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Self-injury and aggression in adults with tuberous sclerosis complex: frequency, associated person characteristics, and implications for assessment

Abstract

Even though self-injury and aggression are common in tuberous sclerosis complex (TSC), understanding of these behaviours in adults with TSC and intellectual disability (ID) is limited. Little is known about their frequency in comparison to other ID-related genetic disorders or their association with other TSC-Associated Neuropsychiatric Disorders (TAND). This study determined the caregiver-reported frequency of self-injury and aggression in adults with TSC plus ID in comparison to Down syndrome (DS) and Angelman syndrome (AS), and assessed demographic and behavioural characteristics associated with the occurrence of each behaviour in TSC. Rates of self-injury and aggression in adults with TSC plus ID were 31% and 37.9% respectively. The odds of self-injury were nearly twice as high for adults with TSC than for those with DS, and the odds of aggression were over 2.5 times higher for adults with TSC than for those with DS. When compared to adults with AS, odds of self-injury in TSC were around half those of the AS group, and odds of aggression were less than a third of those for adults with AS. These differences were not statistically significant. In adults with TSC, poorer communication and socialisation skills, gastric health problems and impulsivity were associated with self-injury; compulsive behaviour and impulsivity were associated with aggression. Caregivers and professionals should be alert to the likelihood of these behaviours in adults with TSC plus ID, and to characteristics associated with increased risk for their occurrence. We suggest assessment strategies to identify those at elevated risk.

Keywords

Aggression; Challenging behaviour; Self-injury; TSC-Associated Neuropsychiatric Disorders (TAND); Tuberous Sclerosis Complex

What this paper adds: This paper adds specific examination of behavioural difficulties in adults with tuberous sclerosis complex who also have intellectual disability, a population at heightened risk of adverse behavioural outcomes which has received limited focussed examination to date. Findings support existing suggestions that there is relatively high risk for both self-injury and aggression, and provide novel insight into characteristics that may be associated with the presence of these behaviours.

1. Introduction

Tuberous sclerosis complex (TSC) is a genetic disorder characterised by abnormal growths in multiple organs, including the central nervous system, caused by mutation of either the *TSC1* gene on chromosome 9q34 (van Slegtenhorst et al., 1997) or *TSC2* gene on chromosome 16p13 (European Chromosome 16 Tuberous Sclerosis Consortium, 1993). Between 70-85% of those with TSC have seizure disorders (Chu‐Shore, Major, Camposano, Muzykewicz, & Thiele, 2010), and it is acknowledged that seizure history and severity can be associated with poorer cognitive and neuropsychiatric outcomes (Bolton, Park, Higgins, Griffiths, & Pickles, 2002; Chu‐Shore et al., 2010). TSC-Associated Neuropsychiatric Disorders (TAND) are seen in the majority of individuals with TSC (Curatolo, Moavero, & de Vries, 2015; de Vries et al., 2015; Leclezio & de Vries, 2015). Approximately 45% of individuals with TSC have intellectual disability (ID) (Joinson et al., 2003), around 40-50% meet criteria for autism spectrum disorder (ASD) (Bolton et al., 2002) and 50% for attention deficit hyperactivity disorder (ADHD) (de Vries, Hunt, & Bolton, 2007). Self-injury and aggression are reported frequently. A recent summary of TAND (Leclezio & de Vries, 2015) estimated rates of self-injury to vary from 17 to 69%, and aggression from 51 to 66%. Most of what we know about TAND is based on studies of children and adolescents, rather than adults.

In the wider population of people with intellectual disabilities, self-injury and aggression affect the physical health and quality of life of affected individuals and their families (Borthwick-Duffy, 1994; Konarski Jr, Sutton, & Huffman, 1997; Nissen & Haveman, 1997; Spreat, Lipinski, Hill, & Halpin, 1986). For TSC specifically, clinically elevated levels of parenting stress are reported by over half of caregivers, and stress levels are associated with problem behaviours (Kopp, Muzykewicz, Staley, Thiele, & Pulsifer, 2008). In adulthood, difficult behaviours are perceived to impact the family negatively, and to affect caregivers' decision-making about potential out-of-home placements (McIntyre, Blacher, &

Baker, 2002). The impact of self-injury and aggression may become more detrimental with age as these behaviours become more difficult to manage. Severe self-injury and aggression can affect access to services, result in exclusion from placements and require more costly services, issues particularly relevant to older individuals likely to live away from home (Emerson, 2001).

A substantial literature describes the prevalence and phenomenology of self-injurious and aggressive behaviours in individuals who have ID. In a total population study of individuals with ID, prevalence rates of 4% for self-injury and 7% for aggression have been found (Emerson et al., 2001). A range of person characteristics have been described in association with the development of self-injury and aggression in individuals with ID. Such characteristics may facilitate identification of those at elevated risk for developing these behaviours. These include specific genetic disorders, ASD, features of ADHD, low mood and communication deficits (Arron, Oliver, Moss, Berg, & Burbidge, 2011; McClintock, Hall, & Oliver, 2003; Oliver & Richards, 2015). Pain and illness also increase the likelihood of self-injury and aggression (Carr & Owen-DeSchryver, 2007). These observations are highly pertinent to TSC, given the high prevalence of ID, ASD and ADHD, as well as the complex health problems potentially associated with pain (e.g. renal angiomyolipomas that can cause flank pain and bleeding, subependymal giant cell astrocytomas that can cause increased intracranial pressure accompanied by headaches, and the discomfort associated with seizures, Roach & Sparagana, 2004).

