Non-celiac gluten sensitivity (NCGS)

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History

The first comprehensively documented case of "gluten sensitivity" (in a non-celiac disease/wh-eat allergy patient) was reported in 1980[6]. That report described eight adult women suffering from incapacitating abdominal pain and chronic diarrhea which rapidly remitted when a gluten-free diet was initiated, with symptomatic relapse after re-exposure to a gluten containing diet (GCD). Jejunal biopsies

TABLE 1. Symptoms in Patients With Nonceliac Gluten Sensitivity

Gastrointestinal	Extraintestinal
Bloating	"Foggy" mind
Diarrhea	Tiredness
Constipation	Fatigue
Abdominal pain	Joint pain
Nausea	Depression
Vomiting	Numbness
Anal fissures	Loss of balance
	Eczema
	Anemia
	Weight fluctuations
	Rash
	Headaches



GI symptom

Non GI symptoms

- Migraine
- Headache



Prevalence

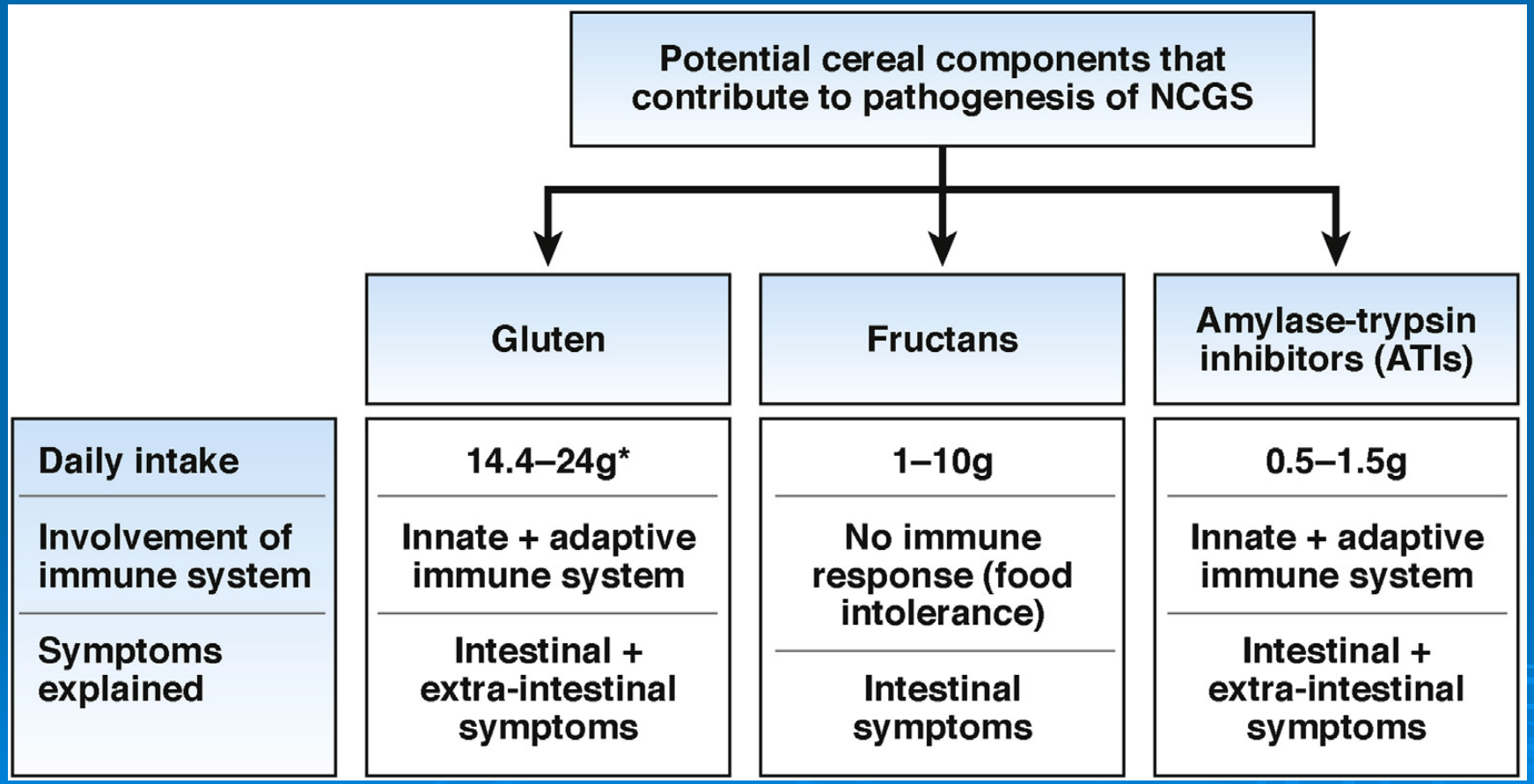
The prevalence of NCGS is **0.6% - 10 %** in Western populations

