Regression in Autism Spectrum Disorders

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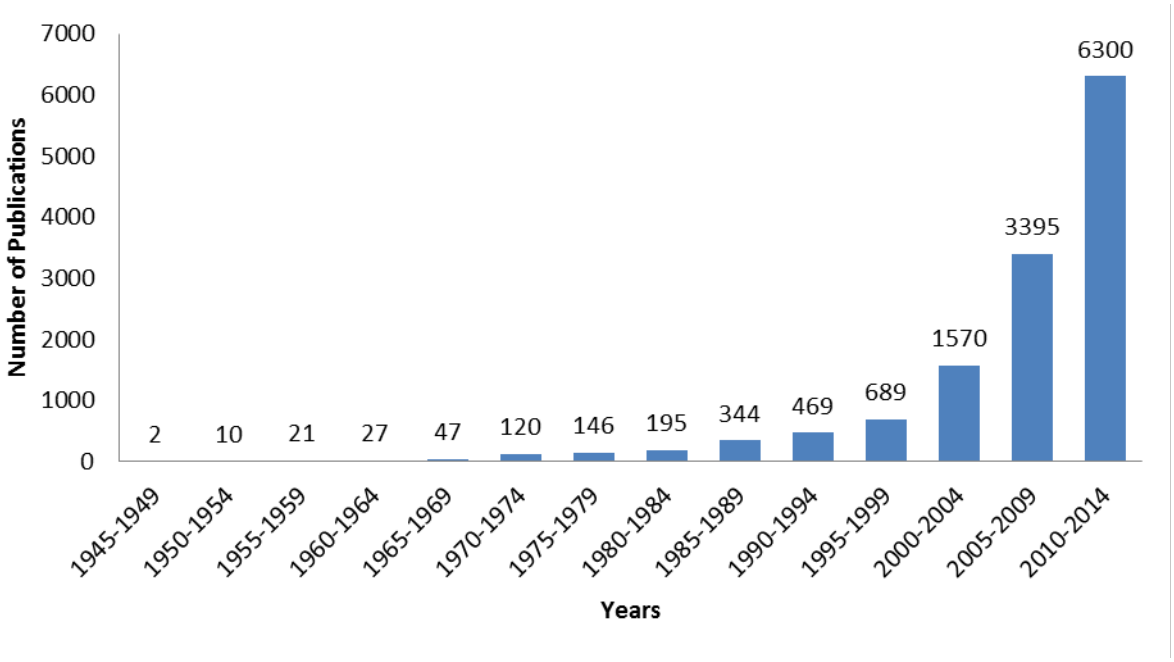
Abstract

Since the Journal of Paediatrics and Child Health was first published there has been substantial change in the field of autism spectrum disorders (ASD) with an exponential increase in the amount of funded and published research. In this paper we focus on regression in children with ASD, a phenomenon which remains poorly understood. We discuss the implications of what we know about regression in ASD for the way we think about ASD more broadly and for paediatric practice.

Background

The clinical features of children who were described as "autistic" were published by Kanner[1] in English 21 years before the Journal of Paediatrics and Child Health was launched. The recent surge of activity and interest in autism spectrum disorders (ASD) is reflected in the number of articles with autism in the title in PubMed, with 90% published in 1994 or more recently (Figure 1). Many reviews about ASD are now available including three published in this journal.[2-4] Major changes that have occurred are shown in Textbox 1, with many of these contributing to the current concept of autism as a spectrum of strengths and difficulties.

Figure 1 Number of publications in Pubmed with autism in the title over time



Changes in the past 20 years

1. Acceptance of the spectrum concept of autism
2. Emergence of many theories purporting to explain the neuropsychological underpinning of ASD, like theory of mind, but with none yet achieving this
3. Acceptance that ASD is biologically (rather than psycho-dynamically) based, albeit with slow progress toward detailing the biological underpinnings
4. Emergence of a plethora of biological theories of causation, many of which have been disproven; the remainder are not yet proven despite extensive research investment
5. Widespread communication about and uptake of interventions based on unproven theories of causation that have been harmful
6. Development of systematic, expert, and sophisticated methods for assessment and diagnosis of ASD, but variations in diagnostic practise remain widespread and inconsistency in diagnosis persists
7. Major growth in our understanding of the cognitive strengths and weaknesses, and preferred learning styles of children with ASD, which can be applied to interventions and educational settings
8. Greater understanding of co-morbid features such as anxiety and hyperactivity, which contribute to the behavioural problems and which need particular treatment and management, with DSM-5 allowing co-diagnoses

