Memorial Children's Hospital, where they were diagnosed according to the Jones criteria for acute rheumatic fever, without signs of alternative causes of chorea (Walker et al. 2012). Non-SC, medically well controls were recruited from schools falling within the Red Cross War Memorial Children's Hospital catchment area.

Patients had been randomly assigned to receive either standard pharmacological treatment, consisting of penicillin (VK 500 mg twice daily for 10 days) and haloperidol (0.025 mg/kg/day) given in 2 to 3 divided doses and slowly titrated to a maximum dose of 0.05 mg/kg/day (n=9), or IV immunoglobulin (1 g immunoglobulin/kg on 2 consecutive days over 6 to 8 h) in addition to standard treatment (n=8). The standard pharmacological treatment group did not receive an IV placebo for ethical reasons.

A cross-sectional assessment was undertaken. Children with SC and controls were administered a once-off standardized battery of structured diagnostic and neuropsychological assessments using a standardized assessment protocol at 6 months follow-up only. These assessments were done by a psychologist with a postgraduate degree in Research Psychology whom was blind to the participant's treatment status. Parents or caregivers of participants were interviewed by a clinical psychologist to ascertain the current neuropsychiatric status of participants (specifics included under Procedures and Measures below). These once-off assessments took place on a scheduled visit at either the US/UCT Medical Research Council Unit on Anxiety and Stress Disorders, Stellenbosch University or at Red Cross War Memorial Children's Hospital in Cape Town.

Written, informed consent was obtained from all parents/caregivers of participants and verbal assent was obtained from all participants prior to study participation. The study was approved by the Research Ethics Committee of the University of Cape Town (REF049/2002; Clinical Trial Registration number NCT 00615797) and the Health Research Ethics Committee of Stellenbosch University (N04/09/156).

Procedures and measures

The study made use of an exploratory, horizontal once-off evaluation. In order to assess for the presence of psychiatric symptoms, the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL) was used (Kaufman et al. 1996). The K-SADS-PL is a standardised, DSM-IV based, clinician-administered diagnostic interview designed to provide an overview of current and lifetime psychopathology (Kaufman et al. 1997).

Additional clinical self-report instruments were administered to the parents/caregivers of each participant. These included a demographic and clinical questionnaire (devised by the authors), which included a socio-economic status scale where respondents were required to identify the presence or absence of basic household necessities, as well as the Children's Yale Brown Obsessive-Compulsive Scale Checklist and Scale (CY-BOCS Checklist and CY-BOCS), used to establish the phenomenology and severity of comorbid OCD symptoms (Scahill et al. 1997).

Neuropsychological instruments were selected taking into account the potential neuropsychological deficits of SC identified in the literature. Administration time of the tests was considered, given the young age of participants. Tests with low cultural bias were included without sacrificing reliability and validity. The scoring of tests was carried out according to standardized procedures. South African, age appropriate normative data was used where available. Not all neuropsychological tests used in the current study are standardized for the South African population. Where participants spoke an African language, an interpreter facilitated the interview. All remaining assessments were administered in English or Afrikaans.

Behavior (i.e., concentration, activity, co-operation, affect, perseveration and impulsivity) during testing was rated by the assessor using a sliding scale rating system. In particular, co-operation was rated as poor, fair, good; impulsivity rated as none, some, marked, extreme; affect was rated as appropriate, shy, very shy, tearful, over cheerful or labile; and concentration was rated as persists well, gives up easily, slightly distractible or very distractible (depicted in Table 2).

Data analyses

Data were analysed using Statistica version 10. Children with SC in the two treatment groups were compared with non-SC controls using chi square tests for categorical variables and one way analysis of variance (ANOVA) for continuous variables. Where ANOVA results were found to be statistically significant, Fisher's least significant test was applied for post hoc analyses. We employed a 5 % threshold as guideline for determining significant differences.

Results

Study participants

The three groups (standard treatment, IVIG+STDT and non-SC controls) were matched on demographic variables of gender (19 males and 15 females; p=0.738), age (mean age 10 years; p=0.92), current school grade (mean grade 4; p=0.64), ethnicity (23 African, 11 mixed ancestry; p=0.31), language (23 with an African first language, 8 Afrikaans first language and 3 English first language; p=0.084) and socio-economic status (p=0.2).

