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Strong multi-sibling presence of manifestations of the condition called the increased cellular permeability syndrome without parental presence adds confusion to the mechanism of inheritance in polygenic disorders

Abstract

The increased cellular permeability syndrome related to relative dopamine deficiency allowing infiltration of unwanted irritants into various tissues may be the most common cause of a great number of chronic disorders including pain or organ dysfunction. Whether the tissue itself is more permeable related to genetic disorders, infection, or even trauma, or relative dopamine deficiency or both can provide the explanation for the association of various pathological entities in different organ systems. They all have in common a very effective ameliorative response to treatment with dopaminergic drugs which supports the hypothetical mechanism stated above. Recurrent aphthous Stomatitis (RAS) is one of these conditions that responds to dopaminergic drugs e.g., dextroamphetamine. Presented are cases of RAS in all 6 siblings and manifestations of other chronic conditions (but not all the same in those who responded very well to dopaminergic therapy) that were markedly ameliorated following dopaminergic drug therapy. However, the parents, almost 70 years old, neither have RAS or other chronic conditions. This manuscript hypothesizes as to how these polygenic disorders can be so strongly represented in the 4 siblings who were evaluated but not the parents. Perhaps these cases can provide more insight into the hereditability of polygenic disorders.

Keywords: Increased cellular permeability syndrome; Recurrent aphthous stomatitis; Dopamine; Heat intolerance; Chronic fatigue.

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Introduction

Many chronic recurrent disorders whose etiology is considered to be of an autoimmune nature (e.g., inflammatory bowel disease, pelvic pain with endometriosis, rheumatoid arthritis, pancreatitis, hepatitis, interstitial cystitis), are considered to be of a heterogeneous nature related to a multifactorial etiology which includes genetic hereditability, combined with environmental factors which combine to produce the clinical syndrome [1-4]. For this reason, many of these disorders are treated by drugs that inhibit the inflammatory pathway e.g., corticosteroids and immunosuppressive drugs (e.g., adalimumab) aimed at blocking tumor necrosis factor alpha and other drugs aimed at inhibiting other downstream pathways leading to invasion of leukocytes into certain tissues. Unfortunately, these drugs are not always effective and yet present increased risk of short-term side effects and even long-term serious complications.

Based on studies of the mechanisms for successful embryo implantation, there was experimental support for the need to stimulate autoimmune stripping of the thick cell walls of some of the uterine arteries during the proliferative phase to develop some thin-walled spiral arteries to allow nutrient exchange

between mother and fetus [5]. The hypothetical mechanism involves the effect of progesterone in blocking the release of dopamine from sympathetic nerve fibers. Dopamine functions to diminish cellular permeability by inhibiting dopamine. This allows infiltration of irritants into pelvic tissues that initiates the inflammatory response [6-9]. Evidence to support this concept is based on very quick, marked amelioration of a wide variety of chronic treatment refractory inflammatory conditions following treatment with dopaminergic drugs that results in long lasting improvement as long as treatment is continued, but usually returns quickly if the treatment is stopped [10,11].

According to this concept, the main genetic factor responsible for these chronic autoimmune disorders is increased cellular permeability modified by other genes, or environmental issues e.g., infection or even trauma [12]. It is common for patients with some of the chronic disease manifestations of the increased cellular permeability syndrome to have a family history of these conditions in one or both parents and possibly siblings e.g., pelvic pain with probable endometriosis or inflammatory bowel disease. If these are 2 separate inherited genes e.g., the one for increased cellular permeability in general, and one that makes pelvic tissues more susceptible to increased permeability from some noxious influence, a mother and daughter may both have developed pelvic pain possibly with the presence of endometriosis documented. However, the gene for relative dopamine deficiency could result in the presence of pelvic pain with or without endometriosis in the mother, but Crohn's disease in either the daughter or son based on other genes making the bowel more susceptible to the damage from environmental factors or relative dopamine deficiency.

Failure for development of any manifestations in children of parents with the increased cellular permeability syndrome could be related to lack of exposure to an environmental initiating factor, or too early in life for manifestation of one of these chronic illnesses which will develop later in life, or not inheriting the gene for increased cellular permeability (or relative dopamine deficiency), plus several other theoretical explanations. The manuscript reports several siblings that share one manifestation of this syndrome (recurrent aphthous stomatitis) yet, also, each of the 4 that we evaluated having different manifestation of the syndrome. Evidence that the various comorbidities were related to the increased cellular permeability syndrome was based on the fact that they all responded quite well to the dopaminergic frug dextroamphetamine sulfate. However, one of the genetic conundrums associated with this strong familiar predisposition to this polygenic condition is the total absence of any manifestation of the increased cellular permeability syndrome in the parents.

Case reports

Case 1

A 22-year-old woman consulted our practice regarding symptoms of vasomotor symptoms (hot flashes) that were worse whenever she was eating, severe fatigue, weight gain of unknown origin, dyspnea on exertion, heat intolerances, and insomnia (possibly related to vasomotor symptoms). She thought that there may be an endocrinology etiology for these symptoms, so she consulted our reproductive and medical endocrinology practice [13].

