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COMMENTARY

Emerging concepts in therapies for autism spectrum disorder†

COMMENTARY ON… DRUG TREATMENT OF AUTISM SPECTRUM DISORDER AND ITS COMORBIDITIES IN CHILDREN AND ADOLESCENTS

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†See pp. 151–161, this issue.

SUMMARY

Autism spectrum disorder (ASD) is a heterogeneous disorder with clearly recognisable core features, but without reliable biomarkers as yet. It has a high rate of comorbid psychiatric disorders which need to be identified and appropriately treated. Emerging concepts in genetics, pathobiology and outcome measurement have potential to significantly advance the treatment of both ASD and its comorbidities over the following decades.

DECLARATION OF INTEREST

None

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder with no established biomarkers. The condition brings with it high morbidity and cost to the individual, their family and services (Buescher 2014). Santosh & Singh (2016, this issue) give a timely review of the evidence for therapies in ASD. ASD has associated psychiatric comorbidities with aggregated rates estimated at 72–94% and these have a significant impact on adaptive function (Simonoff 2008; Mattila 2010). It is important to correctly identify common co-occurring conditions, including attention-deficit hyperactivity disorder (ADHD), behaviour that challenges owing to aggression, oppositional defiant disorder (ODD), anxiety disorders, depression and obsessive–compulsive disorder (OCD). The prescription of psychotropic medication to individuals with ASD has been increasing over the past decade, and it has been estimated that approximately one-third of patients (aged 0–24 years old) with the disorder in the UK now receive it (Murray 2014). National Institute for Health and Care Excellence (NICE) guidelines and quality standards on ASD in children and young people state that antipsychotic medication should be considered for managing challenging behaviour if behavioural interventions are insufficient or could not be delivered because of the severity of symptoms (Kendall 2013). The clinical equipoise in ASD is such that data are often extrapolated from studies of other psychiatric or neurodevelopmental disorders and, as highlighted by Santosh & Singh, more trials for the treatment of comorbidities in ASD itself are required.

Syndromic ASD: guidance for future therapies

Santosh & Singh also stress that the development of therapies has been hindered because specific biomarkers have not yet been identified for the classic ASD phenotypes. Developmental synaptopathies are an example of a group of rare genetic disorders of syndromic ASD and intellectual disability that converge on common pathways involved in synaptic development and signalling (De Rubeis 2014; Pinto 2014; Ebrahimi-Fakhari 2015). Despite the heterogeneity in ASD, patients present with characteristic impairments (American Psychiatric Association 2013). Tuberous sclerosis complex (mutations in the *TSC1* or *TSC2* gene), Phelan–McDermid syndrome (*SHANK3* gene) and PTEN hamartoma tumour syndrome (*PTEN* gene), which cause syndromic ASD, exemplify this rare disease group, collectively responsible for less than 1% of cases of ASD with or without intellectual disability. These conditions share common genetic and molecular pathways. The study of these synaptic abnormalities has allowed the identification of potential therapeutic targets. For example, excessive signalling of the protein 'mammalian target of rapamycin' (mTOR) has been found to explain the molecular basis of tuberous sclerosis complex. Behavioural and molecular abnormalities in *TSC*-deficient mice are reversible by treatment with mTOR inhibitors such as everolimus (Tang 2014). Similar studies of molecular pathways have shown insulin-like growth factor 1 (IGF-1) to be a candidate therapy in

SHANK3 mouse models (Shcheglovitov 2013) and rapamycin in PTEN mouse models (Butler 2005; Zhou 2009; Conti 2012). The Genomics England 100,000 Genomes Project is likely to identify more children with mutations contributing to syndromic ASD (such as the *SYNGAP1* gene, and the neuroligin genes). By further characterising the neurodevelopmental phenotype of syndromic ASD, biomarkers and surrogate markers may be developed that help predict risk for symptom severity and response to treatment. Overlapping pathophysiology would suggest that treatments developed for one condition may be translatable to others. This knowledge may eventually be beneficial in translating therapies to 'idiopathic' ASD.