At the time of assessment, significantly more participants in the standard treatment group had failed at least one school grade compared with the IVIG+STDT and non-SC control groups (50 % compared with 0 and 18 %, respectively) (χ^2 (df=2)=7.17, p=0.028).

Clinical profile

Our results indicated no significant association in children with SC between treatment (i.e., whether participants received standard treatment alone and those on IVIG+STDT) and current psychiatric symptomatology. The standard treatment group reported more psychiatric symptomatology compared with the IVIG+STDT treatment group however these group differences were non-significant (Table 1).

Parents/caregivers retrospectively reported noticing behavior changes in 9 of 17 (52.9 %) children such as less co-operation, impulsivity and distractibility, and obsessive-compulsive symptoms in 1 child in the period before they were diagnosed with SC. Behavioral observations during neuropsychological testing at 6 months after initiating treatment indicated that participants in the standard treatment group were less co-operative (χ^2 (df=2)=9.50, p= 0.009) compared with the IVIG+STDT and non-SC control groups (Table 2).

Post hoc tests indicated a significant difference in impulsivity between standard treatment and non-SC control groups, with the standard treatment group displaying greater impulsivity (χ^2 (df= 2)= 7.738, p= 0.016). There was a trend for the standard treatment group to have more difficulty with concentration compared with the IVIG+STDT group (p=0.068) (Table 2).

Significant group differences were found on one measure of executive functioning (i.e., the Total Correct Standard Score on the Tower of London (F(2, 29)=3.973, p= 0.03). Post hoc tests indicated that the standard treatment group scored significantly worse than both the IVIG+STDT (p= 0.015) and non-SC control (p=0.024) groups.

Discussion

We hypothesized that children with SC would demonstrate neuropsychological and neuropsychiatric impairments compared with non-SC children and that children with SC who received IV immunoglobulins treatment in addition to standard pharmacological therapy would demonstrate less pronounced neuropsychological and neuropsychiatric impairments at 6-months after initiating treatment compared with children with SC who received standard therapy alone.

Our results provide evidence that the effects of IVIG+STDT differ from those of standard treatment alone, with the IVIG+STDT group faring better in terms of observed co-operation during assessment and on one measure of executive functioning. The standard treatment group demonstrated significantly poorer performance compared with both other groups on the Tower of London total correct score. The Tower of London is a task of executive functioning, which most prominently measures efficiency of working memory, along with spatial working memory, planning and problem solving skills (Culbertson and Zillmer 2001). Relatively better performance on this task (as in the case of the IVIG+STDT group), indicates that compared with the comparison groups, these participants may be better at inhibition control and thus able to regulate their own behavior better, to be more self-organised and to be better at developing and organising plans toward a specific action or aim. Worse performance (as exemplified by the standard treatment group) indicated that participants were less likely to plan for actions efficiently (Culbertson and Zillmer 2001).

Working memory has previously been positively associated with academic performance (Gathercole and Pickering 2000; Gutiérrez-Martínez et al. 2011; Swanson 1994). Difficulties with aspects of executive functioning and working memory may therefore have a negative impact on academic functioning. Indeed, Walker et al. reported ongoing learning problems for participants in the standard treatment group compared with those in the IVIG+STDT treatment group, both of which were drawn from the same sample as ours (Walker et al. 2012). Poor working memory functioning has also been associated with reduced emotional self-regulation (Schmeichel et al. 2008).

Our results support the findings by Casey et al., who reported worse performance on Tower of London in participants with SC compared with non-SC control subjects (Casey et al. 1994b). However, they found that their participants with SC scored significantly worse on number of extra moves (move score) as well as average time to solve (execution time) and *not* on percentage solved in the fewest moves (total correct score). Our results are also partially consistent with Cavalcanti et al.'s findings of an association between SC and poor performance on neuropsychological tasks measuring executive functioning and working memory (Cavalcanti et al. 2010). However, this result was not corroborated by our participants' performance on other tests of executive functioning such as the Trail Making Test—Part B. Our results also do not support previous neuropsychological findings reporting poorer performance by SC patients on tests of attention, processing speed, verbal fluency and handwriting (Swedo et al. 1993; Casey et al. 1994a; Cavalcanti et al. 2010; Cunningham et al. 2006).