To date only one study, conducted by Eden, de Vries, Moss, Richards, and Oliver (2014), examined whether rates of self-injury and aggression in TSC are comparable to those seen for other syndromes also associated with ID, and assessed which person characteristics may predict those most at risk for these adverse outcomes. Rates of self-injury and aggression, and a range of characteristics previously found to be associated with these

behaviours, were examined in children and adolescents with TSC aged 4-15 years, using questionnaire methodology. Data for children and adolescents with TSC, as well as those with idiopathic ASD, fragile X syndrome, and Cornelia de Lange syndrome, were contrasted with data for a group with Down Syndrome (DS). DS was chosen as the reference group due to its status as an ID-associated genetic syndrome with a relatively well-characterised behavioural phenotype. The prevalence of self-injury and aggression in children and adolescents with TSC were 27% and 50% respectively (Eden et al., 2014). Whilst these frequencies were considerably higher than estimates of these behaviours in people with ID in general, the odds of children and adolescents with TSC showing self-injury and aggression did not statistically significantly exceed those of the DS reference group (Eden et al., 2014). Presence of self-injury and aggression in children and adolescents with TSC was predicted by a number of anticipated person characteristics including stereotyped behaviours, low mood, overactivity, impulsivity, repetitive use of language, and, importantly, pain-related behaviours.

The developmental course of self-injury and aggression in TSC, including any age-related changes in the prevalence of these behaviours, and stability of their associations with person characteristics across the lifespan, is currently unknown. Such an understanding is important, however, as the behaviours are likely to be associated with negative outcomes both for adults with TSC and those who care for them. Given the absence of any literature examining the issue of self-injury and aggression in adults with TSC, the current study aimed to examine the frequency of these two behaviours in adults with TSC plus ID, to quantify the odds of these behaviours relative to two reference groups and to identify whether the person characteristics associated with self-injury and aggression found in children and adolescents with TSC in the Eden et al. study (2014) were similar in adults. In the current study a DS reference group was employed, in line with the Eden et al study, and an Angelman syndrome

(AS) reference group was added to enable comparison to a genetic syndrome also associated with high levels of epilepsy (around 90% of individuals are reported to experience seizures) and with increased risk of adverse behavioural outcomes, particularly aggression (Pelc, Boyd, Cheron, & Dan, 2008; Arron et al., 2008).

Given the existing literature the following hypotheses were proposed:

1) Self-injury and aggression will occur more frequently in adults with TSC than predicted in the ID population as a whole.
2) The odds of self-injury and aggression occurring will be greater for adults with TSC plus ID than for the DS group, and be similar to the AS reference groups.
3) Levels of low mood, autism spectrum behaviours, hyperactivity, repetitive and impulsive behaviours and behavioural indicators of pain, as well as the presence of painful health conditions, will be greater in adults with TSC plus ID who show self-injury and aggression than in those who do not show these behaviours.

2. Method

2.1. Recruitment and procedure

This study was part of a larger postal survey within the [withheld for blind review] comparing aspects of behavioural phenotypes of genetic syndromes [withheld for blind review]. Covering letters, information sheets, consent forms and questionnaire packs were prepared and sent out by the UK support group (Tuberous Sclerosis Association) to their membership. Caregivers of adults with TSC were invited to take part in the study if they cared for an adult aged 16 or over with TSC plus ID. Adults with TSC were assessed only if they also had ID, due to unsuitability of informant report measures for adults living independently.

2.2. Participants

2.2.1. Tuberous Sclerosis Complex (TSC)

All completed questionnaire packs returned were checked to ensure confirmed clinical diagnosis of TSC from a paediatrician or clinical geneticist and a complete dataset relating to self-injury and aggression.

2.2.2. Down Syndrome (DS) and Angelman syndrome (AS)

Data relating to adults (aged over 16 years) with DS and AS were accessed from a database at the [withheld for blind review]. Individuals with DS and AS were included only if diagnosis had been confirmed by a paediatrician, other suitable clinician or clinical geneticist. Any individuals with a maximum score on the 'self-help' subscale of the Wessex Questionnaire, the measure of adaptive functioning used (Kushlick, Blunden, & Cox, 1973) were excluded to ensure that all participants had ID.

2.3. Measures

Measures evaluated demographic characteristics, frequency of self-injury, aggression and property destruction and a range of person characteristics associated with self-injury and aggression.

2.3.1. Demographic information

A demographic questionnaire provided information on date of birth, gender, mobility, verbal ability and diagnostic status.

2.3.2. Adaptive behaviour

The Wessex scale (Kushlick et al., 1973)

Estimates of adaptive behaviour were obtained using the Wessex scale, an informant measure of adaptive behaviour in children and adults with ID. It comprises five subscales: continence, mobility, self-help skills, speech and literacy. Vision and hearing items are also included. Estimates of adaptive functioning were based on the self-help subscale, with a maximum score of nine. Both item and subscale level inter reliability have been found to be good (Kushlick et al., 1973; Palmer & Jenkins, 1982).

