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Self-Injurious Behavior: Treatment with Disease-Specific Medical Therapies

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Abbreviations

SIBs: Self-Injurious Behavior; PKU: Phenylketonuria; SLOS: Smith-Lemli-Opitz syndrome; DHC: Dehydrocholesterol; CFD: Cerebral Folate Deficiency; 5-MTHF: 5-Methyl-Tetra-Hydro-Folate; MTHFR: Methylene-Tetra-Hydro-Folate Reductase; AGRE: Autism Genetic Resource Exchange; SAMe: S-Adenosyl-Methione

Introduction

Psychological and behavioral symptoms, such as self-injurious behavior (SIBs), can be the expression of an underlying disease entity, sometimes even previously unidentified. When possible, the best approach to self-injury for such individuals is to anticipate the possibilities of these complications long before they actually occur by preventing or ameliorating the disease entity itself. Many diseases of the central nervous system that have self-injury are the symptomatic expression of impaired common final pathways, pathways likely altered well before birth in most cases. The abnormal functions begins to show up as the individual's brain grows, connecting and pruning (or failing to prune) essential developmental pathways. Unfortunately, in the majority of these individuals, the detection of the precise medical mechanism of action in the central nervous system that causes the underlying disease entity has not been found, so the detection and medical treatment of the underlying disease and its symptoms, including self-injury, has not yet been devised.

However both autism [1] and schizophrenia [2] have a number of separate identified underlying disease entities with the possibility of a specific medical therapy. For some of these diseases and some groups of patients, a targeted medical therapy that is based on an understanding of the mechanism of action causing the disease entity in the first place has been found. Such specific therapies can prevent, reverse or ameliorate the symptoms of SIBs and other behaviors. It is never too late to try a known therapy for a specific disease when self-injury presents. Also a biochemical abnormality has been found in individuals with autism that can stop a form of ocular self-injury. These medical approaches should be ruled in or out as other more non-specific approaches to self-injury are used to help the suffering individual.

Targeted medical therapies of specific diseases

Phenylketonuria (PKU)

We shall start with phenylketonuria (PKU) that can underlie autism or schizophrenia because it has a special lesson to teach us today about trying medical therapies no matter how old a patient is Phenylketonuria (PKU) was one of the early examples establishing that autism was a syndrome of more than one disease instead of a single disease [3]. It was first diagnosed in 1934 and its treatment of a very low phenylalanine diet was developed in 1953. However the diet therapy only worked if started within weeks of birth so this led to the institution of neonatal screening which has made PKU an almost vanished disease in most countries by the twenty-first century. Unfortunately for patients missed by the screening and thus not diagnosed in time for dietary therapy, some have prominent autistic symptoms [4,5]. Very rarely PKU can present as schizophrenia - most but not all individuals have some degree of mental retardation [2].

The special lesson PKU has to teach us today involves an elderly man with phenylketonuria who had never received any dietary treatment for his PKU. At an advanced age, he was placed for the first time on a phenylalanine-restricted diet [6]. He had been suffering what was described as "severe self-injury".

Monitoring of plasma phenylalanine levels and his behavioral state at identical intervals indicated that the severe self-injury was definitely reversible, but only when plasma phenylalanine concentrations were titrated to near normal ranges. In other words, in spite of his age, when his underlying disease was treated medically by an adequate protocol, it was possible to at least reverse the self-injury, even if his other symptoms could not be ameliorated.

Smith-Lemli-Opitz syndrome

The Smith-Lemli-Opitz syndrome (SLOS) is congenital anomaly syndrome with an extremely broad clinical phenotype. The syndrome occurs in 1:20,000 newborns with an estimated gene frequency in the US Caucasian populations of 1 to 2% [7]. Various series have found that between 50 to 86% of the children with the SLOS meet the full diagnostic criteria autistic features [2]. For those who survive the neonatal period, both physical and behavioral/cognitive problems persist. Physical anomalies often include microcephaly, a small upturned nose, ptosis, micrognathia, cleft palate and hypospadias. Limb anomalies are common, and 80 to 95% these patients have a distinctive syndactyly of the second and third toes [8], making it easier for clinicians to suspect their underlying disease on the initial examination.

