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Mini Review

Type B Insulin Resistance Syndrome as an H. *Pylori*-Associated Autoimmune Disease

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Abstract

Type B insulin resistance syndrome (IRS) is characterised by production of autoantibodies against the insulin receptor (IR). These autoantibodies block insulin binding to the IR, resulting in severe insulin resistance. Some patients with this syndrome paradoxically exhibit episodic hypoglycaemia. Relatively burdensome therapies, including immunosuppression and plasmapheresis, are reportedly effective in some patients, but there are as yet no established therapeutic strategies for type B IRS. We experienced two cases with type B IRS who also had immune thrombocytopenic purpura (ITP). In one case, eradication of Helicobacter pylori (HP), aimed at treating ITP, cured type B IRS. In the other case, anti-IR and anti-platelet antibodies were detected only during pregnancy, and after delivery, these autoantibodies and hypoglycemic symptoms disappeared. These two cases suggest that elimination of immune-disturbing triggers can lead to a complete cure of type B IRS. In this review, we discuss the pathogenesis of type B IRS focusing particularly on the possible involvement of HP infection and the therapeutic potential of HP eradication for the treatment of this refractory syndrome. We recommend that physicians examine type B IRS patients for HP infection and eradicate this microorganism if present, since HP eradication can easily be performed with few adverse effects.

ABBREVIATIONS

IRS: Insulin Resistance Syndrome; **HP**: Helicobacter Pylori; **ITP**: Immune Thrombocytopenic Purpura

INTRODUCTION

Type B insulin resistance syndrome (IRS), a rare cause of severe insulin resistance, is characterised by production of autoantibodies against the insulin receptor (IR) [1], and is classified into an autoimmune disease. This syndrome is frequently associated with other autoimmune diseases [2]. Although type B IRS induces severe hyperglycaemia, some patients with this syndrome exhibit episodic hypoglycaemia, considerably impairing quality of life. There are as yet no established therapeutic strategies for this syndrome.

We recently experienced a case of type B IRS who also had immune thrombocytopenic purpura (ITP). These two disorders had developed simultaneously. Surprisingly, in this case, eradication of Helicobacter pylori (HP) cured not only ITP but also type B IRS [3], suggesting involvement of HP in the pathogenesis of type B IRS. Consistent with this, HP reportedly affects host immunity [4] and is related to the development of several autoimmune diseases. We recently reported another case of type B IRS with ITP. In this case, anti-IR and anti-platelet antibodies were detected only during pregnancy, followed by the disappearance of these autoantibodies and symptoms after delivery [5]. These two cases suggest that elimination of the triggers which may disturb immune system can stop the production of autoantibodies, thereby leading to complete recovery from type B IRS.

Herein, we discuss the pathogenesis of type B IRS focusing particularly on possible involvement of HP infection, and also the therapeutic potential of HP eradication for type B IRS. The aim of this review is to provide insights for developing a novel therapeutic approach for type B IRS, a refractory syndrome with severe insulin resistance.

SIDE HEADINGS/SUBHEADINGS

Type B insulin resistance syndrome

Type B IRS was first reported in 1976, as an autoimmune disorder characterised by severe insulin resistance and marked hyperinsulinaemia caused by acquired production of antibodies against the IR [1]. On the other hand, type A IRS, which features severe insulin resistance from birth, is caused by mutations in the IR gene. Type B IRS is a rare cause of severe insulin resistance and, to date, there are about 100 case reports. IR antibodies mediate the development of insulin resistance by several proposed mechanisms; 1) Inhibition of insulin-binding to the IR by antibodies [1], 2) IR number reduction via internalization of the receptor elicited by binding of antibodies [6], 3) Inhibition of intracellular IR signaling by antibody-mediated sustained association of the IR with insulin receptor substrates [7]. Although type B IRS usually induces hyperglycaemia via the mechanisms described above, some patients with this syndrome experience hypoglycemic attacks [8]. Although the precise mechanisms underlying occasional hypoglycemia remain uncertain, one possible explanation is the presence of both inhibitory and stimulatory types of IR-antibodies [9]. Autoantibodies associated with type B IRS are generally polyclonal [1,10], and IR-antibodies with various characteristic may exist simultaneously, leading to the appearance of various symptoms. Alternatively, dissociation of inhibitory IR-antibodies from the IR by unknown mechanisms might suddenly induce potent insulin signaling due to hyperinsulinaemia.