2.3.3. Self-injury and aggression

Challenging Behaviour Questionnaire (Hyman, Oliver, & Hall, 2002)

The Challenging Behaviour Questionnaire (CBQ) asks informants to identify the presence of physical aggression, destruction of property, stereotyped behaviour, and specific topographies of self-injury over the last month. This measure is suitable for use with both children and adults. Inter-rater reliability coefficients indicating good reliability, ranging from 0.46 to 0.72, have been reported (Hyman et al., 2002).

2.3.4. ASD phenomenology

Social Communication Questionnaire (Rutter, Bailey, & Lord, 2003).

The Social Communication Questionnaire (SCQ) is an informant questionnaire based on the Autism Diagnostic Interview–Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994) used to screen for presence of autism in individuals over the age of four years. It contains 40 items, using a yes/no response format, forming three subscales; communication, social interaction, and repetitive and stereotyped behaviour. Cut-off points are 15 for ASD and 22 for autism.

Very good agreement has been found between diagnostic classifications obtained using this measure and that found using the ADI–R (Berument, Rutter, Lord, Pickles, & Bailey, 1999; Bishop & Norbury, 2002).

2.3.5. Repetitive behaviour

Repetitive Behaviour Questionnaire (Moss, Oliver, Arron, Burbidge, & Berg, 2009)

The Repetitive Behaviour Questionnaire (RBQ) is an informant report measure of repetitive behaviour in children and adults with ID. It consists of five subscales: stereotyped behaviour, compulsive behaviour, insistence on sameness, restricted preferences, and repetitive speech (the latter 2 subscales require individuals to be verbal to score). Informants rate the frequency of 19 behaviours on a four point scale from 'never' to 'more than once a day'. The RBQ has good item level inter-rater reliability and test-retest reliability of 0.46 - 0.80 and 0.61 - 0.93 respectively (Moss et al., 2009).

2.3.6. Mood

Mood, Interest and Pleasure Questionnaire – Short version (Ross & Oliver, 2003)

The Mood, Interest and Pleasure Questionnaire (MIPQ) assesses affect in adults with ID who are unable to self-report. The 12-item questionnaire has two subscales which focus on the two main constructs of depression in the DSM-IV: 'mood' and 'interest and pleasure'. The MIPQ has strong psychometric properties with test-retest and inter-rater reliability scores of 0.87 and 0.76 respectively and internal consistency of 0.94 (Ross & Oliver, 2003).

2.3.7. Overactivity and Impulsivity

The Activity Questionnaire (Burbidge & Oliver, 2008).

The Activity Questionnaire (TAQ) is an 18-item scale, the three subscales of which provide a measure of overactivity, impulsivity and impulsive speech (applicable only for verbal individuals) for children and adults with ID. Test-retest reliability and inter-rater reliability for the full scale and subscales have been shown to be good with correlation coefficients at 0.70 or above for all participants (Burbidge et al., 2010).

2.3.8. Pain-related behaviour

Non-Communicating Children's Pain Checklist-Revised (Breau et al., 2004)

Frequency of behaviours related to pain was ascertained from the Non-Communicating Children's Pain Checklist-Revised (NCCPC-R), amended to ascertain frequency of behaviours over two weeks (as opposed to two hours) to identify those likely to be experiencing pain associated with chronic health conditions. This type of amendment has been used previously (Breau, Camfield, McGrath, & Finley, 2003; Symons, Harper, McGrath, Breau, & Bodfish, 2009). While the measure was designed for use with children, research using the measure with adults indicates that it is able to identify pain related behaviours in this population. For example, compared to baseline scores, NCCPC-R scores were elevated during an acute pain event both in adults with mild-moderate and those with severe-profound ID (Defrin, Lotan, & Pick, 2006). Furthermore, in another study, 19 of the 27 items on the NCCPC-R were shown to be significantly higher in adults during a pain episode (Lotan et al., 2009).

2.3.9. Health conditions

Health Questionnaire (Hall, Arron, Sloneem, & Oliver, 2008)

This measure asks caregivers to indicate whether the person they care for has experienced 15 health problems, classified according to the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10; World Health Organization 1992), and was based on a measure used previously to obtain informant report of health problems (Hall et al., 2008). The first section asks whether the person has ever experienced the health problem described and if so whether they have received treatment for this. The second section, from which the data used in the current study was derived, asks whether the health problem has affected the person in the past month. Response options are 'no', 'mild', 'moderate' or 'severe'. For the current study each condition was then categorised as being either present (if the caregiver selected 'mild', 'moderate' or 'severe') or absent (if the caregiver selected 'no').

2.4. Data analysis

Data relating to risk of self-injury, aggression and property destruction in TSC were contrasted with data for the DS and AS comparison groups. Comparisons of self-injury, aggression and destruction were conducted using odds ratios, to indicate whether the odds of behaviour occurring in the TSC group significantly differed from those of each of the reference groups. Odds were calculated as the probability of an event occurring divided by the probability of that event not occurring (i.e. the ratio of the odds of a behaviour occurring in TSC divided by the odds of that behaviour occurring in the reference group). This was significant if the lower bound of the confidence interval was greater than one. Using a 99% confidence interval, an interval above one indicated that the odds differed at a significance level of $p < 0.01$. To assess differences in person characteristics between people with TSC who were and were not reported to show each behaviour, chi-square analyses were used for categorical data (e.g. gender), t-tests for continuous data (age) and Mann-Whitney analyses

for ordinal data (questionnaire subscales, the majority of which were also non-normally distributed).