The behavioral phenotype is first seen in infancy with irritability, lack of interest in feeding and preferring not to be held. As they grow, SIBs may begin including self-biting, head-banging and trichotillomania as well as irritability, hyperactivity and sleep disturbances. Many children meet the full diagnostic criteria for autism [2]. The Smith-Lemli-Opitz syndrome is caused by a mutation in the gene DHCR7 encoding 7-dehydrocholesterol ?7 reductase, the enzyme that catalyzes the last step of cholesterol biosynthesis. More than 130 different mutations of DHCR7 have been reported in individuals with SLOS. This defect causes low or low-normal plasma cholesterol levels and increased 7- and 8-dehydrocholesterol (DHC) levels. The clinical suspicion of SLOS is best confirmed by testing for elevated 7DHC by gas chromatography relative to the cholesterol level.

There are a number of reports of treatment of SLOS by cholesterol supplementation [7-13]. Sometimes the treatment is combined with statins or other approaches. These reports often, but not always, show improvements in various aspects of SLOS in small groups of patients. Since dietary cholesterol is not believed to cross the blood brain barrier, it is puzzling but of interest that a number of these reports of cholesterol supplementation show clearcut improvements in many different kinds of SIBs, including trichotillomania. Although one 2.5 month double blind study of cholesterol supplementation failed to find a reduction in behavioral abnormalities [13] and although prospective clinical trials with validated outcome measures of medical therapies have not yet been undertaken, the correction of the biochemistry of an autistic individual with SLOS who is self-injurious might be at least well worth a try.

Cerebral folate deficiency (CFD)

Cerebral folate deficiency is defined as a neurological syndrome associated with a low cerebrospinal concentration of 5-methyltetrahydrofolate (5-MTHF) in the presence of a normal peripheral folate status. Because there are several known, different underlying etiologies with different mechanisms of action [14], cerebral folate deficiency is itself more than one disease entity, that is, it is a syndrome. The classic symptoms of the syndrome consist of intellectual disability, regression and often seizures. The treatment of the folate deficiency is folinic acid. One of the numerous etiologies of the syndrome of homocystinuria (methylenetetrahydrofolate reductase-MTHFR-deficiency) may, in limited cases, may partially respond to folinic acid therapy.

In one study [15,16] where seven children with the syndrome of CFD were studied, five of the seven children also met diagnostic criteria for autism. Moretti et al. (2005) [17] also had published an earlier case history of a six-year old girl with autistic features with cerebral folate deficiency. Folinic acid-responsive seizures are a very rare treatable cause of neonatal epilepsy [18]. Another type of cerebral folate deficiency with severe SIBs has recently been reported [19]. A single case of a child with autism who had folate reduced in both plasma and cerebrospinal fluid is in the medical literature; the MRI of this child was suggestive of some kind of demyelination disorder [20]. The presence of folate receptor antibodies in one or both parents increases the risk of having a child with autism.

Genotype-phenotype correlations in children with autistic features and metabolic disease are just beginning to be understood. Evidence suggests that autistic features sometimes may be associated with errors in folate metabolism that contribute to the hypomethylation of DNA. In a review of the Autism Genetic Resource Exchange (AGRE) collection, four specific behaviors -- including a history of SIBs -- were more common in individuals with at least one copy of the T allele of the 677C-T polymorphism of the gene MTHFR. These behavioral patterns could be explained by the difficulties of converting 5,10-MTHF to 5-MTHF [21]. These patients and others with abnormal folate levels have potentially treatable dysfunctions of folate metabolism.