The standard treatment group had more persistent behavioural difficulties compared with the IVIG+STDT and non-SC control groups. These included significantly more impulsivity and poorer co-operation during the assessment. These observations did not translate into clinically significant psychiatric disorders.

Psychiatric symptomatology among the non-SC control group was fairly high at 12 %, however this is consistent with

Table 1 Current Psychiatric Symptoms of Standard Treatment (STDT), Intravenous Immunoglobulin Treatment (IVIG+STDT) and Non-SC Control (NSC) groups

	STDT (*n*=9)	IVIG+STDT (*n*=8)	NSC (*n*=17)
Depressive disorders			
Major depressive disorder	1		
Dysthymia	1		
Adjustment disorder with depression			1
Anxiety disorders			
Specific phobia			2
Panic disorder with agoraphobia	1		
Separation anxiety disorder	1		
Obsessive compulsive symptoms	1		
Behavioural disorders			
Oppositional defiant disorder			2
Attention deficit hyperactivity disorder		1	2

All symptoms were assessed at 6 months follow-up using the Kiddies Schedule for Affective Disorders and Schizophrenia for school-age children—Present and Lifetime version (K-SADS-PL)

epidemiological data of rates of psychiatric pathology among the general population of children in South Africa. For example, prevalence rates of 17 % for psychiatric symptomatology have been reported among children and adolescents in Cape Town (Kleintjie et al. 2006). A more recent study found that rates of ADHD among school children varied between 5.4 and 8.7 % and that this was commonly associated with conditions of oppositional defiant disorder; conduct disorder and anxiety and depression (Bakare 2012).

We found no significant association between SC and neuropsychiatric disorders, including obsessive-compulsive symptoms/OCD and ADHD in our sample (Asbahr et al. 2005b; Teixeira et al. 2007). The association between SC and obsessive-compulsive symptoms/OCD has been found

Table 2 Behavioural observations of Standard Treatment (ST), Intravenous Immunoglobulin (IVIG) Treatment and Non-SC Control (NSC) groups

	ST (*n*=9)	IVIG (*n*=8)	NSC (*n*=17)	*X*2	*P*
Co-operation				9.50	**0.009**
Poor	0	0	0		
Fair	6	1	2		
Good	3	7	15		
Impulsivity[a]				6.75	**0.034**
Some	6	4	4		
None	2	3	13		
Marked	0	0	0		
Extreme	0	0	0		
Affect[a]				3.51	0.173
Appropriate	3	3	11		
Shy	5	4	4		
Very shy	0	0	0		
Tearful	0	0	0		
Over cheerful	0	0	0		
Labile	0	0	0		
Concentration				*F*=2.002	0.15
Persists well	3	6	11		
Gives up easily	2	0	2		
Very distractible	2	1	1		
Slightly distractible	2	1	3		

All behaviors were rated during neuropsychological assessment at 6 months on a sliding scale

Statistically significant results are highlighted in bold

[a] Indicates missing data

in international research, including in resource poor countries such as Brazil (Ben-Pazi et al. 2011; Swedo et al. 1993; Hounie et al. 2004; Maia et al. 2005; Asbahr et al. 1998, 2005a; Fibbe et al. 2012). However, results across studies have been inconsistent. Our results are also contrary to international findings that have documented an association between SC and ADHD (Maia et al. 2005; Ridel et al. 2010).

While the incidence of rheumatic fever has declined in developed countries in recent years, it remains a significant health issue within the low socioeconomic sectors of resource poor nations (Cardoso 2011; Bonthius and Karacay 2003). The three study groups were comparable on all demographic variables and the majority of participants came from low-income families and communities where standards of education may be poor and academic difficulties are typical (Van der Berg and Berger 2003). Participants in the study appeared to experience academic difficulties which may not have been related to SC. For example, the significantly higher occurrence of school grade failures in the standard treatment group sometimes preceded the onset of SC and almost one fifth of controls also reported previous grade failures. Our findings suggest that South African children diagnosed with SC may be at risk of increased behavioural and cognitive difficulties which may add to these challenges already faced due to the burden of poverty. It is therefore important that follow-up treatment for those children and adolescents diagnosed with SC should include an assessment of not only medical, but also behavioural and academic functioning, and where necessary, should include referral to appropriate services. Our results combined with the findings of Walker et al. provide some evidence that the use of IVIG+STDT may possibly be more beneficial than standard treatment in SC, and may help to more effectively reduce the potential sequelae of SC on an already burdened population (Walker et al. 2012). This would need to be confirmed by additional research.