3. Results

Completed questionnaire packs were returned for 30 individuals with TSC aged over 16 years who also had ID. Demographic details of these participants are described in Table 1. Data from the measure relating to self-injury and aggression were missing for one participant, who was subsequently excluded from analyses resulting in a final sample of 29 adults with TSC and ID.

+++++++++ Insert Table 1 about here +++++++++

Participants with TSC were well-matched to the DS reference group (N = 21) on age, gender and mobility. However, the verbal ability and self-help skills of the TSC group were poorer, whilst their vision and hearing was better. The TSC sample was also well matched to the AS reference group (N = 29) on gender, mobility, vision, hearing, verbal ability and self-help skills, but participants with AS were younger than those with TSC.

3.1. Rates and odds of self-injury and aggression

Rates of self-injury and aggression in adults with TSC were 31% and 37.9% respectively. These were notably higher than in DS where rates were 19% both for self-injury and aggression. In contrast, the rates of both self-injury and aggression were higher in adults with Angelman syndrome (45% and 72% respectively) than in those with TSC. Table 2 shows the frequencies for each group and the odds ratios for self-injury and aggression in adults with

TSC compared to the DS and to the AS reference groups. The odds of adults with TSC showing self-injury (.45) were nearly twice as high as the odds of adults with DS showing self-injury (.24), with an odds ratio of 1.91. However, the odds for adults with TSC showing self-injury were just over half the odds of adults with AS (.81), with an odds ratio of .55. The odds of aggression in adults with TSC were over 2.5 times greater in TSC (.61) than in DS (.24), with an odds ratio of 2.6. The odds for adults with TSC showing aggression were notably lower than the odds of adults with AS (2.63), with an odds ratio of .23.

+++++++++ Insert table 2 about here +++++++++

Inferential analysis of the odds ratios, shown in Table 2, indicate that, while there were large differences between TSC and DS and between TSC and AS in the odds of occurrence of self-injury or aggression (suggesting increased risk relative to DS but decreased risk relative to AS), these differences were not statistically significant.

3.2 Characteristics associated with self-injury and aggression

Differences in demographic characteristics (including age, gender, vision, mobility, verbal ability and self-help skills) between adults with TSC with and without self-injury or aggression. No significant demographic differences were identified (see table 3).

+++++++++ Insert table 3 about here +++++++++

Next, analyses examined whether behavioural characteristics differed between adults with TSC with and without self-injury or aggression (see Tables 4 and 5). Due to the relatively low number of adults with TSC who were verbal or partly verbal (46.4%), these analyses are

not reported for subscales that require the individual to be verbal (the restricted preferences and repetitive speech subscales of the RBQ and the impulsive speech subscale of the TAQ).

+++++++++ Insert table 4 about here +++++++++

Adults with TSC who showed self-injury had poorer communication and socialisation skills, and were more impulsive than individuals who did not show self-injury (see table 4). Adults who engaged in aggressive behaviour had higher levels of impulsivity and compulsive behaviours than those who did not engage in aggressive behaviour (see table 5). No differences were found between those who did and did not show either self-injury or aggression in terms of mood or interest and pleasure, or in behavioural indicators of pain. It was, however of interest to note that behavioural indicators of pain in those who did engage in aggressive behaviour compared to those who did not, approached statistical significance ($p = .06$).

+++++++++ Insert table 5 about here +++++++++

All health conditions identified by caregivers as present in TSC are shown in table 6 (no caregiver reported cleft palette, diabetes/thyroid problems or hernia, and so these are not included in the table). More gastrointestinal problems were reported in those who showed self-injury than in those who did not. Those who showed aggression were reported to have fewer skin problems than those who did not show aggression.

+++++++++ Insert table 6 about here +++++++++

4. Discussion

4.1. General Discussion

The current study examined the frequency of, and person characteristics associated with, self-injury and aggression in adults with TSC who have ID. This is the first study to focus specifically on this population who are at particularly high risk of adverse outcomes. Self-injury and aggression were shown by around a third of adults with TSC, which is dramatically higher than the rates of 4% and 7%, reported for self-injury and aggression respectively, in the broader population of people with ID (Emerson et al., 2001). The odds of self-injury (OR = 1.9) and aggression (OR = 2.6) occurring in adults with TSC and ID were higher than the odds in the DS reference group. Relative to the AS reference group odds of both self-injury (OR = .55) and aggression (OR = .23) were lower in adults with TSC. We acknowledge that these differences may not have been statistically significant due to lack of power in the analysis.

The rates of self-injury and aggression reported in the current study are consistent with those from previous research (de Vries et al., 2007; Hunt, 1983; Staley et al., 2008). This study therefore adds further weight to the argument that TSC is associated with high rates of self-injury and aggression. The findings of the current study also extend this, suggesting a high frequency of self-injury and aggression specifically in the population of adults with TSC who have ID. The contrasts employed in the current study also enable the frequency of self-injury and aggression adults with TSC who have ID to be considered in the context of other genetic syndromes associated with ID. The frequency of both self-injury and aggression adults with TSC who have ID falls between that for adults with DS, a syndrome associated with relatively low risk for adverse behavioural outcomes (Stores, Stores, Fellows, & Buckley, 1998; Walz & Benson, 2002), and adults with AS, a syndrome associated with both

relatively high risk for adverse behavioural outcomes, particularly aggression (Arron et al., 2011) and with high rates of epilepsy (Pelc et al., 2008).

