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ADHD: Is genetics the only cause?

New laboratory diagnostic methods to detect metabolic and immunological causes of ADHD

The following story demonstrates the typical frustrations of the mother of a child with ADHD: "My son would swing between fits of anger and fits of exuberance. His school called me and said that we had to do something about it immediately. The only way to get my child to take part in the classroom was to give him psychiatric medication. It saved him from being an outsider. With the medication, my child became a good pupil and he finally came to know the feeling of success. At home though, he stopped laughing and had suicidal thoughts. Give your child psychiatric medication, and you are a bad mother. Don't medicate your child, and you're still a bad mother."

What advice can a therapist give to this mother? What alternatives are available?

During the past thirty years, various possibilities have been discussed as the cause of attention deficit hyperactivity disorder (ADHD). These include child rearing errors, poor nutrition, heavy metal pollution, sugar or phosphate content in food, food allergies and genetic defects (Fig. 1). How is it possible to find the specific cause in the case of an individual child and provide the optimal therapy? Promising new findings suggest that these questions can now be answered with the help of laboratory diagnostic methods.

ADHD and the limits of the genetic model

The classic example of a hyperactive child is "Zappelphilipp" – the boy who cannot sit still – in "Struwwelpeter", a book of children's rhymes authored by the German physician Heinrich Hoffmann in 1847. Some well-known figures such as the author Hermann Hesse, the musician Wolfgang Amadeus Mozart, and the inventor Thomas Alva Edison are thought to have had ADHD.

> The issue of "inattentive, impulsive children" is not new. In recent years, however, the number of diagnoses has risen sharply.

Depending on the diagnostic criteria and research methods, the prevalence of ADHD (or ADD) in children and adolescents ranges from six to nine percent. In Germany, that is approximately 500,000 individuals (adults not counted).

Despite the many different explanations for the disorder and corresponding therapeutic approaches, one form of therapy has essentially become standard. On diagnosis according to the recognized guidelines of DSM-IV or ICD-10, more than 70% of the affected children and adolescents in Germany are treated with psychiatric medication, with or without accompanying therapy for their specific developmental disorders of scholastic skills (actual figure in 2003: 73%, tending upward).

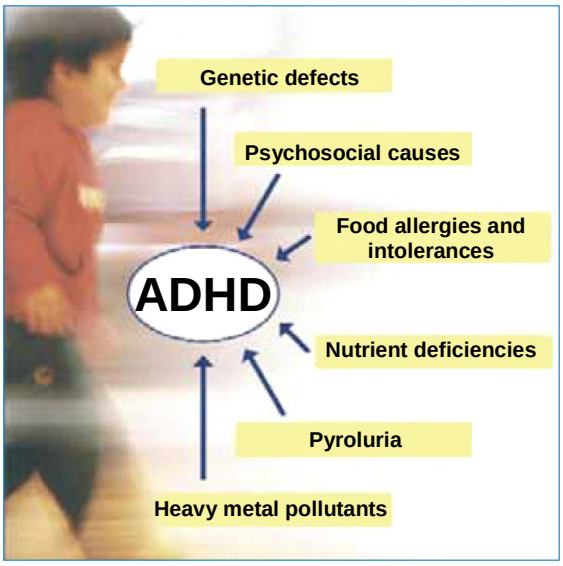

Fig. 1: Possible causes of ADHD

Why do so many receive prescription drugs in spite of parental doubts?

To answer this question, it is first necessary to look at the supposed cause of the symptoms.

The current predominant opinion is that ADHD may be a dysfunction in the areas of the brain responsible for impulse control, problem solution, and planning. It is thought to arise from deficient processing of information between the frontal lobe and basal ganglia due to metabolic disturbances in messenger substances of the brain (neurotransmitters), above all dopamine. The assumption is that insufficient availability of dopamine at the contact sites (synaptic gaps) between the nerve cells impairs the exchange of information between nerve cells (Fig. 2).

> "ADHD can be diagnosed when there is inattentive and impulsive behavior with (ADHD) or without marked hyperactivity (ADD), and when this behaviour is inappropriate to age and developmental status and causes difficulties in social relations, perception, and in school or occupational performance." Excerpt from the guidelines for the diagnosis and treatment of ADHD ("Diagnostik und Therapie bei ADHS") formulated by the German Society for Social Pediatrics and Adolescent Medicine, Deutsche Gesellschaft für Sozialpädiatrie und Jugendmedizin.

