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CELIAC DISEASE AN UPDATED COMPREHENSIVE REVIEW

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Abstract: Celiac disease CD is a chronic autoimmune disorder of the small intestine triggered by dietary gluten in genetically predisposed individuals Advances in understanding its genetic basis immune mechanisms diagnostic tools and management strategies have markedly improved clinical outcomes This paraphrased review highlights contemporary insights into epidemiology pathogenesis diagnostic approaches clinical variants complications and novel therapeutic perspectives

Keywords: celiac disease gluten-free diet HLA-DQ2/DQ8 intestinal permeability zonulin refractory celiac disease larazotide acetate IL-15 blockade

Introduction

CD manifests through characteristic serological markers and mucosal damage provoked by gluten exposure in subjects carrying specific HLA haplotypes Over recent decades enhanced screening has dramatically increased detection rates worldwide although a substantial proportion of cases still go unrecognized

Epidemiology

Global prevalence averages 0.5 to 1 percent with a clear female preponderance approximately 1.5 to 1 Risk rises to 10 to 15 percent among first-degree relatives and is further elevated in conditions such as Down syndrome type 1 diabetes mellitus and selective IgA deficiency In Western populations prevalence surged fivefold from 1975 to 2000 potentially influenced by higher dietary gluten intake and environmental shifts

Pathophysiology

Genetic predisposition HLA-DQ2 and DQ8 are essential but insufficient genome-wide studies have identified over 100 additional risk loci Environmental trigger Indigestible gliadin fragments activate CXCR3 receptors prompting zonulin-mediated tight-junction disassembly and increased intestinal permeability via both paracellular and transcellular routes CD71-mediated retrotranscytosis in active disease Innate immune activation IL-15 amplification TLR-4 stimulation by wheat amylase-trypsin inhibitors and FPR1-driven neutrophil recruitment Adaptive response Tissue transglutaminase 2 TG2 deamidates gliadin enhancing presentation by DQ2/DQ8 to CD4+ T cells resulting in proinflammatory cytokine release and intraepithelial lymphocyte-induced enterocyte destruction Gut microbiota Early-life dysbiosis decreased Bacteroidetes and Lactobacillus precedes autoimmunity in genetically susceptible infants supporting an environment-dependent dysbiosis model rather than a simple hygiene hypothesis

Clinical Presentation

Classical gastrointestinal Predominantly pediatric chronic diarrhea growth faltering Non-classical extraintestinal Iron-deficiency anemia 40 percent osteopenia/osteoporosis 70 percent

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elevated liver enzymes 40 to 50 percent neurological symptoms and fertility issues Atypical forms Subclinical potential seronegative non-responsive and refractory variants Oslo classification

Diagnostic Strategies

Serological testing IgA anti-tTG sensitivity approximately 97 percent EMA specificity nearly 100 percent IgG-DGP valuable in IgA deficiency and young children Histopathology Remains the reference standard Marsh–Oberhüber or simplified Corazza–Villanacci classification At least six biopsies four distal duodenum two bulb recommended Four-out-of-five diagnostic rule Symptoms positive serology compatible HLA histological damage and response to gluten withdrawal Biopsy-free pediatric algorithm ESPGHAN 2020 anti-tTG more than 10 times upper limit of normal plus positive EMA plus HLA-DQ2/DQ8 Seronegative CD Requires histological confirmation and clinical/histological improvement on GFD differential diagnosis includes medication-induced enteropathy infections and immunodeficiency states

Treatment and Monitoring

Strict lifelong gluten-free diet GFD Cornerstone therapy achieving clinical serological and mucosal recovery in the majority Persistent symptoms Distinguish ongoing active CD slow responders refractory disease inadvertent gluten exposure from associated disorders IBS SIBO lactose/fructose intolerance Follow-up Serial anti-tTG nutritional markers bone density gluten immunogenic peptides GIP in urine/stool for adherence monitoring Repeat biopsy reserved for non-responders

Complications

Functional/asplenia 30 to 80 percent vaccination against encapsulated bacteria advised Refractory CD 1 to 1.5 percent Type I polyclonal vs Type II clonal markedly worse prognosis in Type II due to progression to enteropathy-associated T-cell lymphoma Increased risk of small-bowel adenocarcinoma

Emerging Therapeutic Approaches

Larazotide acetate Tight-junction modulator attenuates symptoms from trace gluten contamination Phase III Latiglutenase IMGX003 Oral gluten-degrading enzyme cocktail disappointing histological outcomes in Phase 2b Anti-IL-15 monoclonal antibodies AMG-714/PRV-015 Encouraging early results in refractory Type II Nexvax2 vaccine Epitope-specific immunotherapy aiming at tolerance induction Phase II

Prevention Prospects

Large prospective birth cohorts TEDDY PreventCD found no protective effect of breastfeeding duration or timing of gluten introduction Rotavirus vaccination may lower risk Ongoing CDGEMM study investigates microbiome–metabolome interactions for primary prevention targets

Conclusion

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Despite significant progress CD continues to challenge clinicians due to diagnostic delays and reliance on strict dietary adherence The gluten-free diet remains indispensable yet novel agents targeting barrier function gluten degradation and key cytokines offer hope for adjunctive or disease-modifying therapies ultimately improving patient quality of life

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