Epilepsy in Autism Spectrum Disorder.

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Abstract

The purpose of this review is to provide an overview of the research on epilepsy in autism spectrum disorder (ASD). Topics explored are the prevalence of epilepsy in ASD, the importance of studying epilepsy, as well as the questionnaire measures used to assess epilepsy side-effects. Research on the relationships between epilepsy and parental stress and psychological distress, developmental regression, language and communication, adaptive behavior, social skills, autism severity, challenging behavior, comorbid psychopathology, gastrointestinal symptoms, sleep problems, sensory issues and quality of life are also discussed. Finally, recommendations for treatment are given as well as areas where future research is needed.

Key words: Autism spectrum disorders, Epilepsy, Seizures, Comorbidity, Treatment

1. Introduction

In their review of the literature, Matson and Goldin (2013) found epilepsy to be the most researched comorbid physical condition in Autism Spectrum Disorder (ASD). The authors commented on how there are issues that are yet to be determined about comorbid physical conditions, such as epilepsy. These include how behaviors are expressed and identified, how often the various conditions co-occur and how they cluster together. Intellectual disability is a comorbid condition in those with autism spectrum disorder. In their review of comorbidity in intellectual disability, Matson and Cervantes (2013) found that epilepsy was the second most researched topic of comorbid medical problems. The authors commented that many of the papers focused exclusively on the one comorbidity of epilepsy. It is important for research to incorporate other comorbid conditions also. This review focuses on the relationship between epilepsy and other comorbid conditions in ASD, such as comorbid psychopathology, gastrointestinal symptoms and sleep problems.

Matson and Neal (2009) conducted a literature review on seizures and epilepsy and their relationship to ASD. The review explored prevalence, nosology, etiology, and autistic regression. The review also focused on recent trends in research. The current review aims to expand on Matson and Neal (2009), by focusing on the relationship between epilepsy and other variables in ASD, such as language and communication, autism severity challenging behavior as well as comorbid conditions. While we discuss topics explored in Matson and Neal (2009) such as prevalence and autistic regression, where possible we will include articles published since 2009. The current paper will focus on treatment of seizures, and areas where future research can be conducted.

2. Epilepsy and ASD

2.1. Prevalence

ASD and epilepsy co-occur in approximately 30% of individuals with either ASD or epilepsy (Tuchman, Cuccaro, & Alessandri, 2010). Matson and Neal (2009) discussed prevalence of epilepsy and ASD in their review. The authors commented on the need for systematic studies on prevalence of ASD and epilepsy. Mouridsen, Rich, and Isager (2013) investigated the prevalence of epilepsy in individuals with Asperger's Syndrome, and found that 3.9% of individuals had a diagnosis of epilepsy. This was found to be a significant increase, when compared to the general population, where 2% of the population is estimated to have a diagnosis of epilepsy. Jedrzejczyk-Goral, Flisiak-Antonijczuk, and Kalinowski (2013) examined the frequency of different types of seizures. It was found that complex partial and generalized seizures were the most common types of seizures. The researchers also found that in electroencephalogram (EEG) records, generalized seizures and abnormal activity appeared mostly in temporal and parietal areas of the brain.

Lau et al. (2013) investigated autism traits in individuals with agenesis of the corpus callosum (AgCC). It was found that 45% of children, 35% of adolescents and 18% of adults exceeded the predetermined autism screening cut-off. The authors recommended that individuals with AgCC should be screened for ASD. They also recommended that disorders of the corpus callosum be considered in autism diagnostic evaluations. Matsuo, Maeda, Sasaki, Ishii, and Hamasaki (2010) retrospectively examined patients with epilepsy. It was found that 15.2% of those with epilepsy had ASD. ASD was detected after the onset of epilepsy in 46.8% of patients. The most frequent type of seizure was a complex partial seizure, where 68% of those with ASD presented with this type of seizure. The activity on EEG was located in the frontal lobe in about half of patients. It was found that 85% of seizures occurred before the age of 10.