Type B IRS and HP infection

Type B IRS is frequently associated with other autoimmune diseases. One third of type B IRS patients meet the diagnostic criteria for systemic lupus erythematosus (SLE) or Sjögren syndrome. In addition, cases with other concomitant autoimmune diseases, including ITP, have also been reported [3,11-22] (Table 1). We recently experienced a case with both type B IRS and ITP [3]. The patient had initially presented with hypoglycemic symptoms, and hyperglycemia later became evident. Interestingly, even during the hyperglycemic period, sudden hypoglycemic attacks occurred irregularly. Platelet numbers were markedly decreased. It was recognized in retrospective that the onsets of hyperglycemia and thrombocytopenia were almost simultaneous. This patient had both anti-IR and anti-platelet antibodies at very high titers and was shown to be chronically infected with Helicobacter pylori (HP). In this case, aimed at treating ITP, HP eradication therapy, with amoxicillin, lansoprazole and clarithoromycin, was administered, because HP eradication is already a well-established ITP therapy [23]. HP was fully eradicated by this therapy, resulting in reduced anti-platelet antibodies and increased platelet number to the normal level. Surprisingly, HP eradication ameliorated not only ITP but also type B IRS. Anti-IR antibodies became undetectable, resulting in lowering of the HbA1c level to normal without diabetes treatment. Furthermore, the hypoglycemic attacks completely disappeared [3]. At present, five years after HP eradication, no recurrence has been observed, indicating complete cure of type B IRS by HP eradication.

Table 1: Reported series of type B IRS-associated autoimmune diseases.

Associated autoimmune disease	Author	Year	References
Rheumatoid Arthritis	Kramer et al.	1998	11
Hashimoto Disease	Hirano et al. Fereau et al.	1997 2007	12 13
Systemic Sclerosis	Weinstein et al. Jannette et al. Bloise et al.	1980 1982 1989	16
Mixed Connective Tissue Disease	kramer et al. Semple et al. Malek et al.	1998 2007 2010	11 17 18
Graves Disease	Tran et al.	2009	19
Primary Biliary Cirrhosis	Selinger et al. Arioglu et al.	1987 2002	20 21
Immune Thrombocytopenic Purpura	Selinger et al. Imai et al.	1987 2009	20 3
Autom immune Hepatitis	Fereau et al.	2007	13
Immune Complex Glomerulonephritis	Sims et al.	1987	22

The first report showing the effectiveness of HP eradication against ITP was published in 1998 by an Italian group [24]. Thereafter, similar results were reported by several groups mostly from Japan and Italy, establishing HP eradication as a novel therapeutic approach for ITP. A recently published meta-analysis revealed HP eradication to be effective in more than 50% of HP-positive ITP patients [23]. Since HP eradication is a less-invasive approach than immune-suppression and splenectomy, commonly employed ITP therapies, HP eradication has now become a first-line therapy for HP-positive ITP patients.

In the case with type B IRS associated with ITP, HP eradication simultaneously cured both ITP and type B IRS [3]. Since spontaneous remission of type B IRS was reported [8], the possibility that type B IRS was remitted independently of HP eradication cannot be excluded. However, in addition to the simultaneous developments of type B IRS and ITP, these two disease states improved at exactly the same time after HP eradication. This clinical course strongly suggests HP involvement in the development of type B IRS and that HP eradication was responsible for its elimination.

The case of type B IRS associated with both ITP and primary biliary cirrhosis was previously reported [20]. In this case, main feature of type B IRS was hypoglycaemia.Treatment with prednisolone improved autoimmune features such as thrombocytopenia, liver dysfunction and hypoglycemia. Since that case was reported prior to demonstration of the effectiveness of HP eradication for ITP, HP infection was not examined and eradication therapy was not performed.