females are more involved than males (3:1)

بیماری سلیاک

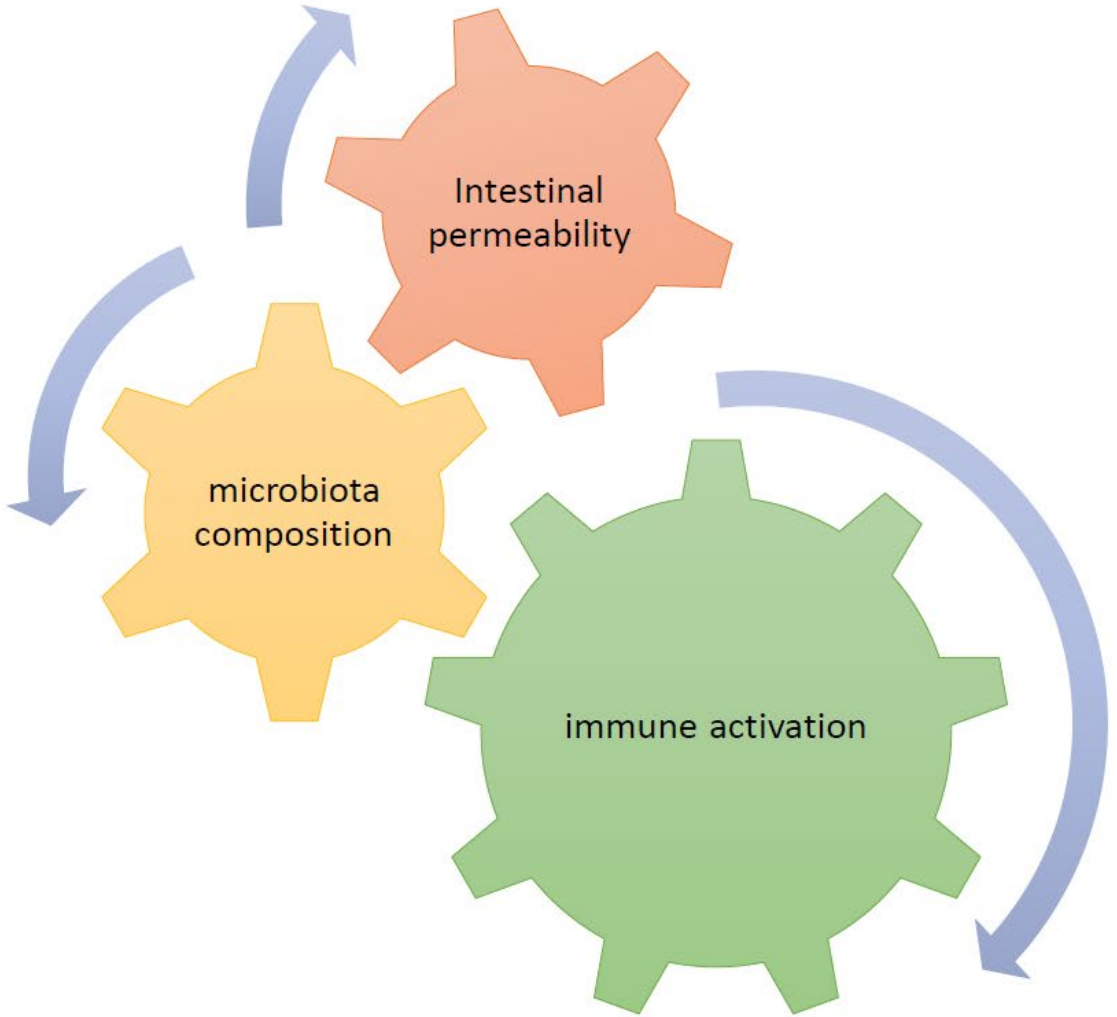


Etiology


Potential cereal components that contribute to pathogenesis of NCGS
Gluten
Fructans
Amylase-trypsin inhibitors (ATIs)
Daily intake
Involvement of immune system
Symptoms explained
14.4–24g*
Innate + adaptive immune system
Intestinal + extra-intestinal symptoms
1–10g
No immune response (food intolerance)
Intestinal symptoms
0.5–1.5g
Innate + adaptive immune system
Intestinal + extra-intestinal symptoms

Wheat contains more than one potential symptom inducer

Gluten
fructans
ATI
WGA



International Journal of
Molecular Sciences

MDPI

Review

Non-Coeliac Wheat Sensitivity: Symptoms in Search of a Mechanism, or a Distinct Well-Defined Clinical Entity? A Narrative Review

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Abstract

Pathophysiology

Table 2. Hypothesised pathophysiological mechanisms in non-coeliac wheat sensitivity.

Mechanism	Hypothesised Effect	Key Evidence/Mediators
Innate Immune Activation	Wheat components trigger an innate immune response in the gut mucosa, leading to low-grade inflammation.	Amylase-trypsin inhibitors activating toll-like receptor 4 [58,59]; increased pro-inflammatory cytokines (e.g., TNF-α, IL-8) [58,60].
Increased Intestinal Permeability	A compromised gut barrier ("leaky gut") allows microbial products and dietary antigens to cross into circulation, causing immune activation.	Increased serum zonulin in some studies [61]; ex vivo studies showing increased permeability upon gliadin exposure [62].

Pathophysiology

Table 2. *Cont.*

Mechanism	Hypothesised Effect	Key Evidence/Mediators
Gut Microbiota Dysbiosis	Alterations in the composition and function of the gut microbiome contribute to symptoms and inflammation.	Altered *Firmicutes*/*Bacteroidetes* ratio; reduced *Bifidobacterium*; changes in microbial profiles vs. controls and CD patients [63–65].