2.2. Importance of studying epilepsy

Due to comorbid physical conditions in ASD, Matson and Goldin (2013) commented on the importance of medical examinations for children identified with ASD. It is important that epilepsy is diagnosed if present, so that seizures can be treated appropriately. A key aim of this review is to examine the relationships between epilepsy in ASD and other variables, such as challenging behavior, autism severity and adaptive behavior. By understanding more about the relationships between epilepsy in ASD and these variables, the effect epilepsy has on challenging behavior, autism severity and adaptive behavior can be better understood. Also, the relationships between epilepsy and comorbid conditions such as sleep problems and gastrointestinal symptoms can be better understood. In investigating any comorbid condition, it is important that the focus is on learning more about it, to provide the best possible treatment for children, adolescents and adults with ASD and a comorbid condition or multiple comorbidities.

2.3. Subjective Measures to assess seizures and side-effects of medication

EEG is an objective measure used in the measurement of epilepsy. Webb et al. (2013) conducted research on guidelines and best practices for electrophysiological data collection, analysis and reporting in autism. Questionnaire measures can be used to measure the side-effects of seizures and epilepsy. Mayville and Matson (2004) conducted a thorough review on the assessment of seizures and related symptomatology in individuals with intellectual disability. The Scale for the Evaluation and Identification of Seizures, Epilepsy. and Anticonvulsant Side-Effects-B (SEIZES-B) (Matson, Laud, González, Malone, & Swender, 2005) is a 52 item scale designed to assess side effects common with anti-epileptic medications (AEDs). It is divided into 14 categories: (1) hematological disturbance, (2) electrolyte disturbance, (3) hepatic disturbance, (4) weight disturbance, (5) respiratory disturbance, (6) gastric disturbance, (7) dermatological disturbance, (8) hair changes, (9) gait

disturbance, (10) tremor, (11) sedation, (12) affect disturbance, (13) cognitive disturbance, and (14) drug-related dizziness.

3. Relationships between Epilepsy in ASD and other variables

3.1. Parental Stress and Psychological Distress

Cushner-Weinstein et al. (2008) investigated parenting stress in parents of typically developing children with epilepsy. It was found that 45% of the parents had high levels of stress. Child depression was found to significantly increase parental distress. Learning disabilities also had a significant impact on parental stress. The authors commented that parental stress has important implications for overall clinical care, and if clinicians can understand relevant sources of that stress, outcomes may improve for children with epilepsy. Rodenburg, Meijer, Deković, and Aldenkamp (2007) investigated predictors of parenting stress in parents of typically developing children with enduring epilepsy. The research found that parent's perceptions of the child's functional status increased parental stress. The authors commented that the degree to which parents perceive child's behavioral problems are due to illness, the increase there is in parental stress. The authors also commented that parents may benefit from parental training programmes that focus on the management of children with difficult temperament, the availability of social support and the modification of inadequate parent coping behaviors. While this research was involved parents of typically developing children with epilepsy, future research should focus on parental stress and well-being of parents of children and adolescents with ASD and epilepsy. Evidence-based parent training programs should also be designed and validated for this population.

3.2. Developmental Regression

Matson and Neal (2009) explored autistic regression in their review of seizures and epilepsy and their relationship to ASD. Tuchman (2006) conducted a review exploring the relationship between autism, epilepsy and regression. Tuchman (2006) commented that there is no evidence to suggest that epilepsy is a cause of autistic regression. He also recommended the importance of addressing cognitive, language and behavioral deficits, and not only treating seizures. He also suggested that there are multiple variables that can guide clinical management where epilepsy, ASD and regression overlap, such as type of regression; age of onset of seizures or epileptiform activity, and the location, orientation, and quantity of the epileptiform activity.

Giannotti et al. (2008) reported that epilepsy and frequent epileptiform EEG abnormalities were more frequent in regressed children. The researchers reported that the data does not support the hypothesis that EEG abnormalities may play a causal role in autistic regression. Baird et al. (2008) found that regression was not associated with epilepsy. Jones and Campbell (2010) found that there was a similar risk for seizure disorder, regardless of whether language regression occurred for children with ASD.