While this study's findings relating to frequency of self-injury and aggression may not generalise directly to adults with TSC without ID, findings add to current understanding about risk of adverse outcomes in TSC across development. One might intuitively expect significantly lower rates of self-injury and aggression in TSC adults without ID. Findings in children, however, suggest this may be the case for self-injury, but not necessarily for aggression (de Vries et al., 2007). Future research comparing risk of aggressive and self-injurious behaviours in adults with TSC with and without ID may identify differential pathways to these behaviours, particularly for aggressive behaviours.

To consider self-injury and aggression in their developmental context, findings of the current study can be discussed alongside those reported by Eden et al. (2014), who assessed a sample of children and adolescents with TSC aged 4-15 years using the same measure of self-injury and aggression utilised here. It is important to note from the outset that their child sample included individuals with TSC with and without ID. This complicates direct comparison given the known association between ID and self-injury/aggression. It is important also to emphasise that these differences have not been subject to inferential analysis. Rates of self-injury were similar in the current sample of adults with ID and the Eden et al. child and adolescent sample (occurring in 27% of adults and 31% of children and adolescents). Rates of aggression were lower in the adult sample (37.9%) than in the Eden et al. child sample (50%). These comparisons may suggest that self-injury remains relatively stable across development in TSC, but that the rates of aggressive behaviours may decrease with development. Needless to say, this preliminary suggestion will require larger-scale and longitudinal research.

Several characteristics were found to be associated with self-injury and aggression in adults with TSC who have ID. It is possible that these characteristics may be 'risk markers' for the development of these behaviours, thus potentially facilitating early identification of those at risk of developing self-injury and aggression. Caution must be employed here, however, as the relationships identified here may not be causal. Poorer communication and socialisation, both features of ASD, were associated with self-injury in adults with TSC who have ID. This suggests that adults with TSC who have ID and a diagnosis of ASD may be at particularly heightened risk of self-injury. Compulsive behaviour, another feature of ASD phenomenology, was associated with occurrence of aggression. Impulsivity, which forms part of the diagnostic criteria for ADHD, was associated with both aggression and self-injury. ASD and ADHD represent two of the high-frequency psychiatric disorders as part of TSC-Associated Neuropsychiatric Disorders (TAND). Given the highly variable nature of TAND in TSC, the findings of the current study imply a need for awareness of TAND-related characteristics (together with physical characteristics such as health) that may lead to increased risk for self-injury and aggression in adults with ID. This is reflected in the recommendations for assessment presented here (see Box 1).

Only one health condition, gastrointestinal difficulties, was specifically associated with the presence of self-injury in this study. Gastrointestinal difficulties/digestive problems have been found to be associated with self-injury in other syndromes, for example Cornelia de Lange syndrome (Luzzani, Macchini, Valade, Milani, & Selicorni, 2003) and ASD (Richards, Davies, & Oliver, 2017). Richards et al (2017) noted that (unlike skin problems) these difficulties are unlikely to be the consequence of self-injury, and thus a causal relationship between gastrointestinal difficulties and self-injury may be implicated. To evaluate this suggestion in relation to TSC further, future research would benefit from more robust evaluation of gastrointestinal difficulties (the current study assessed this using a single

questionnaire item), for example direct assessment by medical professionals as in the Luzzani et al. study (Luzzani et al., 2003). More broadly, the association between gastrointestinal difficulties and self-injury potentially supports suggestions that pain and illness increase the likelihood of self-injury (Carr & Owen-DeSchryver, 2007).

Interestingly, however, several potentially painful health problems that might be expected to be more common in TSC (e.g. kidney problems, epilepsy) were not associated with the presence of self-injury or aggression in this study. This may suggest that these problems, although common, are not associated with adverse behavioural outcomes in adults with TSC who have ID. However, we propose that it is more likely attributable to measurement difficulties where health conditions were measured in broad categories and behaviour was recorded as simple dichotomous variables. Utilising more specific health categories, more detailed descriptions of severity, and more detailed measures of behaviour (including severity) may reveal relationships between these health-conditions and behaviour. Finally, an unexpected association between skin problems and aggression was identified, such that those adults for whom skin problems were reported were much less likely to show aggressive behaviour. Skin manifestations are highly characteristic of TSC (Roach & Sparagana, 2004), but it is unclear why those who have experienced skin problems in the past month might be less likely to be aggressive in that time period. Further research is needed to evaluate whether this was simply a spurious finding.