HP infection and autoimmune diseases

How is HP infection involved in the development of type B IRS? As mentioned above, HP infection is known to be involved in the pathogenesis of ITP. Additionally, a relationship between HP infection and MALT (mucosa-associated lymphoid tissue) lymphoma is widely accepted [25]. HP reportedly affects the functions of several host immune cells such as macrophages, mast cells, antigen presenting cells and T-cells [4]. These findings allow us to hypothesise that HP infection modulates the host immunity system by multiple mechanisms.

In this regard, a number of previous reports have shown that HP eradication ameliorated other autoimmune diseases besides

ITP [26-32] (Table 2). For instance, HP eradication reduced both blood inflammatory markers and improved symptoms in patients with rheumatoid arthritis [26]. In addition, when HP eradication therapy was administered to a patient with antiphospholipid antibodies syndrome, the autoantibodies diminished, thereby ameliorating symptoms in this patient [27]. Taken together with the case of type B IRS cured by HP eradication [3], these observations suggest the immune system to be disturbed by HP, which is likely to be involved in the common pathogenesis of these autoimmune diseases. HP eradication is speculated to effectively promote recovery from HP-associated autoimmune diseases.

Many elderly Japanese people contracted HP infection early in life, because, in the 1950s, the hygienic environment of Japan was not adequate [33]. In fact, the HP prevalence rate is much higher in elderly than in young people in Japan [34]. Therefore, it is very unlikely that a new HP infection occurred in the old (84 y.o.) patient we experienced [3] at the onset of type B IRS and ITP. Chronic infection with HP would presumably have been present for many years before the development of type B IRS and ITP. Therefore, another trigger, i.e. a so-called second hit, must be necessary for simultaneous development of these two autoimmune diseases. This speculation may be also applicable to the induction mechanism of other HP-associated autoimmune diseases.

What then is the second hit triggering the development of autoimmune diseases induced by HP? As for ITP, there are several hypotheses regarding disease induction by HP [35]. First, antibodies against HP components, such as CagA, cross-react with platelet antigens [36]. Second, Lewis (Le) antigens, which are expressed by HP, are absorbed to platelets and serve as targets for anti-Le antibodies [37]. Third, HP antibodies activate platelets by binding to them via the FcγRIIA or through an interaction between the HP-bound von Will brand factor to platelet glycoprotein 1B, and this activation promotes platelet clearance [38]. Finally, HP infection alters the expression pattern of monocyte Fcγ receptors, thereby enhancing the phagocyte capacity of monocytes [39]. However, these platelet-specific hypotheses cannot explain why autoimmune diseases develop acutely in chronically HP infected individuals or why HP infection induces several other autoimmune diseases besides ITP.

HP interacts with the host gastric epithelial cells via several adhesion molecules and does not typically invade the gastric mucosa. Thus, gastric epithelium disruption might allow HP to invade gastric tissues, leading to HP antigen-presentation [40]. In addition, monoclonal anti-HP antibodies reportedly cross-react with several human tissues, such as the duodenal epithelium, salivary glands and renal tubular cells [41]. Therefore, a trigger, such as gastric epithelium inflammation, which disrupts the gastric epithelium, might be the second hit which promotes the development of autoimmune diseases (Figure 1). However, considering that HP infection is associated with a number of autoimmune diseases, including type B IRS, and that these diseases often co-exist, molecular mimicry of HP antigens to those of human tissues is unlikely to be the main mechanism.

What then is the mechanism whereby multiple autoimmune diseases, e.g. ITP and type B IRS [3], develop simultaneously and can be cured together by HP eradication? One possible answer to this question is that, urease, produced by HP, activates B-1 cells, a subpopulation of B lymphocytes, leading to the production of autoreactive antibodies [42]. In addition, HP infection is reportedly associated with helper T-cell polarization [43]. This helper T-cell polarization may disrupt the host's immune tolerance, leading to simultaneous development of multiple autoantibody-induced diseases. These mechanisms may contribute in complex ways to acute and simultaneous development of diseases induced by multiple autoantibodies (Figure 1), although further investigations are required to elucidate the precise mechanism.