What is the cause of this dopamine deficiency? At present, genetic factors are thought to be of great importance. One of the reasons for this is that ADHD is seen to occur more often in some families than in others. Approximately half of all parents with ADHD have a child with ADHD. Twin research has provided similar findings.

These observations lead to the conclusion that the symptoms of an inherited dopamine deficiency can only be treated with medication, since the causal factor (genetic change) cannot be treated.

The stimulants which are prescribed have the same effects as dopamine and thus bring dopamine levels into balance. The effect is maintained for several hours before it is necessary to administer the stimulant again.

Medical literature reports that stimulant therapy achieves a response rate of 70–85 % in ADHD patients. The first long-term studies have shown no negative psychiatric or somatic effects due to therapy with psychostimulants. The adverse effects observed (loss of appetite, sleep disorders, dysphoria, tearfulness, headache, abdominal pain, dizziness, triggering or exacerbation of

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an existent tic disorder) are considered to be caused by doses which are too high at the beginning of treatment or which are administered at incorrect time intervals.

The experiences of some parents contradict these study results.

Other causes?

It is therefore important to ask what causes other than a genetic predisposition might be possible – keeping in mind that stimulant treatment remains ineffective in 15–30 % of the patients. One must ask furthermore, whether the genetic cause can be solely responsible for the multitude of diagnosed cases. The sharp increase in ADHD diagnoses in recent years seems to indicate that there may be other significant causative factors as well. Otherwise, the genetic status of the population must have undergone a dramatic change in a very short period of time – and this scenario is quite improbable.

First of all, emotional or social aspects may play a role in ADHD symptoms, for example if an affected child is brought up in a difficult family situation, difficult relationships between parents and children, or if the parents are overburdened with the responsibility of raising children.

Social and family counseling, parent training, and psychotherapy generally produce positive results. One important goal is to provide the children with a clearly structured daily routine and responsibilities in order to improve their capacity to solve everyday problems with homework or when playing with friends. Dedicated kindergartens and schools are other supportive measures, as they can provide small groups and the possibility for more intensive teaching support, sometimes also with occupational therapy, psychomotor training, as well as reading and writing exercises to improve specific areas of weak performance. Parents and children need a great deal of perseverance and patience, because behavioral therapy can take a number of years to be effective.

It is also particularly important to realize that a dopamine deficiency may result from causes other than the genetic predisposition.

Here it is helpful to take a look at the metabolism of food:

Neurotransmitters are generally formed from amino acids with the help of various enzymes. In general, these enzymes require co-factors such as vitamins and minerals in order to produce an adequate number of neurotransmitters from the relevant precursors. In order to provide adequate amounts of amino acids, vitamins, and minerals to the body, the intestines must have an adequate uptake of these nutrients. If the body is undersupplied with these necessary building blocks, for example in the case of intestinal disorders or metabolic diseases, this can also lead to a dopamine deficiency.

These facts explain why products that contain the essential building blocks for neurotransmitter synthesis can sometimes provide further help in the treatment of ADHD – omega-3 fatty acid products or AFA algae, which are rich in vitamin B and zinc.

The discussion concerning the influence of heavy metals in ADHD is also consistent with an exogenous induction of a deficiency in nutrients for the synthesis of neurotransmitters. Heavy metals can inhibit the action of enzymes in general. Some ADHD patients are found to have a concentration of aluminum that is elevated by approximately 30%, and it is possible that this causes them to have a nutrient deficiency. Aluminum affects the metabolism of zinc and vitamin B6, both of which are important for the synthesis of neurotransmitters.

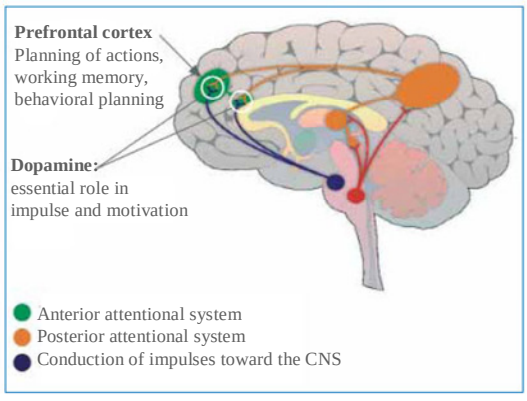

Fig. 2: Site of dopamine action

Finding alternatives with new laboratory diagnostic methods

There are now a number of indications that food intolerances and nutrient deficiencies are significant causative factors in ADHD, along with genetic and psychosocial factors. But how can we assess the relative significance of genetic factors and the various environmental factors? To find a diagnostic method capable of an individual determination of causal factors in each patient – in order to provide the appropriate therapy – would be an enormous step forward.