Pyridoxine-dependent epilepsy

Even rarer than the cerebral folate deficiency syndrome is pyridoxine-dependent epilepsy. Autistic features often develop [22,23]. In the case described by Burd et al. [24] (2000), SIBs accompanied the autistic disorder. Usually the seizures and other symptoms occur in the neonatal period but they can start as late as 2 years of age. The seizures are resistant to antiepileptic drugs but can be controlled by lifelong oral pyridoxine.

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Lesch-Nyhan syndrome

The Lesch-Nyhan syndrome is a classic disease of SIBS - it presents with self-mutilation and other self-injurious behavior [25]. Serious self-biting of lips and fingers to the point of mutilation plus other types of self-injury are found in this syndrome.

Lesch-Nyhan syndrome is caused by a nucleotide depletion of purine nucleotides (e.g. ATP, GTP), due to hypoxanthine phosphoribosyltransferase deficiency. A compound, S-adenosylmethione (SAMe), appears to partially alleviate the purine depletion in some patients and result in a reduction of the self-injury. First described by N. Glick in 2006 [26] as a dramatic reduction of self-injury in a Lesch-Nyhan individual, a number of other patients have since been helped by SAMe. Five children from Malaysia, including a girl, had a positive outcome [27]. In another series of fourteen patients, whose authors included WL Nyhan, only four patients tolerated the drug and reported beneficial effects; the remainder experienced worsened behavior [28]. SAMe appears to help only certain selected individuals with the Lesch-Nyhan syndrome but it certainly is worth a try in any individual with this severe disorder.

Tuberous sclerosis

Individuals with tuberous sclerosis can present clinically as either autism or schizophrenia, but autism is by far the more common presentation. Between 20 to 50% of children with tuberous sclerosis have autistic features [2]; tuberous sclerosis can present with autistic regression. This is a genetic disease that causes benign tumors to grow in the brain and other organs. One of two different genes underlies this disease entity; individuals with tuberous sclerosis are found to have mutations either in the gene TSC1 or the gene TSC2. There is increased risk for developing autistic behavior in children with tuberous sclerosis in the presence of the following features - TSC2 mutations, temporal lobe tumors, history of infantile spasms, early age of seizure onset and resistance to antiepileptic treatment. Between 85% to 90% of individuals with tuberous sclerosis have seizures; however early surgical removal of tubers in the brain can sometimes result in freedom from seizures [29].

The frequency of SIBs in tuberous sclerosis is about 10%, most often seen in children with the TSC2 mutation, autistic features, history of infantile spasms, history of seizures and intellectual disability [30]. There is one child with tuberous sclerosis published in the medical literature that became blind from self-inflicted ocular injuries [31].

The Food and Drug Administration has approved two treatments for tuberous sclerosis complex - these are everolimus and vigabatrin [25]. Both drugs have a number of side-effects and have not yet been systematically studied in children with tuberous sclerosis with autistic features. But a trial of these medications would be indicated in an individual with tuberous sclerosis who was suffering from SIBs.

Neurosyphilis

Neurosyphilis, infection of the brain by the spirochete treponema pallidum, has long been known in some cases (19% in one series) to be so characteristic of schizophrenia that the signs of general paresis when detected in the CSF can come as a great surprise [32]. Like all types of severe schizophrenia, SIBs is occasionally seen. Penicillin is a proven therapy for neurosyphilis.

Hartnup disease

Hartnup disease is a recessive hereditary disorder characterized by neuropsychiatric symptoms, a pellagra-like rash and temporary cerebellar ataxia. Although the disease can very rarely present with autism, its usual age of onset is either late childhood or adolescence with bizarre delusions, hallucinations, and feelings of depersonalization, meaningless talk and rarely SIBs. If there is no clouding of consciousness, the symptoms may mimic schizophrenia. Treatment with nicotinamide can be successful in reversing the symptoms in some cases [32].

Targeted Medical Therapy of a Biochemical Abnormality

In 1974, a large study was conducted of 78 children with autism in Washington D.C., soliciting families from all over the country to participate. The children were matched with age, sex and parent-income controls. After all the analyses were completed, the results were published in 1976 [33].