Kanner's original description (1943) did not report regression, rather that autism was congenital or occurred shortly after birth.[1] However, reports emerged in the 1960s that noted behavioural regression in children with autism[5, 6] and in the mid 1980s studies were published that focused specifically on the loss of early speech in autism.[7] Since that time substantial research has accumulated about a subgroup of children with ASD who experience some form of developmental change, plateau, or regression in the first few years of life[8, 9], with a recent review of the prevalence of regression in ASD identifying 85 relevant publications.[10]

In an attempt to disentangle the types and possible causes of ASD, a dimensional approach is being recommended and subtypes within the autism spectrum are being explored. It is thought that children displaying regression could form one important subgroup. There are a number of reasons why regression in ASD has sparked interest: it could i) provide clues as to cause and underlying neurobiological mechanisms; ii) assist in the delineation of potential subgroups in what is currently a heterogeneous condition; iii) inform prognosis. However, questions remain about whether the reports of loss of skills in ASD is regression as we think of it for other progressive neurodevelopmental disorders. For the remainder of this article we will focus on what is known about this phenomenon, and what this means for paediatric practice.

What is regression in ASD?

Regression is described by parents of children with ASD as apparently normal development for the first one to two years of life, followed by an abrupt or gradual loss of previously acquired skills. The developmental skills that are typically reported to regress in ASD are language and/or social communication. A frequently used tool to assist in characterising regression is the Autism Diagnostic Interview-Revised (ADI-R) because it includes specific questions and guidance about regression.[11] The characteristics required by the ADI-R for a diagnosis of language regression

are that prior to the reported loss "communicative use of at least five different words (other than 'mama' and 'dada') on a daily basis for at least 3 months" is established and that there has been a loss of the skill for at least three months.[11(p 17)]. Some studies have suggested that the majority of children show some subtle signs of social difficulties, perhaps unrecognisable to their parents, prior to regression being reported.[9] However, some reports based on home videos suggest at least some children have advanced skills prior to regression (e.g.,[12])

How common is regression in ASD and other developmental problems?

A recent meta-analytic review which included 85 studies (n=29,035) reported the overall prevalence of regression in ASD to be 32.1%, (CI: 29.5-34.8), and the mean age of onset of regression as 1.78 years (CI: 1.69-1.89).[10] Prevalence rates of regression vary according to how regression is defined.[10, 13] No significant difference in the risk of regression between males and females has been reported [8, 10, 14] and regression is not more common amongst any particular socioeconomic group.[13, 15] One hypothesis is that the age of regression depends on the stage of brain maturation and developmental level of the child rather than their chronological age.[8]

Regression is rare in other neurodevelopmental disabilities, apart from a select few, including seizure disorders (eg Landau-Kleffner syndrome, acquired epileptic aphasia), genetic disorders (e.g Rett syndrome) and known disorders of metabolism (eg glycogen storage disorders). In these there is continued deterioration unless the underlying cause can be treated or there are treatments to decrease the secondary consequences of the underlying cause. Childhood Disintegrative Disorder (CDD) is one other rare condition in which regression occurs with no known underlying cause. Under the Diagnostic Statistical Manual of Mental Disorders-fourth edition (DSM IV)[16] CDD was defined separately as apparently normal development in the first two years after birth followed by loss of skills before the age of ten, with skill loss that could extend beyond social communication and language. With the release of the Diagnostic Statistical Manual of Mental Disorders-fifth edition (DSM-5)[17] CDD is now included under the diagnosis of Autism Spectrum Disorder and is no longer a separate disorder.

The occurrence of reported regression is higher in ASD than other idiopathic developmental conditions. For example only 1% of children with specific language impairment regressed compared to 15% with ASD in one study [18], and 3% of children with developmental delay were reported to regress compared to 38% in ASD in another.[19] In both of these studies the non-ASD children who regressed had significant medical or neurodevelopmental problems such as encephalitis, Down Syndrome with leukaemia, a stroke and epilepsy.