3.3. Language and Communication

It is important to consider the relationship between intellectual disability and verbal ability. In their meta-analysis, Amiet et al. (2008) found that intellectual disability was a risk factor for epilepsy in those with ASD, where the prevalence of epilepsy was 21.5% in those with intellectual disability, and 8% in those without intellectual disability. Bolton et al. (2011) found that epilepsy in ASD was associated with poorer verbal abilities. It was found that 45% of those with epilepsy had a very limited verbal ability, while 25% of those without epilepsy had a very limited level of language. The study reported that epilepsy was significantly more common in individuals with very limited overall level of language. Those

with epilepsy had significantly lower verbal ability and non-verbal IQ. Matson, Neal, Hess, Mahan, and Fodstad (2010) investigated the effect of seizure disorder on symptom presentation in toddlers aged 18-34 months with ASD, with and without seizures and in atypically developing children, with and without seizures. Children with seizure disorders scored significantly lower in personal-social and communication scores than children without seizure disorders. The same was true with cognitive scores.

3.4. Adaptive Behavior

Turk et al. (2009) found that children with ASD and epilepsy showed delayed daily living skills when compared to children with ASD alone. Matson et al. (2010) found that toddlers with ASD and atypically developing toddlers who presented with seizure disorders had lower adaptive scores than children without seizure disorders. Eriksson et al. (2013) found that epilepsy was present in 6.3% of preschool children with ASD, and in 8.6% at follow-up two years later. The study reported that children with any medical condition, including epilepsy had significantly lower adaptive behavior scores at 2 year-follow up. The authors commented that this result may be affected to some extent by incomplete seizure control, or that antiepileptic treatment may carry a risk for negative cognitive side-effects, but that these factors were not examined in the study.

3.5. Social Skills

Smith and Matson (2010c) found that adults with combined ASD and epilepsy were more severely impaired in Positive Verbal and Positive Non-Verbal social skills than those with ASD alone, epilepsy alone, and control participants. It was found that those with combined ASD and epilepsy had significantly more impaired social skills than those with ASD alone, epilepsy alone, or those with intellectual disability alone. Hara (2007) found that

lower social maturity was observed in those with ASD and epilepsy and those without a diagnosis of epilepsy.

3.6. Autism Severity

Matsuo et al. (2010) found that an amelioration of symptoms of autism occurred after epilepsy treatment in 8% of patients. Hara (2007) observed no differences between autistic disorder and atypical autism.

3.7. Challenging behavior

Turk et al. (2009) reported that those with ASD and epilepsy showed greater challenging behavior in public places than those with ASD only. Cuccaro et al. (2012) found that epilepsy was a high rate of epilepsy (29%) in individuals with ASD who also displayed high rates of repetitive object use. The authors commented that behaviors common to ASD may also be part of an epilepsy phenotype. The authors emphasised the importance of correctly identifying the nature of the observed behavior. Therefore, one must consider the possibility that seizures present as repetitive behaviors in ASD, and also that repetitive behaviors may appear very similar to seizures.

Robinson (2012) conducted a review on childhood epilepsy and ASD and examined the relationship between epilepsy in ASD and psychiatric or behavioral problems. Robinson concluded that additional research is required, as at present no definite conclusions can be made regarding the prevalence or presentation of psychiatric or behavioral problems for children with epilepsy and ASD.

Smith and Matson (2010a) investigated challenging behavior in adults with combined ASD and epilepsy. It was found that the ASD group was significantly more impaired in self-injury than those with intellectual disability, and the additional diagnosis of epilepsy did not

add to this. Those with ASD and epilepsy were more impaired on measures of disruptive behavior than those with intellectual disability alone, ASD alone or epilepsy alone. There was also a surprising finding that epilepsy contributed more on the disruptive behavior scale than ASD did. The authors commented that this may be due to direct care staff considering seizures to be more disruptive than the disruptive behaviors of those with ASD.

3.8. Comorbid Psychopathology

In the typically developing literature, Zeber, Copeland, Amuan, Cramer, and Pugh (2007) examined the association between psychiatric diagnoses and self-reported health status in veterans with epilepsy. Nearly half of those with epilepsy had at least one comorbid psychiatric diagnosis. In addition to epilepsy, veterans had an average of 4.5 medical diagnoses, along with multiple mental health conditions. The research concluded that patients with epilepsy are at risk for high physical-psychiatric comorbidity profiles, with losses in perceived health status.