FODMAP Intolerance	Fermentation of short-chain carbohydrates (especially fructans from wheat) by gut bacteria leads to gas, bloating, and pain.	DBPCC trials showing fructans induce more symptoms than gluten in some self-reported NCWS individuals [6,66].
Neuro-immune Interactions	Increased interaction between immune cells (mast cells) and the enteric nervous system enhances visceral hypersensitivity.	Increased mast cell density in close proximity to submucosal nerve fibres, correlating with pain and bloating severity [67].
Mild Adaptive Immunity	A low-level adaptive immune response, distinct from and less intense than that seen in CD.	Presence of IgG-AGA in some patients [37]; slight increase in Th1/Th17-related cytokines and duodenal IFN-γ mRNA [68,69].

Table 1. Clinical manifestations reported in non-coeliac wheat sensitivity.

Category	Symptoms
Gastrointestinal	Abdominal pain, bloating, altered bowel habits (diarrhoea/constipation), flatulence, dyspepsia [16,17,37–39]. Symptoms often overlap with irritable bowel syndrome.
Extra-intestinal/Systemic	Fatigue, lethargy ('brain fog'), headaches (often migraine-like), musculoskeletal pain (fibromyalgia-like), anaemia [40–44].
Neurological/Psychiatric	Cognitive disturbances, peripheral neuropathy, ataxia, anxiety, depression [40–43,45,46].
Dermatological	Eczema-like or psoriasis-like skin rashes, dermatitis herpetiformis-like lesions [47].
Other Associations	Gynaecological issues (menstrual irregularities, recurrent vaginitis) [48], increased prevalence of atopy and nickel allergy [49],

nutrients

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Article

Clinical Utility of Anti-Gliadin IgG Antibody (AGA IgG) and Characterization of Patients with Suspected Non-Celiac Gluten Sensitivity: Prospective, Observational Study in Japan

