Autistic regression linked to autoimmunity

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> ***Predisposition to autoimmunity and autoimmune NMDAr encephalitis in toddlers are associated with autistic regression***

Regression into autism, loss of language and developmental skills linked to family history of autoimmunity

'Autistic regression' is a phenomenon where a previously normally developing child suddenly loses his or her developmental milestones and previously acquired language and social skills, and regresses into autism. While the majority of patients who are later diagnosed with autism present with developmental delay from the time of their birth, an estimated quarter to a third of all autism cases demonstrate normal, that is neurotypical, development for the first 12-24 months of age, followed by a regression and loss of previously achieved developmental and verbal skills.

Symptoms such as **fever, irritability, vomiting, incessant crying, sudden changes in sleep patterns and emergence of motor abnormalities** are often noted around the time of autistic regression. There are also an increasing number of reports of unusual patterns of regression—including **repeated regressions**, regressions involving loss of gross motor function,

and/or **regressions after age three years**, and there seems to be a clear association between regression and negative long-term functional outcomes.

The reasons why autistic regression happens are largely unknown, as **regressions are rarely a subject of detailed clinical investigations**.

Emerging evidence suggests that immune dysregulation may be involved in the pathogenesis of at least some cases of autistic regression. Scientific literature abounds with case studies describing autistic regression following viral and bacterial encephalitis in previously healthy and typical children and even adolescents, as well as regression into autism in cases of autoimmune proliferative syndrome, or autoimmune anti-N-methyl-D-aspartate receptor encephalitis (see next chapter). Literature from the wider field of psychiatry points to the presence of pathological antineuronal antibodies in some patients with sudden-onset psychiatric symptoms, and resolution of those symptoms following immunological treatments.

In some of these recorded cases the patients respond remarkably well to corticosteroid or IVIG treatment. One such example is a case reported by Akcakaya and colleagues of a previously normally functioning girl who lost all eye-contact, ability to communicate, interest in socializing, and whose interests and behaviours became extremely restrictive and repetitive following viral encephalitis. In addition, this patient also displayed rigid hand postures and abnormal gait and motor function, lack of attention, all frequently present in children and adults with idiopathic autism. In this case the patient was given a prolonged hospital treatment of IVIG injections, resulting in full recovery from all autism symptoms.

In the most recent study by Scott and colleagues the authors reviewed the medical records of 240 children diagnosed with an autism spectrum disorder, including 33 cases with a documented “autistic regression variant”. The results from their analysis indicate significant associations between autistic regression and **family history of autoimmunity**, such as Type 1

diabetes and autoimmune thyroiditis, as well as preceding febrile illnesses in the child. Other non-immune risk factors did not differ between the two groups.

"Our study demonstrated that children with autistic regression differ from those with ASD with respect to family history of autoimmunity – and, in particular, maternal autoimmunity – and occurrence of a febrile illness in the 6 months prior to first concern." *(Scott et al. 2017)*

Treatable clinical condition NMDAr encephalitis can mimic autistic regression

N-methyl-aspartate receptor antibodies (NMDAR-Ab) encephalitis is an acute form of encephalitis. It is a well-recognized, clinical-immunological syndrome caused by an autoimmune reaction to neuronal NMDA receptors. While in adults the initial symptoms are mostly psychiatric in nature, there is often a rapid deterioration to medically urgent symptoms including hypoventilation, catatonia, cerebellar ataxia and loss of consciousness. The **symptoms in children can be less severe and more difficult to recognise**.

"*Patterns of presentation and etiology of anti-NMDA-receptor antibody encephalitis are dependent on age and can be challenging to recognize in very young children.*"

One of the main presenting features of NMDAR-Ab in children is **loss of language and social skills and reduced interest in surroundings**, all hallmarks of idiopathic autism.

Other presenting features in children can include: **seizures**, status epilepticus, sleep disturbances, temper tantrums, lack of appetite, dystonia, **abnormal gait, tics, hyperactivity**, psychotic episodes, irritability and agitation, including physical **aggression**. All of these features, in varying degrees of severity, are commonly present in many cases of idiopathic

autism.

In their recently published paper Hacohen and colleagues describe two cases of toddlers who presented with developmental regression that mimicked an autistic regression. The symptoms included **behavioural change, irritability, disrupted sleep, and loss of motor, language, and social communication skills**, all of which are almost universally present in idiopathic autistic regression.

NMDAR-Ab were found in the serum and cerebrospinal fluid, and both patients responded well to standard immunotherapy consisting of a combination of intravenous methylprednisolone and immunoglobulin, plasma exchange and rituximab. In one of the two patients a total and lasting remission of all symptoms was noted, including **recovery of lost language**. These improvements match those seen in other cases of autism-mimicking NMDAR-Ab previously reported in the literature, where immunotherapy treatments also resulted in resolution of movement disorders and **reacquisition of language and social skills**.

*"Patterns of presentation and etiology of anti-NMDA-receptor antibody encephalitis are dependent on age and can be challenging to recognize in very young children…The EEG usually shows nonspecific slowing without epileptiform discharges or subclinical seizures. Much more difficult to recognize are **psychiatric symptoms**…, where multiple visits to the emergency room were dismissed as very young child separation **anxiety and temper tantrums**."* (Hacohen et al. 2016)

- *Familial autoimmunity is more prevalent in autistic regression variant… (including) higher rate of familial type 1 diabetes and autoimmune thyroid disease*
- *Incidence of febrile illness preceding symptom onset is higher in autistic regression variant*
- *We suggest **immune activation as a possible aetiology of autistic regression**.*

(Scott et al. 2017)

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