Smith and Matson (2010b) compared comorbid psychopathology in those with intellectual disability alone, ASD alone, epilepsy alone and those with combined ASD and epilepsy. On the irritability/ behavioral excesses subscale, those with combined ASD and epilepsy, and those with ASD alone had significantly higher ratings than those with intellectual disability alone. On the attention/hyperactivity subscale, those with combined ASD and epilepsy had significantly higher scores than those with epilepsy alone or intellectual disability alone. On the depressive symptoms subscale, those with ASD and epilepsy had higher scores than those with intellectual disability. The combined group was significantly higher than the epilepsy alone group in Anxiety/Repetitive behavior, Attention/Hyperactivity and Depressive symptoms. Therefore ASD is significantly more serious complicating factor in comorbid psychopathology than epilepsy is.

3.9. Gastrointestinal Symptoms

Turk et al. (2009) found that those with ASD and epilepsy showed greater incontinence, such as not being clean and dry in day and at night, than those with ASD alone. Gobbi (2005) conducted a review on Coeliac Disease, epilepsy and cerebral calcifications. It is unknown if this association is a coincidence or a genetic condition. Research is needed to determine if there is a relationship between gastrointestinal symptoms and epilepsy, both in typically developing populations and in individuals with ASD.

3.10. Sleep Problems

In the typically developing literature, sleep disturbances were found to be twice as prevalent as in healthy controls (van Golde, Gutter, & de Weerd, 2011). In their review, van Golde et al. (2011) discussed how sleep disorders that co-exist in individuals with epilepsy have a detrimental effect on their quality of life. The authors commented that future research should focus on (1) the occurrence of sleep disorders, especially insomnia and circadian rhythm sleep disorders, in larger groups of people with epilepsy measured with Video-Polysomnography studies, and (2) the effect of treating co-existing sleep disorders on seizure control and quality of life.

Giorelli et al. (2011) investigated excessive daytime sleepiness in patients with epilepsy. Complaints about daytime sleepiness were reported by 47.5% of the sample. The authors commented that the association between excessive daytime sleepiness does not seem to be related to epilepsy itself, but to other factors such as neck circumference, and anxiety. This shows the importance of understanding the relationship between epilepsy, sleep and comorbid psychopathology, such as anxiety in typically developing individuals and those with ASD. Giorelli, Passos, Carnaval, and Gomes (in press) conducted a systematic review on excessive daytime sleepiness and epilepsy. The authors reported that excessive daytime

sleepiness seems to be related more frequently to undiagnosed sleep problems than to epilepsy related factors. The authors also commented in how quality of life can be improved by treating the comorbid sleep problems in those with epilepsy.

Giannotti et al. (2008) commented that comorbid sleep problems and higher incidence of epilepsy that they found in children with ASD and regression, suggests a disruption of neuronal circuitry, which might be a reflection of the underlying pathology. The authors also commented that seizures and sleep problems could possibly be caused by the underlying pathological process, and also have a confounding effect on the evolving neurocognitive dysfunction in autism.

Mannion, Leader, and Healy (2013) found that epilepsy was not a predictor of sleep problems. However, as the research only had a prevalence of 10.1% of participants having a diagnosis of epilepsy, a bigger sample would be needed to investigate predictors of sleep problems in those with epilepsy. Studies with larger samples of individuals with epilepsy are needed in order to investigate the relationship between sleep problems and epilepsy in those with ASD and comorbid epilepsy.

3.11. Sensory Issues

Turk et al. (2009) found that children with ASD and epilepsy showed more staring behavior than those with ASD alone. Those with ASD and epilepsy showed less abnormal fascination with objects than individuals with ASD alone. Cuccaro et al. (2012) found a high rate of epilepsy in individuals with unusual sensory interests. The relationship between sensory issues and epilepsy in ASD is one that needs to be better understood by conducting future research.