Comparison of the current findings with those from the Eden et al. child and adolescent sample shows overlap in terms of behaviours relating to the broad psychiatric categories of ADHD and ASD symptomology. In terms of specific behaviours, however, there was overlap only for impulsivity, a risk marker for aggression and self-injury in both the current adult sample and in the child sample. This convergence, despite differences in ability between the samples, suggests that impulsivity may be a particularly robust risk

marker for adverse behavioural outcomes in TSC. In the current study differences in pain-related behaviour in those who did and did not show aggression seemed to approach statistical significance ($p = .06$, with a medium effect size) and there was an association between gastrointestinal difficulties (which are often painful) and self-injury. In the Eden et al. (2014) child and adolescent sample an association between pain-related behaviour and aggression was also evident, suggesting that pain-related behaviour may have a relationship with aggression that is evident across the lifespan, although the evidence presented here was less robust in adults than in children and adolescents. While negative affect was associated with increased frequency of both self-injury and aggression in the Eden et al (2014) child and adolescent sample, this was not observed in the current study. As negative affect is a potential behavioural indicator of pain (Breau, McGrath, Camfield, & Finley, 2002), the associations between negative affect and self-injury and aggression may in some part be due to the role of pain (Eden et al., 2014). The differences between the two samples relating to associations between negative affect and self-injury and aggression could therefore be accounted for by the stronger relationship between pain and both self-injury and aggression in the Eden et al (2014) child and adolescent sample than in the current study.

4.2. Recommendations for assessment

A number of assessment recommendations can be made based on the findings of the current study in conjunction with those of (Eden et al., 2014) and the broader ID literature (see Box 1). These may facilitate identification of those at elevated risk for developing self-injury and aggression. Depending on which risk factors are identified, there are a number of potential interventions that could also be considered. Timely and effective treatment of health conditions is clearly implicated. Pain identification for those who have communication deficits may be improved by enhancing communication, for instance by teaching signing (e.g.

Makaton) or using symbols (e.g. the Picture Exchange Communication System, PECS). Empirically supported interventions targeting ASD symptomology include comprehensive treatment models such as the TEACCH structured teaching approach used with both children and adults (Mesibov & Shea, 2010; Virues-Ortega, Julio, & Pastor-Barriuso, 2013), and focussed interventions, including reciprocal imitation training (Ingersoll, 2010, 2012) and pivotal response training (Koegel, Koegel, Harrower, & Carter, 1999), both used with children. Walton and Ingersoll (2013) evaluated social skills interventions for adults with ASD with severe/profound ID, including structured teaching (e.g. TEACCH) and peer mediated approaches and behavioural interventions. Given the paucity of ASD interventions suitable for use with adults with severe/profound ID, who account for around 30% of adults with TSC (Joinson et al., 2003), this review may be particularly informative for interventions for adults with TSC with ID. For ADHD symptoms judicious use of pharmacological interventions may be effective (Banaschewski et al., 2006), but given possible side effects and potential interactions with existing medications (e.g. seizure medication), behavioural treatments should always be prioritised. There is evidence that psychological interventions (cognitive training, neurofeedback and behavioural interventions) reduce ADHD symptoms as rated by parents and teachers, although in blinded trials these interventions did not reduce core ADHD symptomology (Sonuga-Barke et al., 2013).

Box 1. Recommendations for assessment of children and adults with TSC to identify risks and correlates of self-injury and aggressive behaviours

- Individuals with TSC who have ID should be assessed to identify characteristics associated with increased risk for self-injury and aggression. These include stereotyped and compulsive behaviours, overactivity, impulsivity, low mood, repetitive use of language, poor communication, poorer socialisation, and presence of pain-related behaviours.
- The TAND checklist provides a standardised, reliable and efficient tool for obtaining such information (de Vries et al., 2015).
- Assessment of TAND should be repeated over the lifespan to identify change in, or emergence of, characteristics associated with increased risk for self-injury and aggression.
- Regular health checks should be carried out, following consensus clinical guidelines (Krueger & Northrup, 2013). Between such checks, caregivers should be alert to signs of pain. For nonverbal individuals consider use of tools for behavioural observation of pain, including the NCCPC-R (Breau et al., 2004). Early intervention for painful conditions may reduce the likelihood of behaviours becoming operant.
- Presence of ASD phenomenology, features of ADHD, mood disorder or painful health conditions should alert caregivers and professionals to increased likelihood of self-injury and aggression. Similarly, the presence of self-injury and/or aggression should alert the clinical team to consider ASD, ADHD, mood disorder and/or a pain-related health problem.
- Presence of behaviours indicative of ASD, ADHD, mood disorder or a painful health condition should trigger formal assessment to enable appropriate interventions to be implemented. Given evidence for relationships into adulthood, being older should not preclude an assessment of difficulties relating to ASD and ADHD.
- Even where a person with TSC does not meet criteria for psychiatric diagnosis, caregivers and professionals should look out for behavioural characteristics that may suggest heightened risk of self-injury and aggression.

4.3. Limitations

While the current study provides novel information about self-injury and aggression in adults with TSC who have ID, there are limitations that should be considered when interpreting results and their implications. TSC is a rare disorder, and potential sample size was limited further by restricting the study to adults with ID. Inferential analyses may therefore have had insufficient power to detect significant differences. However, sample sizes in the current study are comparable to those of the Eden et al. (2014) study, which recruited children and adolescents with TSC both with and without ID. Further, non-significant differences in person characteristics were not associated with large effect sizes, where these could be calculated, suggesting that where differences likely to be clinically meaningful were evident, these were identified in analyses. One analysis where power may have been more of an issue was in the comparison of odds of self-injury and aggression in TSC compared to the odds in DS and AS. The results showed large differences in these odds ratios but inferential tests did not support this.