Type B IRS and pregnancy

We recently reported another case of type B IRS with ITP. The patient was a 32-year-old woman with an unremarkable past medical history. Severe hypoglycemic attacks accompanied by sudden loss of consciousness had started to occur during gestational week 9. After hospitalization, intrauterine fetal death became apparent and hypoglycemic attacks remitted. Two years later, hypoglycemia recurred during gestational week 8 of her

Table 2: Reported series showing improvement of autoimmune diseases with HP eradication.

Autoimmune disease	Therapeutic outcomes of HP Eradication	Author	Year	References
Rheumatoid Arthritis	•Improvement of clinical presentation such as arthralgia, swollen joint and morning stiffness •Lowering of laboratory pararmeters including ESR and CRP	Zentilin et al.	2002	26
Antiphospholipid Antibodies Syndrome	•Improvement of symptoms such as Raynaud's phenomenon, migraines •Disappearance of antiphospholipid antibodies	Cicconi et al.	2001	27
Autoimmune thyroid diseases	•Significant reduction of thyroid autoantibodies	Bertalot et al.	2004	28
Behçet Disease	•Improvement of clinical presentation such as oral and genital ulcer and arthralgia	Apan et al.	2007	29
Schönlein-Henoch Purpura	•Disappearance of cutaneous lesions •Improvement of proteinuria	Machet et al.	1997	30
Idiopathic Chronic Urticaria	•Disappearance of cutaneous symptoms	Di Campli et al. Wustlich et al	1998 1999	31 32

second pregnancy. Thrombocytopenia also appeared during this pregnancy. Clinical examination on admission revealed anti-IR antibodies and anti-platelet antibodies in this patient. *In vitro* study revealed that her anti-IR antibodies stimulated tyrosine phosphorylation of the IR, presumably resulting in hypoglycemia. Fortunately, a healthy baby was delivered by Caesarian section at gestational week 39, despite frequent hypoglycemic attacks and thrombocytopenia. It was noteworthy that, after delivery, anti-IR and anti-platelet antibodies disappeared along with complete resolution of both hypoglycemia and thrombocytopenia. In this case, hypoglycemia occurred only during two her pregnancies and the anti-IR antibodies disappeared after delivery, suggesting a significant causal relationship between pregnancy and the development of type B IRS [5]. Taken together with the aforementioned HP-eradication case, the course of these patients suggests a common mechanism to underlie the production of anti-IR and anti-platelet antibodies. Pregnancy is often accompanied by alterations of systemic immune function such as helper T-cell polarization [44]. Therefore, certain immune system-altering conditions, such as HP infection and pregnancy, can trigger the development of type B IRS. More importantly, these cases strongly suggest that type B IRS, a refractory syndrome, can be cured by elimination of immune-disturbing triggers.

HP eradication for type B IRS

There is no established therapy for type B IRS. Since type B IRS is regarded as an autoimmune disease, immunosuppressive drugs such as prednisolone [9,16,20,22,45,46], cyclophosphamide [16,18,22,46-48], cyclosporine [11,48] and azathioprine [21] have been used for treatment. In some cases, these immunosuppressive drug combinations were reported to be effective (Table 3). Additionally, type B IRS was successfully treated with immunoglobulin [19], plasmapheresis [45, 48, 49], IGF-1[50] or rituximab, an antibody against B-cell surface antigen CD-20 [18] (Table 3). However, cases not responding to these therapies have also been reported [21, 50]. Due to the rarity of type B IRS cases,

