

the silence within

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There can be little worse than seeing – and feeling - your own child retreat into a world that doesn't involve yours. Especially at a period of life when contact with a mother and a father is such a vital component of an infant's development. And such a pleasurable one for the parents. Autism hits about one child in a thousand – although the contours of the affliction remain hazy. There are many forms. Some more serious than others. Some widespread while others are rare, or even unique. The common denominator is what could be described as a characteristic aloneness, where those suffering from the illness are unable to interact socially and communicate in the way most of us do. Today, researchers believe that autism has a strong genetic component and that certain mutations are at the heart of autistic behaviour. One such mutation affects an enzyme known as BCKDK and may well be responsible for a rare hereditary form of autism that could be treated with a specific diet.



'Look at me', by Beth Hanson ©

founder of Autism Art Project

Courtesy of the artist

One of the earliest descriptions of autism involves a certain Hugh Blair of Borgue, an 18th century Scottish landowner, whose marriage was annulled by his brother on the grounds of a woman seeking to take advantage of psychic fragility. Her motives were apparently less for reasons of love than the prospect of gaining her spouse's inheritance. The term 'autism' was coined in 1910 by the Swiss psychiatrist Eugen Bleuler whilst defining symptoms linked to schizophrenia, and the word was chosen to describe the morbid self-absorption his patients showed. It was only in the early 1940s that the word 'autism' began

to appear in the realm of child psychopathologies and, in the 1960s, the condition was established as a syndrome per se and distinct from various forms of schizophrenia, for example.

In the mid-1970s, things were taken further and it became apparent that autistic behaviour had a genetic origin. Today, researchers believe that mutations are in fact the affliction's main cause, and autism is likely to be caused by not only one mutation but many, situated on different genes, the combination of which gives rise to autistic behaviour. This could explain why there are so many different forms of autism. And also the reason some forms appear to be unique.

Autism related to the BCKDK (or branched-chain alpha-ketoacid dehydrogenase kinase) enzyme is rare and hereditary and, so far, has only been described in eastern European families where consanguine marriages are frequent. BCKDK is a kinase involved in stopping a larger enzyme complex, BCKDH (or branched-chain ketoacid dehydrogenase), from degrading branched amino acids – namely leucine, isoleucine and valine – that humans are unable to synthesize. The kinase does this by inactivating one of the dehydrogenase's subunits. As a result, BCKDH activity is blocked. The branched amino acids are subsequently not destroyed and can be used in certain metabolisms such as protein synthesis

for instance. BCKDK will refrain from deactivating BCKDH when the levels of these particular amino acids become toxic for the body, and thus acts as a supervisor in branched amino-acid metabolism.

But what does this have to do with autism? Autism is a case of defective information processing in the brain, itself caused by nerve cells and their synapses whose organisation and connections have been altered. How this happens, and in what way, is far from understood. And there are, no doubt, as many ways as there are forms of autism. Leucine, isoleucine and valine are found in the brain where they are involved in neurotransmission. When everything is working properly, specific transporters taxi these particular branched amino acids from the blood into the central nervous system. When BCKDK is deficient, however, transport across the blood-brain barrier is modified. The seats left free in the transporters can be taken up by other molecules – amongst which glycine and tyrosine, which also happen to be neurotransmitters but of a different nature.

This particular type of autism seems, then, to depend on the metabolism of branched amino acids and, hence, their presence, or absence, in the blood. If so, would a simple diet of leucine, isoleucine and valine be sufficient to counteract a deficiency in BCKDK? Well, it seems to be the case...in mice. Mice, in which BCKDK was rendered inactive, showed signs of a disturbed

neurological system with bouts of epilepsy – precisely one of the symptoms of this particular form of autism. When the mice were given a diet of the missing branched amino acids, within a week their troubles disappeared. The same diet was fed to patients suffering from the similar form of autism – and their blood levels of leucine, isoleucine and valine did indeed increase. However, there was no observable effect on their behaviour.

Mother Nature always has the last word: life is more than just a sum of parts. However, with these tests, scientists have demonstrated that it is possible to treat a certain neurological disorder, albeit murine, by adapting an individual's diet. Scientists currently estimate that 5 to 10% forms of autism are the result of metabolic disorders. This means that these types of autism could be treated by adapting a patient's diet. Such a discovery also implies that tests could now be developed to diagnose metabolic autisms – of which there are no doubt many.

In the human population, the occurrence of autism is increasing. This is no doubt because doctors are able to diagnose it better. But our lifestyle may have something to do with it too. Metabolic analyses of cerebrospinal fluid in newborns, for instance, might help to unveil lurking forms of treatable or preventable forms of autism. And relieve the despair that runs through a family when a child moves into its silent world.

Cross-references to UniProt

BCKDK, *Homo sapiens* (Human): O14874

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