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Abstract

Background/Objectives: Non-celiac gluten sensitivity (NCGS) is a syndrome characterized by intestinal and extraintestinal symptoms triggered by gluten ingestion. Although anti-gliadin IgG antibody (AGA IgG) has been proposed as a potential biomarker for NCGS, its sensitivity and specificity in real-world clinical settings remain unclear. This study aimed to evaluate the clinical utility of AGA IgG in NCGS and to characterize its clinical features, including psychological distress and physical quality of life (QOL), in patients with clinically suspected NCGS attending a specialized outpatient unit in Japan, where patients reported symptoms related to the ingestion of gluten-containing grains (primarily wheat). Methods: We evaluated plasma AGA IgG levels in 45 patients with suspected NCGS based on clinical presentation and in 83 age- and sex-matched healthy controls.

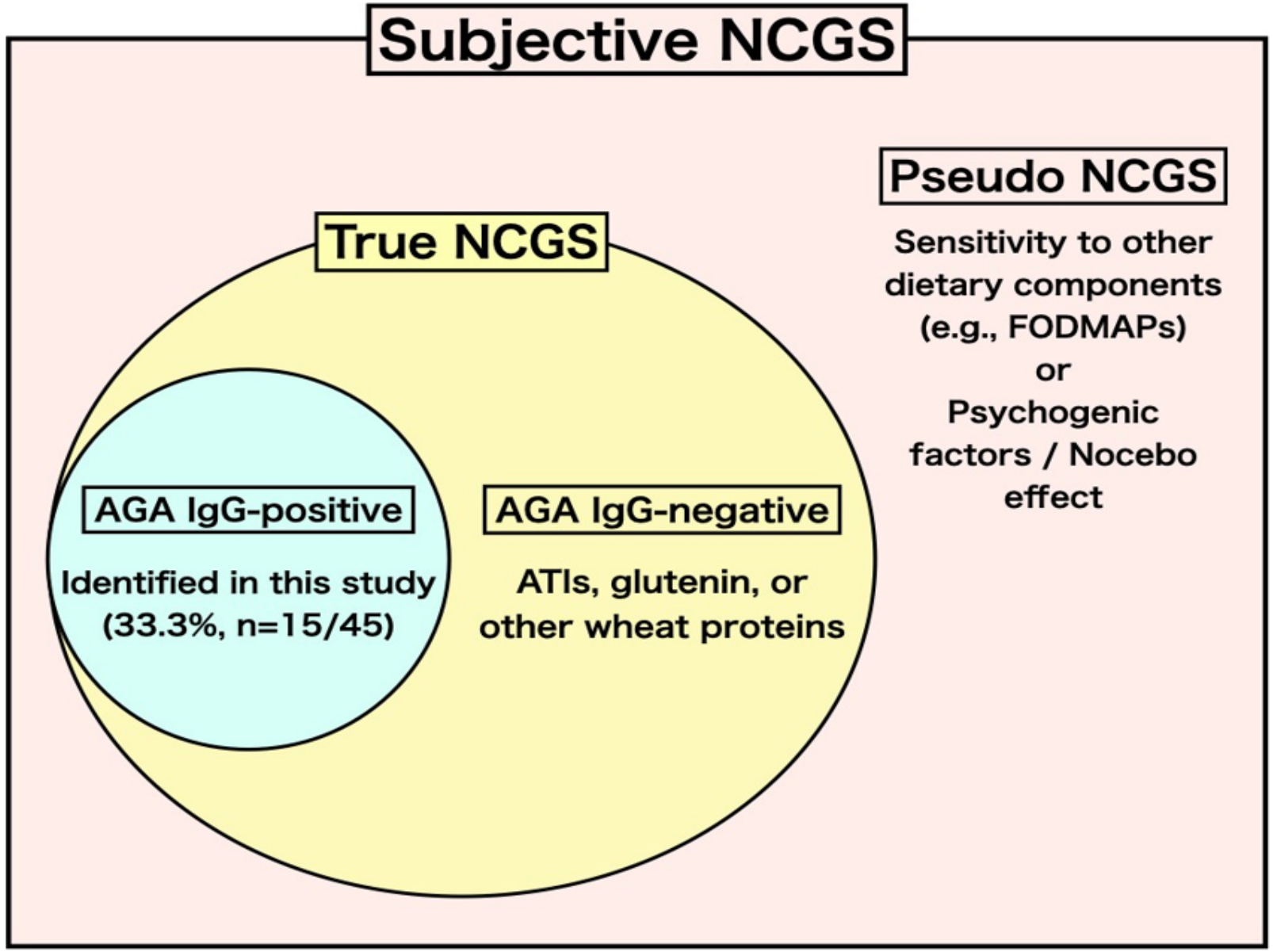


Figure 2. A hypothetical conceptual model for the subclassification of Non-Celiac Gluten Sensitivity