Psychosocial factors cannot be measured using laboratory diagnostic methods, but they can be revealed in direct interchange between the patient and a therapist. Neither is there a test that can reveal genetic changes connected with ADHD. However, it is now possible to determine the influence of metabolic and immune system parameters using laboratory methods, and this allows an indirect assessment of the genetic contribution.

In the first step, a blood sample is taken for examination by way of a so-called nanoparticle analysis (NPA). Nanoparticle analysis makes it possible to analyze typical metabolic products and identify deviations from the standard concentrations and to detect and identify abnormal metabolic products. This method identifies possible disorders in the body and their influence on metabolic changes. NPA results are particularly predictive because this method analyzes not only the serum parameters but also the blood cells. This can show, for example, that the absorption of nutrients through the intestinal wall is inhibited, that there is a deficiency in mineral nutrients, and/or that there is a problem in the immunological processes.

A retrospective analysis of several hundred patient cases has shown three factors which turn up particularly often in the histories of ADHD children (refer to Fig. 3) (4):

- Zinc and vitamin B6 deficiency due to pyroluria,
- Gastroenteropathies (above all impaired absorption in the intestines),
- Food allergies of delayed type (Type III).

Pyroluria

This is a metabolic disorder in which a fault in hemoglobin synthesis results in

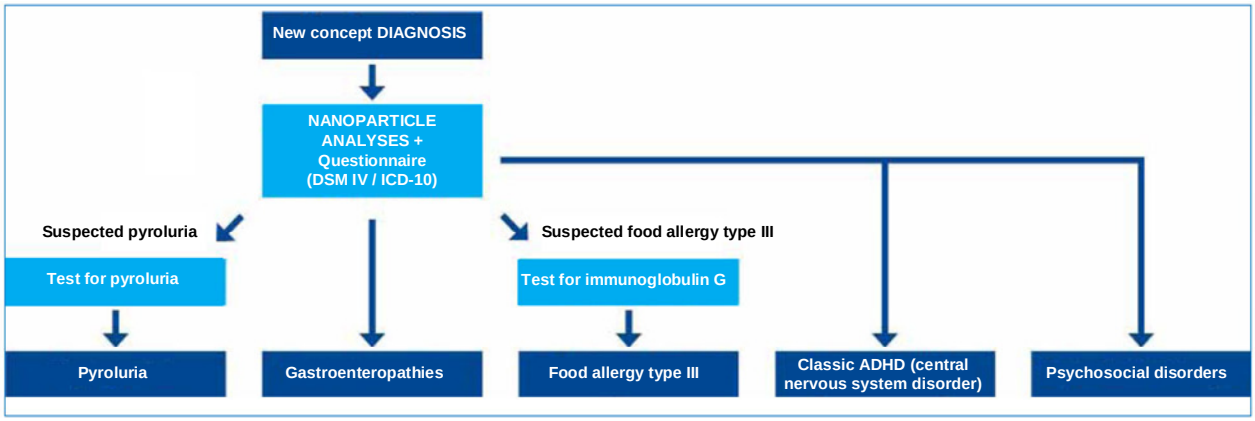

Fig. 3: New laboratory diagnostic approach for ADHD

the formation of kryptopyrrole. This binds zinc and vitamin B6 in a chelate complex and washes these nutrients from the body via the urine. Vitamin B6 is an important co-factor for the synthesis of the sleep-inducing and mood-enhancing neurotransmitter serotonin. Zinc accelerates the release of neurotransmitters, and it is a co-factor in the metabolism of fatty acids. A lack of vitamin B6 and zinc due to pyroluria can exert a negative influence on neurotransmitter balance.

If NPA raises a suspicion of pyroluria, this method can be followed by a specific analysis of the urine for kryptopyrrole in order to determine the severity of the disorder and the appropriate therapy (high doses of vitamin B6 and zinc, monitored by laboratory tests). There are often also secondary nutrient deficiencies caused by impairment of the immune defense in the intestinal mucous membranes; pathogenic bacteria and fungi can then spread, impairing nutrient uptake. In many cases, this explains why pyroluria therapy is only successful in the long-term if it is accompanied by colon cleansing.