Environment, the immune system and the microbiome: implications for therapies in ASD

Santosh & Singh note that several papers have indicated that genetic predisposition and environmental factors might be among the mechanisms underlying the pathophysiology of ASD. There is indeed a growing interest, for example, in the role of the immune system in the neurobiology of the disorder. Genome-wide expression studies and post-mortem brain analysis indicate abnormalities in immune system gene transcripts in patients with ASD (Lintas 2012). Animal and initial human point to activation and active inflammation of microglia (resident central nervous system macrophage cells) in ASD (Zhan 2014). There has also been an increasing interest in activation of the maternal immune system and childhood ASD (Knuesel 2014). Vitamin D, a hormone with increasingly recognised immunomodulatory effects on disease, has also been implicated as having a role in ASD (Mostafa 2012; Patrick 2014). Small case–control studies investigating the intestinal microbiome in people with ASD compared with healthy controls have reported differences, including increased clostridial species, which may result from a number of environmental factors, such as antibiotic usage and improved sanitation. The microbiome is postulated to make a significant contribution to the immune function of individuals, and hence therapies aimed at improving intestinal health may have an effect on symptoms (Buie 2015).

Although the study of the contributions of environment, the immune system and the microbiome in ASD is at a very early stage, the identification of potentially suitable biomarkers in a subset of patients with ASD may guide future developments for disease monitoring and therapeutics.

Pharmacogenetics and ASD

The article by Santosh & Singh also illustrates challenges faced by clinicians in identifying treatments that have suitably balanced safety and efficacy profiles for treating comorbid psychiatric disorders. Specific adverse drug reactions have been reported commonly in young people with ASD receiving psychotropic medication, and there is evidence that young people with ASD may have more frequent and troubling adverse drug reactions (Owley 2010). Dosing is complicated by the fact that there appears to be no relationship between weight and effective dose, and only a weak correlation between age and effective dose.

Pharmacogenetics can show how genetic determinants affect an individual's response to a medication. Applying its techniques has the potential, on an individual level, to achieve better response to prescribed medicines and lessen the risk of adverse drug reactions. At the population level, it will increase the risk–benefit ratio associated with this widely used group of drugs. The application of pharmacogenetics in psychiatry is gaining increasing interest (Hawcutt 2013), but it has yet to be shown whether pharmacogenetics offers meaningful advantages over clinical titration in psychiatric conditions. A position paper by the European Medicines Agency (Committee for Medicinal Products for Human Use 2013) recommends that further trials are conducted in order to guide the use of medication in young people in ASD. Small studies in which physicians used pharmacogenetic tests to guide their prescribing of psychotropics for various disorders have reported improved treatment efficacy and reduced adverse drug reactions, but the beneficial effects of testing have been inadequately studied in larger groups or specifically in patients with ASD and psychiatric comorbidities. Pharmacogenetic testing is hence rarely used in clinical practice in the UK. A recent genome-wide association expression study (Malhotra 2012) assessing weight gain associated with 12 weeks of antipsychotic treatment implicates the *MC4R* gene in extreme weight gain and related metabolic disturbances. *A priori* identification of patients at high risk of such drug side-effects could be beneficial in clinical practice.

Treatment of core ASD features

Finally, as emphasised by Santosh & Singh, there is a lack of effective treatments for the core symptoms of ASD and a need for a range of interventions. Effective interventions early in life may make long-term differences in the trajectory of the condition. Sulforaphane, for example, has been

shown in a recent double-blind placebo-controlled randomised trial ($n=44$, randomisation roughly 2:1, White males aged 13–27 years) to target core clinical features (social responsiveness) with a very favourable safety profile (Singh 2014). Larger confirmatory trials are needed.

Conclusions

Autism spectrum disorder is a common neurodevelopmental disorder that affects adaptive functioning from early childhood and is associated with a high rate of neuropsychiatric comorbidity. Given that there are likely to be ASD-specific differences in therapeutic response, high-quality evidence for treatment of psychiatric comorbidity such as anxiety is still needed from both pharmacological trials and well-controlled trials of psychological therapies. In addition, as a result of breakthroughs in technology, biology and the genetics of ASD, there has been an increasing interest in therapies for core ASD features. Recent interest in objective outcome measures, including advancement of the field of ASD biomarkers, has potential to benefit the design of ASD clinical trials.

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