Conclusion

- AGA IgG
  sensitivity of 33.3%
  specificity 86 % for suspected NCGS

- Future studies should explore whether a multi-marker panel could improve the identification of “True NCGS” in diverse clinical populations.

Serology

- No specific lab marker yet identified
- Up to 50% AGA IgG is positive
- HLA DQ 2 & DQ 8 are present up to 50%

Histopathology of NCGS

- Increase in **intraepithelial lymphocytes and eosinophils (Marsh I)**

- **Increase the number of mast cells**

NCWS diagnosis ?

Table 4. Key differences between of NCWS, coeliac disease, wheat allergy, and irritable bowel syndrome.

Feature	Non-Coeliac Wheat Sensitivity	Coeliac Disease	Wheat Allergy	Irritable Bowel Syndrome
Pathophysiology	Innate immunity [58,79], barrier dysfunction [61,62], microbial dysbiosis suspected [60].	HLA-DQ2/DQ8 associated adaptive T-cell response to gluten [78,104].	IgE-mediated or non-IgE-mediated reaction to wheat proteins [103].	Visceral hypersensitivity, altered motility, gut–brain axis dysfunction [107].
Key Symptoms	IBS-like GI symptoms + diverse extra-intestinal (fatigue, 'brain fog', headache, pain) [16,17,38,40–43].	GI symptoms (diarrhoea, malabsorption) + extra-intestinal [78,104].	Rapid onset (mins–hrs) urticaria, angioedema, asthma; or delayed GI symptoms [103].	Recurrent abdominal pain related to defecation, change in stool frequency/form [107].
Symptom Onset	Hours to days after ingestion [9,13].	Variable, can be delayed [78,104].	IgE-mediated: minutes to 2 h. Non-IgE: hours to days [103].	Chronic, fluctuating; can be triggered by food (incl. wheat), stress [107].
Serology	Negative CD/WA serology. IgG AGA may be positive (~50%) [108–110].	Positive anti-tTG, anti-EMA, anti-DGP IgA [78,104].	Positive wheat-specific IgE (for IgE-mediated WA) [103].	Negative for specific markers [107].

continue

Table 4. *Cont.*

Feature	Non-Coeliac Wheat Sensitivity	Coeliac Disease	Wheat Allergy	Irritable Bowel Syndrome
Genetics (HLA)	HLA-DQ2/DQ8 in ~50% (vs ~30% in general population) [41].	Strong association with HLA-DQ2/DQ8 (>95%) [78,104].	No specific HLA association [103].	No specific HLA association [107].
Histology (Duodenum)	Normal or minimal changes (Marsh 0-I), mild IEL increase, eosinophils [68,108,111–114].	Villous atrophy, crypt hyperplasia, significant IEL increase (Marsh III) [78,104].	Usually normal [103].	Usually normal [107].
Diagnosis	Exclusion of CD/WA, followed by DBPCC (Salerno criteria) [12].	Positive serology + duodenal biopsy showing villous atrophy [78,104].	Clinical history + positive IgE tests or skin prick tests [103].	Symptom-based criteria (Rome IV) after excluding organic disease [107].
Primary Trigger	Gluten, fructans, ATIs, other wheat components [32,58,66].	Gluten [78,104].	Wheat proteins (gluten and others) [103].	Various foods (FODMAPs), stress, visceral sensitivity [107].