A further issue with comparison to the reference groups is that, whilst we were able to ensure that participants were well matched for age and that all had ID, the DS group had a greater proportion of verbal individuals, which may suggest that the DS sample may have been more able. Given the potential association between ID and self-injury and aggression, it is possible that if groups were matched on ability, the relative odds of self-injury and aggression in DS may have been higher. There was also a gender difference in the samples (more males in the TSC sample, 62% compared to 38% in the DS sample), although this difference was non-significant. To date no gender differences have been identified in any TAND characteristics, however, and therefore we did not specifically seek to match based on gender. The AS sample were younger than the TSC sample, however past research has found

that age does not affect presence of self-injury or aggression in AS (Arron et al., 2011). Whilst both differences in sample demographics and small sample size limit inferences regarding relative risk, it is evident that rates of self-injury and aggression in this sample of adults with TSC and ID are high and of potential clinical concern. Comparison with ID-related genetic disorders adds further context to this, but it is important to be mindful of the limitations of such comparisons.

Limitations relating to the relatively limited amount of detail provided by the measures of behaviour and health in the current study have been identified. Future research, building on the first steps taken in this study, may benefit from focussing on specific factors identified in the current study as influencing self-injury and/or aggression. With a more focussed examination, more detailed measures can be employed e.g. of TSC specific health issues, including a robust measure of epilepsy severity and also of any medications used to control seizures.

4.4. Summary

The current study highlighted the increased likelihood of self-injury and aggression in adults with TSC plus ID, indicating that caregivers and professionals should be alert to this risk. It also identified specific behavioural characteristics that may facilitate identification of adults at most risk of adverse outcome, including features of TAND such as ADHD and ASD. These findings formed the basis of a series of recommendations regarding strategies for assessment to identify those at increased risk.

Conflict of interests

The authors declare that they have no conflict of interests.

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Table 1. Demographic characteristics of the participants. Mean age and percentage of participants who were males, fully mobile, had normal vision and hearing, were partly verbal/verbal and partly able/able in each syndrome group. ***** indicates if the value is significantly different compared to the Down syndrome and Angelman syndrome reference groups ($p \leq .05$).

	N	**Mean age[A] (SD)**	**% male (n)**	**% verbal/ partly verbal (n)**	**% mobile (n)**	**% able/partly able (n)**	**% normal vision (n)**	**% normal hearing (n)**
TSC	29	27.69 (8.88)	62.1 (18)	46.4*[B] (13)	65.5 (19)	37.9* (11)	82.8* (24)	100*[B] (28)
Down syndrome (reference group)	21	30.48 (12.08)	38.1 (8)	85.7 (18)	85.7 (18)	76.2 (16)	47.6 (10)	57.1 (12)
Angelman syndrome (reference group)	29	22.00 (6.36)*	55.2 (16)	31 (9)	41.4 (12)	31 (9)	93.1 (27)	100 (29)

[A] In years

[B] Data missing from one participant

Table 2. Percentage of individuals engaging in self-injury, aggression and destruction in each group. ***** indicates significantly greater risk of challenging behaviour in TSC compared to the Down syndrome and Angelman syndrome reference groups, calculated using odds ratios and 99% confidence intervals ($p < .01$[1])

	Self-injury		**Aggression**	
Syndrome (N)	**%**	**Odds ratio for reference group and TSC (99% CIs)**	**%**	**Odds ratio for reference group and TSC (99% CIs)**
TSC (29)	31.00	-	37.90	-
Down syndrome reference group (21)	19.00	1.91 (.33-11.21)	19.00	2.60 (.46-14.81)
Angelman syndrome reference group (29)	45	.55 (0.13-2.28)	72	.23 (0.05-1)

[1] Alpha of p < 0.01 was selected to enable direct comparison with Eden et al. (2014).

Table 3. Analyses showing the association between participant demographic variables and self-injury and aggression in individuals with TSC. ***** indicates if there is a significant difference in the demographic variables between individuals with and without challenging behaviour ($p \leq .05$).

		Self-injury					Aggression				
		Present (n = 9)	**Absent (n = 20)**	**t/[B]**	***p***	**Effect size[B]**	**Present (n = 11)**	**Absent (n = 18)**	**t/[A]**	***p***	**Effect size[B]**
Age	Mean (SD)	30.67 (10.49)	26.35 (8.00)	-1.22	.23	0.46	26.82 (9.80)	28.22 (8.53)	.41	.69	.15
Gender	% Male	66.67	60.00	-	1.00	-	54.55	66.67	-	.70	-
Self Help[A]	%Partly able/ Able	11.11	50.00	-	.10	-	36.36	38.89	-	1.00	-
Mobility[A]	% Fully mobile	55.56	70.00	-	.68	-	63.64	66.67	-	1.00	-
Vision[A]	% Normal	88.89	80.00	-	1.00	-	90.91	77.78	-	.62	-
Hearing[A]	% Normal	100.00	100.00	-	#	-	100.00	100.00	-	#	-
Speech[A]	%Partly verbal/ Verbal	33.33	52.63	-	.44	-	50.00	44.44	-	1.00	-

[A] Scores derived from the Wessex questionnaire

[B] Fishers exact test used, therefore no test statistic or effect sizes are reported

Table 4. Differences in mood, autism spectrum behaviours, impulsivity/overactivity and repetitive behaviours and behavioural indicators of pain between adults with TSC with and without self-injury. ***** indicates if there is a significant difference in the person characteristics between individuals with and without challenging behaviour ($p \leq .05$).