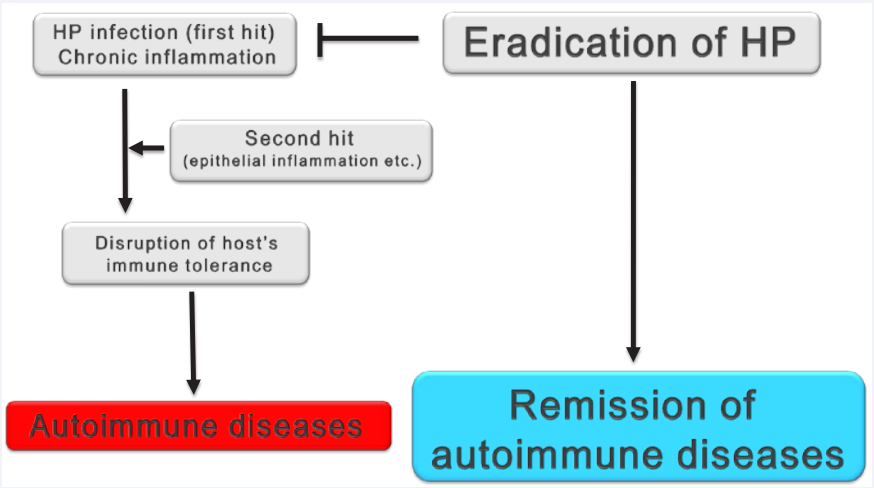

Figure 1 Hypothetical mechanism of autoimmune disease remission with HP eradication.

Table 3: Reported therapeutic approaches for type B IRS.

Therapeutic approach	Therapeutic outcome	Author	Year	References
Predonisolone	Remission	Taylor et al. Selinger et al.	1982 1987	9 20
Cyclophosphamide Predonisolone	Remission	Kawanishi et al. Simset al. Bloise et al.	1977 1987 1989	46 22 16
Cyclophosphamide and Mycophenolate mofetil	Remission	Gel et al.	2003	47
Plasmapheresis	Remission	Muggeo et al.	1979	49
Plasmapheresis and Predonisolone	Remission	Page et al.	2007	45
Plasmapheresis, Cyclophosphamide and Cyclosporin	Remission	Eriksson et al.	1998	48
Cyclosporin	Remission	Krerner et al	1998	11
IGF-1	(Plasmapheresis, cyclophosphamide and cyclosporin Yamamoto et al. combined therapy was not effective)	Yamamota et al.	2000	50
Azathioprine	Remission	Arioglu et al.	2002	21
Rituximab, Cyclophosphamide and Pulse steroids	Remission (All seven treated patients achieved remission)	Malek et al.	2010	18
Immunoglobulin	Remission	Tran et al.	2009	19
Eradication of Helicobacter Pylori	Remission	Imai et al.	2009	3

it is difficult to conduct cohort studies to examine the effectiveness of these therapies.

The case with type B IRS cured by HP eradication [3] suggests this to be a promising therapeutic strategy for type B IRS. As mentioned above, an established therapy for type B IRS is lacking. HP eradication is a relatively benign therapy with fewer adverse effects compared with previously reported therapeutic approaches such as immunosuppressive therapies. In addition, HP eradication can easily be performed with no need for specialised equipment, and unlike immunosuppressive therapy, the required treatment period is very short, only one week. In fact, administrations of immune suppressors for several months to years were required to maintain remission in previously reported cases [9,45,48]. In addition, the remission durations of 7 type B IRS patients receiving intensive combination immune suppressive therapy ranged from 2 to 16 months [18], while the case with type B IRS associated with ITP [3] has maintained remission status for more than five years since HP eradication. Therefore, if the effectiveness of HP eradication for type B IRS is confirmed, this therapeutic strategy may be of major benefit to patients with this syndrome. We recommend that physicians worldwide screen type B IRS patients for HP infection and attempt eradication therapy in those who are HP-positive.

DISCUSSION AND CONCLUSION

In this review, we have shown the therapeutic potential of HP eradication for type B IRS. However, at present, HP infection rates in type B IRS patients are unclear and whether chronic HP infection is a common feature of type B IRS remains an open question. Therefore, future studies are necessary to examine HP infection rates in type B IRS patients. In addition, the effectiveness of HP eradication in HP-positive type B IRS patients should be examined in cohort studies. However, the rarity of type B IRS makes it difficult to perform clinical surveillance. Therefore, we hope that this review will inspire physicians worldwide to examine HP infection in type B IRS patients and attempt eradication therapy in HP-positive type B IRS patients. Accumulation of these data would clarify the significance of HP infection in the pathogenesis of type B IRS and allow HP eradication to be established as a curative therapy for this disease.

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