The study included 24 hour urine samples for calcium, phosphorus, magnesium, creatinine, uric acid, sodium and potassium. 24 hour urine samples are difficult to obtain in any child; in children with autism it is indeed quite difficult, but the highly motivated parents obtained them and a check by creatinine levels showed almost all were successful. Two abnormalities were found to be statistically significant in the autistic children compared to the controls in the 24 hour urines. The first one, levels of uric acid, was abnormal in children under 12 years of age but was not significantly different in older children. This finding was later replicated in later patients and the age cutoff was found to be correct; the meaning of this finding of purine dysfunction in younger children with autism is unknown.

The other finding from the study was a lower level of calcium, with a significant difference of between autistic and control urines of $p < 0.01$ [33,34]. Accurate 24 hour urines had been obtained for this variable in 72 patients and 67 controls. Sixteen of the seventy-two children with autism (22%) had hypocalcinuria (levels below two standard deviations for controls). Serum levels of calcium for all children in the study were within normal limits except for one of the children with hypocalcinuria who had a serum of 8.1mg% and a urine of 0.0 mg%.

A second study by Rosenthal [35] (1985) also conducted in the United States included calcium in serum and 24 hour urines. Of the 37 children with autism tested, all had normal serum

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levels and 7 had hypocalcinuria (18%). A third study in France of 21 children with autism [36] found normal levels of calcium in both serum and urine.

Later studies of children with autism and hypocalcinuria in the clinic found no evidence of kidney dysfunction, or abnormalities in parathormone, calcitonin or 1,25 dihydroxyvitamin D3. However a clinical abnormality was noted in a few of the hypocalcinuria patients - a SIBs of ocular damage ranging from simple eye poking to corneal lacerations to vitreous hemorrhage to retinal detachment to actual nucleation of the eye itself in one case. One young boy explained to the examiner that he was eye-poking because his eyes "felt funny."

Most patients in the clinic with hypocalcinuria did not have ocular self-mutilation. However all the patients in that clinic with autism and ocular self-injury did have hypocalcinuria when tested and they did cease their ocular damage when they were placed on liquid supplements of calcium large enough to cancel out their hypocalcinuria, often quite big doses [35]. Each patient had their own individual dose based on his own urine level. Since excess calcium is not good for other organs, such as the heart and brain, patients on calcium supplementation need to be monitored by 24 hour urines twice a year as they grow.

Recently an autopsy study reported that six children with autism had calcium levels significantly elevated in their temporocortical gray matter [37], a finding that might help explain why the kidney was conserving calcium - trying to prevent hypocalinemia - in some individuals with such self-destructive ocular behavior. Also genetically there is a list of nine proteins encoded by calcium-related genes found involved in autism; mutations in those genes all result in abnormal calcium homeostasis in the patients [38]. Although the mechanisms and locations in the cell involved in each gene mutation are different, they each result in amplifying Ca (2+) signaling. This need for extra calcium in the brain might help explain why the kidney, whose job it is to regulate calcium levels in the blood, was conserving calcium in one out of five of the patients with autism - trying to prevent hypocalinemia which could harm other organs in these individuals. One example might be to try to prevent the osteoporosis that can develop as early as adolescence in some individuals with autism. Another way to elevate calcium in a child with autism is add vitamin D; there is a single case in the literature of a 32-month-old male whose head banging against objects almost stopped with vitamin D supplementation [39].

These studies with ocular self-mutilation indicate that irritating, abnormal neurological sensation in the eye underlies this kind of SIBs in many individuals. It is possible that this principle applies to some other disease entities with ocular SIBs. Since publication of the 1994 paper, the author has received information from physicians treating schizophrenia with ocular SIBs where calcium supplementation appeared to help (Coleman, not published).

Conclusion

In children and adults with autistic features and self-injurious behavior, it is important to do a diagnostic check for disease entities which have the possibility of medical treatment. In those individuals with ocular self-mutilation, it also is important to obtain calcium levels in 24 hour urines.

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