3.12. Quality of Life

Ronen, Rosenbaum, Law, and Streiner (1999) investigated health-related quality of life in childhood epilepsy. Children and their parents provided descriptions of their experiences of epilepsy. Five dimensions emerged from this research. These were (1) the experience of epilepsy, (2) life fulfilment and time use, (3) social issues, (4) impact of epilepsy, and (5) attribution. The authors recommended that clinicians use these concepts as part of routine care of children with epilepsy and their families as well as examining the physical features of epilepsy such as seizure frequency, severity, and the effect of medication. Future research is needed to investigate quality of life in individuals with ASD and epilepsy. Research is also necessary to investigate if there is a relationship between quality of life of other variables such as autism severity, challenging behavior and adaptive behavior in individuals with epilepsy alone, autism alone, and combined epilepsy and autism.

4. Recommendations for treatment

Eriksson et al. (2013) commented on the necessity of having a structured follow-up of all children with diagnosed ASD in order to catch additional disorders that evolve over time. Hara (2007) found that epileptiform EEG findings predicted subsequent onset of epileptic seizures in adolescence. Hara (2007) commented that routine EEG examinations after diagnosis of autism, especially over 8 years of age, could be a significant tool in predicting the development of epilepsy. Robinson et al. (2012) commented on the need for routine investigations of ASD in children with epilepsy, and of epilepsy in children with ASD.

Tuchman (2000) conducted a review on the treatment of seizure disorders and EEG abnormalities in children with autism spectrum disorders. Tuchman (2000) commented that anecdotal evidence suggests that anticonvulsants are used to treat EEG abnormalities but that there is inadequate evidence on which to base specific recommendations. Tuchman (2000)

also commented that there is no scientific justification for considering epilepsy surgery in the absence of intractable clinical seizures.

Tuchman, Alessandri, and Cuccaro (2010) reported that there is no single treatment or treatment protocol for ASD or epilepsy. The authors reported that comprehensive treatment should be based on a combination of therapeutic psychosocial interventions in combination with pharmacological agents. Perrin et al. (2012) reported that higher rates of complimentary and alternative medicine (CAM) were associated with seizures in children with ASD. Those with a history of seizures also reported higher CAM use for special diets. The authors commented that it is unclear why children with seizures have higher rates of CAM use, but suggested that the presence of seizures may indicate more clinical severity to parents, encouraging them to seek alternative therapies.

4.1.Medication

Robinson et al. (2012) commented that there is a lack of evidence regarding the selection of appropriate anticonvulsants in relation to seizure type, epilepsy syndrome, co-medication, and comorbidity. Hirota, Veenstra-VanderWeele, Hollander, and Kishi (2013) conducted a systematic review and meta-analysis on antiepileptic medications in autism spectrum disorder. The researchers found no evidence of efficacy of antiepileptic medication for those with ASD. The researchers reported that there is not adequate evidence to support the use of antiepileptic medication for those with ASD who have epileptiform EEG abnormalities.

4.2.Behavioral Treatment of seizures

Dahl and Lundgren (2005) reviewed the behavior analysis of epilepsy. The authors discussed conditioning and behavioral techniques such as desensitization and competing responses. They also discussed how biofeedback techniques have been used in the treatment

of seizures. Dahl and Lundgren (2005) discussed the use of Acceptance and Commitment Therapy (ACT) and behavior technology in seizure control. The authors commented that seizure reduction should be coupled with building a repertoire towards a valued life.

4.2.1. Acceptance and Commitment Therapy

Lundgren, Dahl, Melin, and Kies (2006) evaluated Acceptance and Commitment Therapy (ACT), combined with some behavioral seizure control technology for drug refractory epilepsy in South Africa. Changes in quality of life were measured, as were seizure index (frequency × duration). ACT was compared to Supportive Therapy (ST). Significant effects were shown for ACT, when compared to ST at six- and twelve-month follow-ups. Lundgren, Dahl, and Hayes (2008) evaluated the mediators of change in the treatment of epilepsy with ACT in Lundgren et al. (2006). Lundgren et al. (2008) showed that changes in seizures, quality of life, and well-being outcomes were mediated to a degree by the ACT processes of epilepsy-related acceptance or defusion, values attainment, persistence in the face of barriers, or a combination of these processes.