ACA: anti-gliadin antibody; ATIs: amylase-trypsin inhibitors; CD: coeliac disease; DBPCC: double-blind; placebo

NCGS definition

- Symptoms triggered by gluten ingestion after hours or few days
- Absence of celiac serology and pathology & wheat allergy
- Resolution of symptoms on GFD after a hours or few days

Nutrients 2015

NCGS Diagnosis

Primarily diagnosis of exclusion

- Exclusion of CD
- Wheat allergy excluded by serum IgE levels
- Gluten elimination diet at least for 3 weeks
- Salreno expert's criteria

Nutrients – April 2015

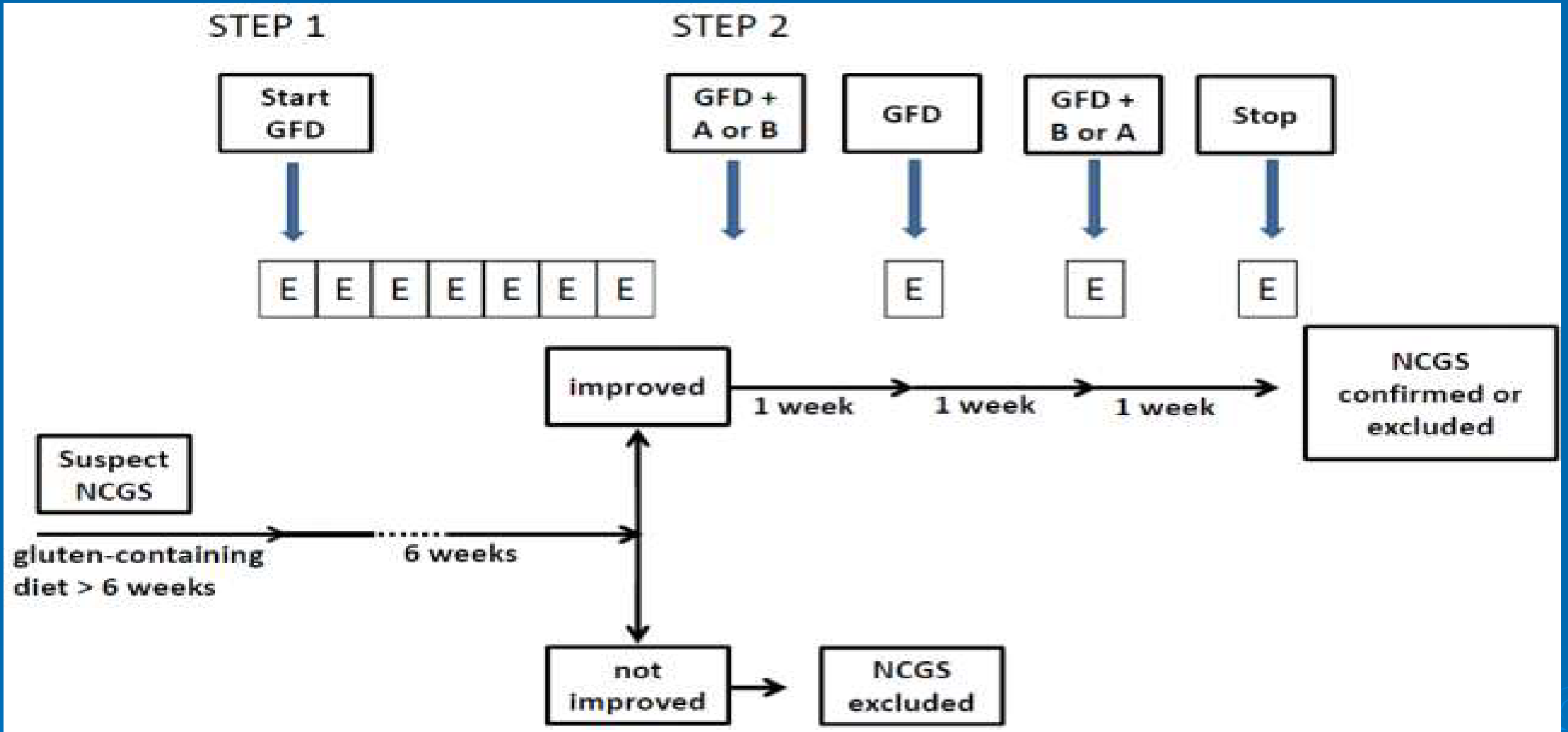


Figure 2. The flow diagram of the NCGS diagnostic process. GFD = gluten-free diet; A = product A (gluten or placebo); B = product B (placebo or gluten); E = evaluation (questionnaire). The evaluation is performed weekly during Step 1 and daily during Step 2.