		Median (Interquartile range)				
Measure	**Sub-Scale**	**Self-injury present (n = 9)**	**Self-injury absent (n = 20)**	**U Score**	***p value***	**Effect size (r)**
MIPQ	Mood	18.00 (12.5-20.23)	20.50 (16.25-21.75)	65.00	.24	-.22 *(small-medium)*
	Interest and Pleasure	10.00 (6.5-13.73)	11.00 (6.00-15.50)	81.50	.69	-.07 *(small)*
SCQ	Communication	13.00 (12.5-13.00)	11.19 (7.25-13.00)	43.00	.02*	-.43 *(medium-large)*
	Socialisation	15.00 (10.55-15.00)	11.00 (7.50-13.00)	45.00	.03*	-.43 *(medium-large)*
	Repetitive	4.00	3.50	70.50	.35	-.17

	behaviour	(2.5-6.00)	(2.00-5.00)			*(small)*
TAQ	Over-activity	19.00 (5-20.13)	9.00 (1.25-15.00)	60.50	.16	-.26 *(small-medium)*
	Impulsivity	20.00 (12.00-23.00)	13.50 (5.50-19.00)	49.00	.05*	-.36 *(medium)*
NCCPC-R		16.00 (9-34)	12.00 (5.00-19.00)	57.50	.13	-.28 *(small-medium)*
RBQ	Compulsive behaviour	0.00 (.00-6.5)	.00 (.00-2.21)	75.00	.42	-.15 *(small)*
	Stereotyped behaviour	8.50 (4.00-11.50)	5.00 (.75-8.00)	54.00	.18	-.25 *(small-medium)*
	Insistence on sameness	2.00 (.00-4.00)	.00 (.00-4.00)	78.50	.55	*-.11 (small)*

Table 5 Differences in mood, autism spectrum behaviours, impulsivity/overactivity and repetitive behaviours and behavioural indicators of pain between adults with TSC with and without aggression. ***** indicates if there is a significant difference in the person characteristics between individuals with and without challenging behaviour ($p \leq .05$).

Measure	**Sub-Scale**	**Mean (SD)**				
		Aggression present (n =11)	**Aggression absent (n = 18)**			
		Median (Interquartile range)		**U Score**	***p* *value***	**Effect size**
MIPQ	Mood	19.00 (14.00-22.00)	19.50 (16.754-21.11)	91.50	.74	-.06 *(small)*
	Interest and Pleasure	10.00 (6.00-16.00)	11.23 (7.5-14.5)	91.50	.74	-.06 *(small)*
SCQ	Communication	13.00 (8.00-13.00)	11.38 (7.25-13.00)	83.00	.45	-.14 *(small)*
	Socialisation	11.00 (8.00-14.00)	12.00 (9.50-14.50)	93.00	.79	-.05 *(small)*
	Repetitive behaviour	4.00 (2.00-5.00)	4.00 (2.00-5.50)	91.50	.73	-.06 *(small)*

TAQ	Over-activity	15.00 (5.00-20.25)	9.00 (1.50-16.00)	70.00	.19	-.24 *(small-medium)*
	Impulsivity	20.00 (15.00-23.00)	12.00 (4.50-18.00)	48.50	.02*	-.42 *(medium-large)*
NCCPC-R		20.00 (10.00-36.00)	12.00 (5.50-18.50)	57.50	.06	-.35 *(medium)*
RBQ	Compulsive behaviour	2.00 (.00-6.00)	0.00 (.00-.25)	53.00	.02*	-.44 *(medium-large)*
	Stereotyped behaviour	7.00 (3.00-11.00)	6.00 (1.50-8.00)	80.00	.52	-.12 *(small)*
	Insistence on sameness	3.00 (.00-4.00)	.00 (.00-4.00)	70.50	.16	-.*26* *(small-medium)*

Table 6 Analyses showing the association between presence of health conditions in the previous month and self-injury and aggression in individuals with TSC. ***** indicates if there is a significant difference in health conditions between individuals with and without challenging behaviour ($p \leq .05$)[2].

Health condition category	Self-injury			Aggression		
	Present (n = 9)	**Absent (n = 20)**	***p***	**Present (n = 11)**	**Absent (n = 18)**	***p***
Eye problems (% present)	.00	15.00	.31	.00	16.67	.22
Ear problems (% present)	.00	10.00	.47	9.09	5.56	.62
Dental problems (% present)	11.11	10.00	.69	9.09	11.11	.68
Gastrointestinal difficulties (% present)	44.44	5.00	.02*	22.27	11.11	.27
Bowel problems (% present)	11.11	30.00	.27	18.18	27.78	.45
Heart abnormalities (% present)	11.11	5.00	.53	18.18	.00	.14
Problems with genitalia (% present)	.00	5.00	.69	.00	5.56	.62
Limb abnormalities (% present)	11.11	15.00	.64	9.09	16.67	.51
Epilepsy/Seizures/Neurological referrals (% present)	85.00	77.78	.50	81.82	83.33	.64
Lung/respiratory problems (% present)	11.11	.00	.31	9.09	.00	.38
Liver/kidney problems (% present)	22.22	20.00	.63	18.18	22.22	.59
Skin problems (% present)	44.44	55.00	.45	18.18	72.22	.007*

[2] Fishers exact test used, therefore no test statistic or effect sizes are reported