Cause and underlying neurobiological mechanism

To date studies that have investigated the processes that may be involved in regression have been based on cross-sectional associations. Studies have examined a potential association between the measles mumps and rubella (MMR) vaccination,[20] gastrointestinal problems[13, 19] and mitochondrial diseases.[21] None of these have found differences in risk factors that are substantial enough to differentiate subgroups of children with regressive and non-regressive ASD, nor have they been fruitful in identifying a potential cause. Studies investigating

traditional risk factors such as pre or post-natal complications and viral infections have also failed to yield a cause.[13, 15]

There has been substantial exploration of epilepsy as a cause of regression but to date the findings have been inconsistent. In one study a high proportion of children, most (90%) with an IQ less than 70, who had experienced regression with ASD had comorbid epilepsy. [22] In another increased seizure activity was associated with regression. [23] However, in this study there was no a significant difference between the risk of epilepsy in children with ASD who had regressed when compared to those who had not.[24] Many other studies have found no association between epilepsy and ASD.[13, 14, 19]

A number of theories have been proposed to help explain the neurobiology of regression. It has been suggested that regression in ASD may occur in a particular genetic subgroup. While this may seem logical, research has so far failed to identify any genetic differences between children who regress compared to those who do not.[25] One study found the risk of regression for children with ASD in multiplex families was similar to the rate of regression in singleton families.[25] In the same study, later born children who were diagnosed with ASD were not found to be at increased risk of regressive ASD if they had an older sibling who has regressive ASD. Another study found similar rates of the broader autism phenotype in parents of children who had both regressive and non-regressive forms of ASD.[26] To date none of the suggested neurobiological theories, many based on neuroimaging findings, have consistently explained regressive ASD.[27, 28] New computer modelled theories are emerging but are also unproven.[29]

Is there a clear regression subtype?

In the last seven years studies have looked at the onset of ASD prospectively, including population sample studies [30, 31] and studies of high-risk siblings.[32] In one study around 50% of children who were later diagnosed with ASD showed typical development (apart from exhibiting fewer gaze shifts) prior to 14 months but then experienced a period of developmental change which involved arrest, slowing and/or regression.[33] A continuum of impairment, where children reach a threshold for diagnosis of ASD at different points in time in the first 3 years of life, was described.[33] Another study reported that the symptoms of ASD emerged over a period of time beginning around the second year of life. Repeated observations of children in this study found a decline in social communication skills in 86% of children.[9] It remains to be established whether these prospective studies have captured the full range of patterns of onset of developmental problems that are later diagnosed as ASD and all the ways regression may occur. To date few have reported the more dramatic, rapid loss of skills, which may represent an important subtype of regression. The methodological limitations of prospective studies to date (e.g. primarily high-risk siblings and small sample sizes) prevent us from forming firm conclusions.

Prognosis

There have been mixed findings in the literature about whether children with ASD who experience regression have better or worse long term outcomes than children who do not experience regression. Some studies have reported no difference in outcome for children who

regressed versus those who did not (e.g.,[34]) and others have found that those who regressed were more impaired in areas such as language, comorbid psychopathology, adaptive function, challenging behaviours and social skills than their counterparts.[7, 19, 35, 36] In one study the loss of *nonspecific vocalisations* was associated with lower IQ and higher ASD symptomology (as measured on the Autism Diagnostic Observation Schedule (ADOS)).[8] However, for those children who developed words and phrases by five years of age, those with word loss had similar outcomes to the children without word loss.

No changes yet for clinical care

For the paediatrician the approach to a child who presents with regression and problems of the type seen in ASD is unchanged. A thorough history to tease out the developmental trajectory will assist with assessing if regression has occurred and what developmental dimensions are involved. When regression has occurred, investigation and referrals should take into account important potential underlying pathophysiology, like seizure disorders, metabolic and genetic causes. When ordering genetic tests, like microarray, a history of suspected regression should be provided along with the diagnosis of ASD. If this is done consistently it may assist in identifying genetic underpinnings for some children and families that are unlikely to be found in research studies, due to sample size limitations. If the presence of regression is uncertain then review to monitor progress against baseline abilities and difficulties is needed.

Still no answers but maybe now we are asking the right questions

Research about regression in ASD, including prospective studies of early development, has not yet provided clear answers about whether there is a distinct subtype of children with autistic regression. A lack of clarity about the subtype is likely to explain why findings are still mixed about possible causes and prognosis of children who are reported to regress. However, evidence from ASD research focusing on regression has contributed to an emerging interest in the dimensions of developmental difficulties for children with ASD, including timing of onset and subsequent trajectory. This approach, rather than a categoric approach to the diagnosis of ASD, provides hope as an important new framework from which to ask the right questions about causes of and interventions for ASD, and how it is associated with other developmental difficulties and disorders. If this dimensional thinking can underpin research using new technology for both genetic and epigenetic research and neuroimaging and computer models of brain function, there could be more rapid progress towards providing the sorts of answers we need to assist children and families in ways that are tailored to their needs. However, we do not see biological advances as all that are needed to create a better life for children with ASD, and their families. In fact biological advances will need to be embedded in strong human rights and ethical frameworks to ensure they do not create more problems than they solve.

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