Though she did not think that her history of severe Recurrent Aphthous Stomatitis (RAS) was connected to the above symptoms since these new comorbidities started about 1 year before we evaluated her, but the RAS was present since age 3. The RAS caused severe pain and mouth ulcers which frequently exceeded 50 at a time and would occur at least 20 days per month. If she developed a febrile illness from a viral illness the RAS may occur daily for months at a time [13]. Following Treatment with the dopaminergic drug, dextroamphetamine, all of these symptoms subsequently completely resolved. These symptoms have remained completely eradicated for the 13 years she has remained on amphetamine therapy. Her career sometimes requires her to reside in Ireland for several months at a time. Sometimes she runs out of her dextroamphetamine for a few weeks. There are never any withdrawal symptoms from quick cessation of the drug, but all of her symptoms return within a few days of stopping (the RAS activity resumes within 1 day) but resolve again within a few days of resuming the drug. She did lose the 10-pound weight that she gained during the previous year, no longer had dyspnea on exertion, or fatigue, or mild heat intolerance and most importantly, no RAS.

Case 2

Based on the great improvement with dopaminergic treatment, case 1 referred her 17-year-old brother. He also had RAS since childhood but not as often and not as severe as his sister. He too had heat intolerance, but his symptoms were much worse than his sister's. In fact, he had some episodes that were so severe it would feel to him that he was on fire, and he was given permission in high school to immediately leave the classroom, go to the men's room, strip off his clothes and douse himself with water [13]. Similar to his sister, he has no heat intolerance or RAS for the 12 years he has been taking dextroamphetamine sulfate 30 mg/day.

Case 3

Based on the great improvement in his sister and brother, a third sibling sought our help for his RAS but also severe gastrocolic reflex that prevented him from finishing a meal without having to find a bathroom to defecate [11]. Besides the urge to defecate he had severe abdominal pain relieved by defecation. Following treatment with 15.5 mg dextroamphetamine sulfate he has not had a recurrence of the RAS (which he would have for about 25% of the year) and no longer has gastric colic reflex. He has also had marked improvement of chronic fatigue similar to his sister [11].

Case 4

Another sibling also had a history of RAS but not as bad as case 1, but similar to case 2 and 3. After recounting the history of her 2 siblings and their good response to dextroamphetamine her family physician treated her with 6.7 mg dextroamphetamine sulfate for 2.5 months before we saw her. She also had a history of pelvic pain.

She was 33 and wanted to discuss possible oocyte freezing for the future since she was not married at the time. Her serum Anti-Mullerian Hormone (AMH) level was borderline low. (Low AMH is less than 1 ng/ml and she was 1.08). Also indicative of decreased oocyte reserve was her increased day 3 serum FSH o0f 16.4 with a serum estradiol of 45 pg/nl. She was only able to obtain 3 metaphase II eggs which were frozen.

She was increased to 18.8 mg dextroamphetamine sulfate which she continues to take for the last 5 years. There has been

no recurrence of the RAS, and the pelvic pain has been eradicated. She is still not ready to conceive so the eggs remain frozen and not fertilized.

There are 2 other siblings who have mild RAS also, but the frequency and severity are not sufficient for them to seek our help with dopaminergic therapy. Also one of these 2, a brother, developed a severe myeloproliferative disorder and was treated with chemotherapy and is under the care of hematologists.

Discussion

There are several reasons for recounting the 3 cases that have been previously published concerning the increased cellular permeability syndrome and the new presentation of a 4th case (case 4). One purpose is to familiarize the reader with the very common increased cellular permeability syndrome concept of autoimmune chronic pathologic disorder, and the marked benefit of dopaminergic drugs. Though most medical professionals are familiar with the specific clinical manifestation of the increased cellular permeability syndrome, they are generally not cognizant of the theory that they all have in common the inability to preclude infiltration of irritants into certain tissues causing inflammation and pain, or disrupting mitochondria function causing chronic fatigue or allowing transudation of fluid from intravascular to extravascular space causing edema and weight gain or vasomotor instability probably related to infusion of irritants into the heat regulation center in brain tissue causing disruption of the temperature regulation system related to increased cellular permeability as seen in these 4 cases [14-25].

Furthermore, related to chronic inflammation of the ovaries, the increased cellular permeability syndrome may be the most common etiologic factor causing DOR as seen in patient 4 [26]. The fact that all 6 siblings have some form of RAS indicates that there are some genetic factors causing relative dopamine deficiency leading to not only the RAS but the various morbidities of edema and weight gain, chronic fatigue, heat intolerance, DOR, pelvic pain, and gastrocolic reflex. The RAS is probably also related to increased cellular permeability syndrome involving the oral mucosa but also implies that there is another hereditable genetic defect making the oral mucosa especially susceptible to some environmental factor or just very severe permeability leading to 6 siblings with RAS, and some of them sharing other comorbidities of this syndrome e.g., heat intolerance, weight gain (case 4 also had weight gain) and chronic fatigue, but also individualized pathological entities e.g., dysmenorrhea, DOR, and gastro colic reflex. Evidence that all of these morbidities were related to increased cellular permeability is supported by the amelioration with dopaminergic drugs which function to diminish cellular permeability.