Impaired absorption

If NPA indicates impaired intestinal absorption, reconstruction of the intestinal barrier is the main objective of treatment. For extreme dysbiosis, it is necessary to reduce the population of pathogenic bacteria and fungi, and above all to establish a physiological intestinal milieu by regulating the pH level, to nourish the substrate of beneficial intestinal flora with the help of probiotics, and to regenerate mucous membranes of the intestines.

Food allergy type III

NPA often raises a suspicion of type III food allergies. These so-called “delayed food allergies” must not be confused with the classic type I allergies. Type III allergies can occur after damage to the intestinal wall (for example due to antibiotic therapy or viral infections) which can make the immune system hypersensitive to foods by way of IgG antibodies. Overloading the immune system as a result of continuous IgG production can lead to the formation of immune complexes consisting of the food antigen and IgG antibodies. Such immune complexes are stored in the body and are then broken down by means of an inflammatory reaction. This releases inflammatory mediators, above all TNF-alpha. TNF-alpha can activate an enzyme in the presynaptic gap between nerve cells – monooxygenase – which cleaves dopamine. When a delayed allergic reaction to food increases the production of the inflammatory mediator TNF-alpha, it increases the monooxygenase enzyme activity, and this can lead to a dopamine deficiency (Fig. 4).

If NPA identifies a type III food allergy, the next step is to undertake a food-specific IgG test to identify exactly what type of food this antibody targets. It is recommended to use a test for antibodies to foods which children eat in particular (for example, the ImuPro AD(H)D Test).

Diets

An individual elimination-rotation diet based on the test findings may stop the inflammatory reaction and thus relieve one of the causes of dopamine deficiency in the ADHD patient.

It is interesting that the success of the approach agrees very well with the connection between nutrition and ADHD which has been discussed for several decades. Comprehensive experience as well as the results from several studies are available now.

The Feingold diet and the phosphate diet are considered to be less successful medical-nutritional approaches. The Feingold diet helps in some individuals (approximately 1–2 %). It was developed in 1975 by the American medical doctor and scientist Benjamin F. Feingold. According to Feingold, ADHD is caused by artificial coloring and preservatives as well as salicylates in food. Salicylates are found naturally in, for example, oranges, apples, apricots, tomatoes and some spices.

The phosphate theory currently appears to be disproven. About 25 years ago, the pharmacist Hertha Hafer developed the theory that foods containing phosphates decrease the body's acid level and shift the acid-alkaline balance to the alkaline range, thus inhibiting the function of the neurotransmitter noradrenalin. Because of the lack of minerals (above all magnesium) and the presence of phosphate in such a variety of foods, this diet is not recommended.

On the other hand, the oligoantigenic diet developed by Professor Egger of Munich University’s Hanauer’schen Kinderspital has been successful since the 1980s and 1990s. He found a correlation between ADHD and food intolerances and/or food allergies. This led to the creation of his “oligoantigenic diet”, which consists of only a small number (= oligo) of foods (known by experience to very seldom trigger allergies and intolerances) which

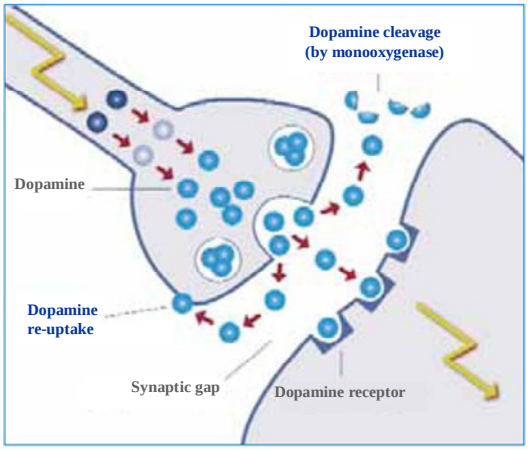

Fig. 4: The dopamine pathway in the synaptic gap

are administered with vitamin and mineral supplements under medical supervision for a period of three to four weeks. After improvement of the symptoms, various foods are reintroduced to the diet one by one, while continuing to monitor the symptoms. The process takes three to six months. Improvement of the hyperactivity, concentration, memory, impulsiveness, and social behavior as well as relief of sleep impairment could be achieved in up to 70 % of the patients in a variety of studies. Out of 48 different foods and food additives, cow milk, chocolate, wheat, cheese and eggs were those which triggered behavioral disorders most often. It is particularly interesting that similar results were presented already at the end of the 1970s by Professor Doris Rapp and were also published in a medical practice handbook in 1996. Other studies (2, 7) have shown as well that elimination diets can reduce symptoms significantly.