Lundgren, Dahl, Yardi, and Melin (2008) compared ACT and yoga in the treatment of drug refractory epilepsy. Both ACT and yoga reduced seizure index, and increased quality of life over time. However, ACT reduced seizure index significantly more as compared to yoga. ACT significantly increased quality of life more than yoga, when using one quality of life measure. However, yoga increased quality of life significantly more than yoga on the other quality of life measure. Both ACT and yoga protocols contained similar processes, such as mindfulness training, acceptance of private events, discussions of losses of meaningful life directions, and inclusion of significant others during both individual and group sessions. The authors concluded that complementary treatments, such as ACT and yoga decrease seizure index and increase quality of life. Lundgren (2011) discussed the above studies and the use

of ACT in his dissertation. Future research should examine the use of ACT for children, adolescents and adults with high functioning ASD and epilepsy.

4.2.2. Cognitive-Behavioral Therapy

Walker, Obolensky, Dini, and Thompson (2010) combined cognitive-behavioral therapy (CBT) with mindfulness as an intervention called Project UPLIFT for people with epilepsy and depression. Participants in both the focus group and pilot study viewed the program favourably. Pilot study participants favoured the mindfulness-based exercises, but found benefit in the CBT exercises also. Those in the phone groups expressed somewhat greater satisfaction than those in the Web-based groups. Macrodimitris et al. (2011) used group cognitive-behavioral therapy for patients with epilepsy and comorbid depression and anxiety. The intervention demonstrated improvements in depression, anxiety, negative automatic thoughts, and cognitive therapy knowledge and skills. The group was also found to be acceptable to patients.

In a pilot study, Crail-Meléndez, Herrera-Melo, Martínez-Juárez, and Ramírez-Bermúdez (2012) evaluated CBT for depression in patients with temporal lobe epilepsy. The sessions were for 16 weeks, and from week 8, CBT had a significant positive effect on the severity of depression that lasted until the end of treatment. Quality of life also improved. Blocher, Fujikawa, Sung, Jackson, and Jones (2013) conducted a pilot study of computer-assisted CBT intervention, called Camp Cope-A-Lot (CCAL) which was modified for children with epilepsy and anxiety. There were significant reductions in symptoms of anxiety and depression, as reported by the children, at completion of the intervention, and at three-month follow-up. Parents reported fewer symptoms of anxiety and fewer behavior problems.

Given the effectiveness of CBT in the treatment of anxiety and depression in individuals with epilepsy, future interventions are necessary to be developed for individuals

with ASD, epilepsy and comorbid anxiety and depression. As can be seen, CBT was conducted in individual sessions, group sessions, and by a computer-assisted program. These are areas where future research is needed for individuals with ASD and epilepsy.

5. Future research

Matson and Neal (2009) commented on the need for developmental course to be studied in those with ASD and epilepsy. Matson and Neal (2009) also commented that much more needs to be learned about the possible links between seizures and epilepsy and ASD. Besag (2009) commented on the need for a long term prospective examination of a large population of children with ASD and epilepsy, identifying those at the earliest possible time and following up with repeated assessments for a number of years. Besag (2009) recommended that the follow up period should continue into the teenage ages, and later, as many children with autism who develop epilepsy do so in their teens. Besag (2009) emphasised the importance of matching participants in studies comparing with ASD who also have epilepsy to those without epilepsy. Tuchman, Cuccaro, et al. (2010) identified future directions that research on autism and epilepsy should take in the next decade. The authors commented that the research question that needs to be addressed is whether there are specific causes or genes that differ in individuals with both ASD and epilepsy versus those with either disorder alone.

Hara (2007) followed individuals with ASD over a 10 year period where they were evaluated almost every year. More longitudinal studies of this kind need to be conducted to follow those with ASD and epilepsy. By doing so, the relationship between epilepsy and variables, such as cognitive abilities, challenging behavior, social skills, language and quality of life can be explored more thoroughly, as well as how these relationships change over time. The relationship between epilepsy in ASD and other comorbid conditions, such as sleep

problems, gastrointestinal symptoms, attention-deficit/hyperactivity disorder (AD/HD), depression, anxiety and other psychological disorders should also be explored in future research. Research needs to be conducted across the lifespan with infants, children, adolescents, young adults and older adults.

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