We decided to reintroduce cases 1-3 and present the never reported case 4 to demonstrate longevity of treatment benefit with dopaminergic drugs. However, we also were waiting another 14 years to see if the parents, who previously had no clinical manifestations of the increased cellular permeability syndrome, would over time develop a pathological condition consistent with the increased cellular permeability syndrome. Sometimes a phenotypic disorder of a polygene nature can develop later in the parent than the child.

The mother and father are approaching age 70 and still do not demonstrate any manifestations of this disorder. Thus, this created for us a genetic puzzle. How do 6 siblings have RAS and other manifestations of the increased permeability syndrome, yet no evidence of this syndrome presents in either parent? A de novo mutation can occur in a child causing a condition that is frequently an inherited condition for future generations but not in the parents. However, 6 siblings with RAS plus these other morbidities cannot be explained on a de novo mutation since it would have had to happen in all 6 children.

Thus, one purpose of writing this manuscript was for us to further explore the genetic etiology of polygenetic conditions and hopefully find an answer to explain this conundrum and if so, possibly provide more insight into the role of genetics in the etiology of the increased cellular permeability syndrome and possibly other polygenic conditions.

RAS is usually a benign idiopathic disorder which only requires supportive care. However, in some cases that show a systemic disorder, genetics might be involved. RAS can possibly be a multifactorial condition, influenced by both genetic susceptibility and environmental triggers, especially through immune and inflammatory pathways [27]. In patients with a family history of RAS, genetic factors play a significant role where the disease tends to appear earlier and with more severity. Different genetic variants and inflammatory agents are associated with the risk of RAS. Gene polymorphisms in specific cytokines of immune-related genes including IL-10, IL-1 beta and IL-6, as well as folic acid deficiency and serotonin transporter gene (5-HTTLPR), are showing notable association with predisposition to RAS [28].

In this case, there was no family history of any symptoms of RAS, increased cellular permeability syndrome or other inflammatory disorders. A possible explanation for the mechanism of transmission of RAS in the offspring is through germline mosaicism. It occurs when a parent's reproductive cells carry the mutation, while other body cells do not. This can lead to the transmission of a genetic condition even if the parents themselves do not exhibit the condition [29]. We suggest that there was a germline mosaic mutation of RAS genes including Signal Transducer and Activator of Transcription 1 (STAT1) Gain-of-Function (GOF) mutation and Tumor Necrosis Factor Alpha Induced Protein 3 (TNFAIP3) negative regulator gene which magnified the susceptibility to increased cellular permeability syndrome as well as the different inflammatory disorders manifested in the offsprings.

According to studies, it was found that RAS patients, especially in the pediatric population, may carry pathogenic mutations which respond better to different treatments and are associated with other conditions. RAS has been linked to STAT1 GOF mutation which disrupts normal STAT1 signaling leading to increased phosphorylation and prolonged activation of STAT1 [30]. This results in massive inflammation at mucosal surfaces resulting in RAS and ulcers correlated with candida as a complication of the mucositis, as well as a manifestation of Crohn's disease [31]. Following diagnosis with STAT1 GOF mutations, JAK inhibitors were proposed for better disease control. RAS has also been associated with haploinsufficiency of A20 which is encoded by TNFAIP3 gene as a negative regulator of the signaling pathway [32]. It has been reported that several autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and type I diabetes are associated with TNFAIP3 gene polymorphisms [33]. This is diagnosed as SLE-like feature and behcet's disease which is a triad of aphthous stomatitis, genital ulcers and uveitis. Typically, it is treated with adalimumab due to colchicine resistance of

that gene. Furthermore, diagnosis with both STAT1 GOF and A20 haploinsufficiency, has shown that there is an overlap of these causative genes of RAS in pediatric patients with SLE and/or BD [34].

Overall, both STAT1 GOF mutation and TNFAIP3 negative regulator genes are potential explanations to the manifestation of RAS in all the offspring, without a family history. Environmental factors combined with effects of modifying genes involved in phenotypic manifestations, may have played a role by interacting with the genetic predispositions to RAS [31].

An alternative hypothesis is that one of the parents has the strong polygenic predisposition to developing RAS, but does not have the clinical manifestations of RAS because the phenotypic expression will not occur unless one also has relative dopamine deficiency as seen in the increased cellular permeability syndrome. Thus, possibly neither parent has the genetic constitution for the increased cellular permeability syndrome but that occurred in the germline resulting in not only RAS but other manifestations of the increased cellular permeability syndrome.

One other possibility is that 1 or both parents have an increased number of abnormal nucleic acid sequences compared to the normal population but still insufficient to cause the gene mutation(s) leading to RAS in which these abnormal nucleic acid sequences are expanded in the germ cells line leading to the syndrome in the children but not in the parents, similar to fragile x-syndrome [35].

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