Limitations

The following limitations of the study should be considered. First, treatment groups were small in size, resulting in lower statistical power to detect inter-group differences. The small sample size can be explained by the relative rareness of patients presenting with SC. Second, it is important to note that, as this was an exploratory, cross-sectional one time evaluation study, we did not correct for multiple testing. Findings need to be confirmed through further research in larger samples or clinical verification. Third, the reliability of the data on participating children's psychiatric status may be biased due to the diagnostic information being based on the parents or caregivers' retrospective recall of their children's psychiatric health approximately 6 months previously. Moreover, many of these interviewees have had minimal exposure to psychiatric/psychological concepts and most of them have limited time available to spend with their children. Nevertheless, our results suggest that children with a history of SC may require additional support with reintegration into social or academic environments following treatment. Fourth, it is to be noted that this was a once-off evaluation 6 months after initiating treatment. Baseline data with respect to behaviour changes was limited as only their presence/absence was noted on the Walker Wilmshurst Wendy clinical rating scale. Similarly, no baseline information on the neuropsychological functioning of participants with SC was available. Basic information on participants' academic performance before developing Sydenham's chorea was available however. Implementation of better designed studies—i.e., with comprehensive assessments of patients' neuropsychological functioning at baseline—is of major importance for SC research. Sixth, as noted earlier, the significantly greater number of school grade failures in the standard treatment group compared with the IVIG+STDT group and non-SC controls may not necessarily be linked to SC. This suggests a possible baseline difference in cognitive functioning between the two groups. It is likely that differences in performance on these tests may be explained by differences in pre-morbid cognitive functioning. Indeed, the IVIG+STDT group may have had a higher cognitive potential than the other children as they had never failed a grade previously; this may have favorably biased their performance on testing. Seventh, as noted previously, at the 6 month follow-up a number of patients in the standard treatment group were still receiving haloperidol for control of chorea whereas none of the IVIG+STDT patients were still on haloperidol at time of testing. It is possible that side-effects of this pharmacological agent may have influenced the neurocognitive performance of patients in the standard treatment group.

Despite these limitations, we believe that these findings contribute to the relatively scant literature on SC. While most of the literature originates from resource poor countries such as Brazil, this is the first SC study in South Africa that has investigated neuropsychological manifestations in children with SC after adjunct intravenous immunoglobulin and standard treatment. In conclusion, our findings suggest that SC within a resource poor context may lead to some behavioural and academic difficulties. As such, the difference between the IVIG+STDT treatment compared with standard treatment alone provides motivation for the use of intravenous immunoglobulins treatment in order to reduce the burden of disease associated with SC. The importance of holistic assessment following a SC diagnosis, including assessment of emotional, behavioural and academic functioning, may be highlighted. Future research should also consider the use of larger samples to corroborate or disconfirm these findings. Longitudinal research is also needed in order to examine the longer term, cumulative effects of SC, especially within resource poor contexts, and to assist in the design of appropriate intervention

strategies targeting psychopathology and neurocognitive deficits in these children.

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Author contributions CL is a clinical psychologist who assessed participants' significant others with a psychiatric assessment battery. KW was the principal investigator in the medical treatment trial comparing the use of IVIG plus standard treatment to standard treatment alone in the treatment of Sydenham chorea. She contributed to the development of the Walker, Wilmshurst, Wendy SC clinical rating scale. The other authors contributed in the following ways. CG assisted with the neuropsychological assessments. LM assisted with administrative and funding matters, and entered all data that were collected. MK advised the researchers on the data analyses. CS contributed to the writing and proof reading of the manuscript. SS provided supervision. JW contributed to the writing of the proposal of the study and to the development and validation of the WWW clinical rating scale for SC and the proof reading of the manuscript. All authors contributed significantly to writing of the manuscript.

Declaration of conflicting interests The authors declared a potential conflict of interest (e.g., a financial relationship with the commercial organizations or products discussed in this article) as follows: The National Bioproducts Institute donated the intravenous immunoglobulin (polygamy) used in this study.

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