When implementing an elimination diet, taking the individual situation of the child into consideration is decisive.

The elimination diets that have generally been used up to now are tedious and cannot be as targeted as a nutritional change that is based on an individual diagnosis. This might also explain why no or only minimal effects could be determined in several of the earlier studies. With the help of a specific IgG diagnostic method to be used on suspicion of a type III food allergy, it is now possible to apply a very closely targeted therapy. (It is important to test for total IgG, because the only subtypes that can form immune complexes and thus induce a release of TNF-alpha are IgG_1, IgG_2 and IgG_3. IgG_4 does not have that capacity, so it is not reasonable to test for this in connection with ADHD.)

In the meantime, several hundred children with ADHD have been examined by this method and have been treated successfully with appropriate elimination diets (4).

It is interesting to note that medical guidelines also mention the helpfulness of specific diet therapies conducted under medical supervision in improving the overall situation in cases that are accompanied by allergic disorders. This can be evaluated as a cautious trend toward metabolic and/or immune system conditions as causative factors of ADHD.

ADHD therapy – need for rapid and lasting effects

Prescription of a psychiatric drug is currently the main treatment form, often in spite of doubt on the part of the parents. How can this be explained? It is essentially because medical teaching with regard to ADHD is based on the model of a genetic disorder affecting neurotransmitter balance. In this model, other causes are considered as supportive or secondary aspects at most. As a consequence, the treatment recommended by the wide majority of pediatricians is a symptomatic therapy with psychostimulants.

Looking at the often desperate situation of the parents and children makes other motives discernible. Pressure from the school and social environment is frequently so strong – and the time window for finding a solution is so narrow – that a rapid and effective solution in the form of psychiatric medication becomes the treatment of choice.

The “genetic” cause also relieves these children from the pressure of being considered “bad” and frees the parents from criticism of their supposed lack of child-rearing capabilities or other errors that could be made when raising children – because no one can be made responsible for their genes.

Another important element is the recognition of these therapeutic methods by mainstream medicine in the form of medical guidelines. The resultant cost reimbursement by health insurance companies also supports the acceptance of psychiatric medication by the parents.

The importance of everyday routines in the home and medical practice is not to be underestimated. Taking medicine fits relatively smoothly and discretely into the daily life of the person who needs therapy. More complicated and time-consuming alternative approaches – such as a change in nutrition – often require a major change in daily routines and family life, so they do not appear suitable as an immediate measure. In addition, many pediatricians feel they lack the time to explain and implement complicated therapeutic approaches, so these therapies find little interest.

A combination of all these factors is what makes the use of psychiatric drugs so attractive as the standard therapy. Most importantly, they provide rapid help. With this medicine, the child usually settles down and become more attentive and less aggressive – the personality appears to be in better balance.

All the same, more and more voices are calling for multiaxial diagnostic methods, for example at annual conferences of the European pediatricians (in Bregenz, Austria, September 2006 to name one). In the most recent medical publications, certain genetic disorders which influence ADHD are no longer described as the sole cause, but as “risk inducing” (6).

It is time now to give the genetic model as “the” cause of ADHD a thorough reconsideration. New diagnostic options show that the metabolism-based – and possibly widespread – causes of ADHD can be differentiated and that the current standard therapy can be optimized in the interests of those it concerns.

Identifying and eliminating individual causes is a better option than long-term symptomatic treatment.

The definite elimination of causes, for example in a change of nutrition in the case of type III food allergies, is often not a rapid or simple solution – but it is a lasting solution in those cases.

This option is worth careful consideration, in particular once the acute social pressure is relieved by the use of psychiatric drugs. It can also be valuable to look for further causes other than those which have been assumed up to now. The new laboratory diagnostic methods make it possible to provide treatment of the metabolic causes of ADHD and thus to provide the hope of lasting efficacy for some who live with ADHD.

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