Natural history

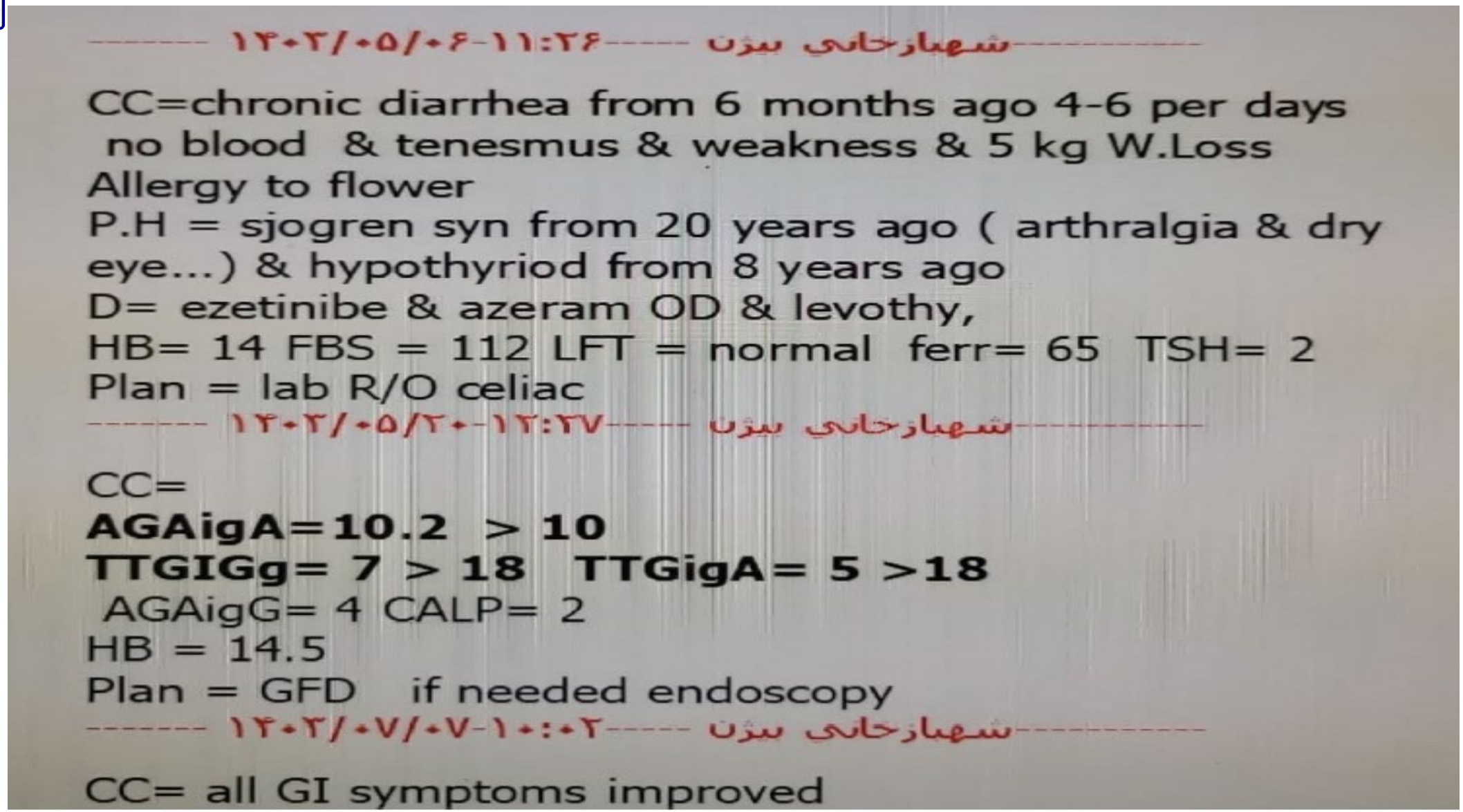
- Symptoms usually disappear soon with withdrawal of gluten and relapse following challenge with in hours or few days

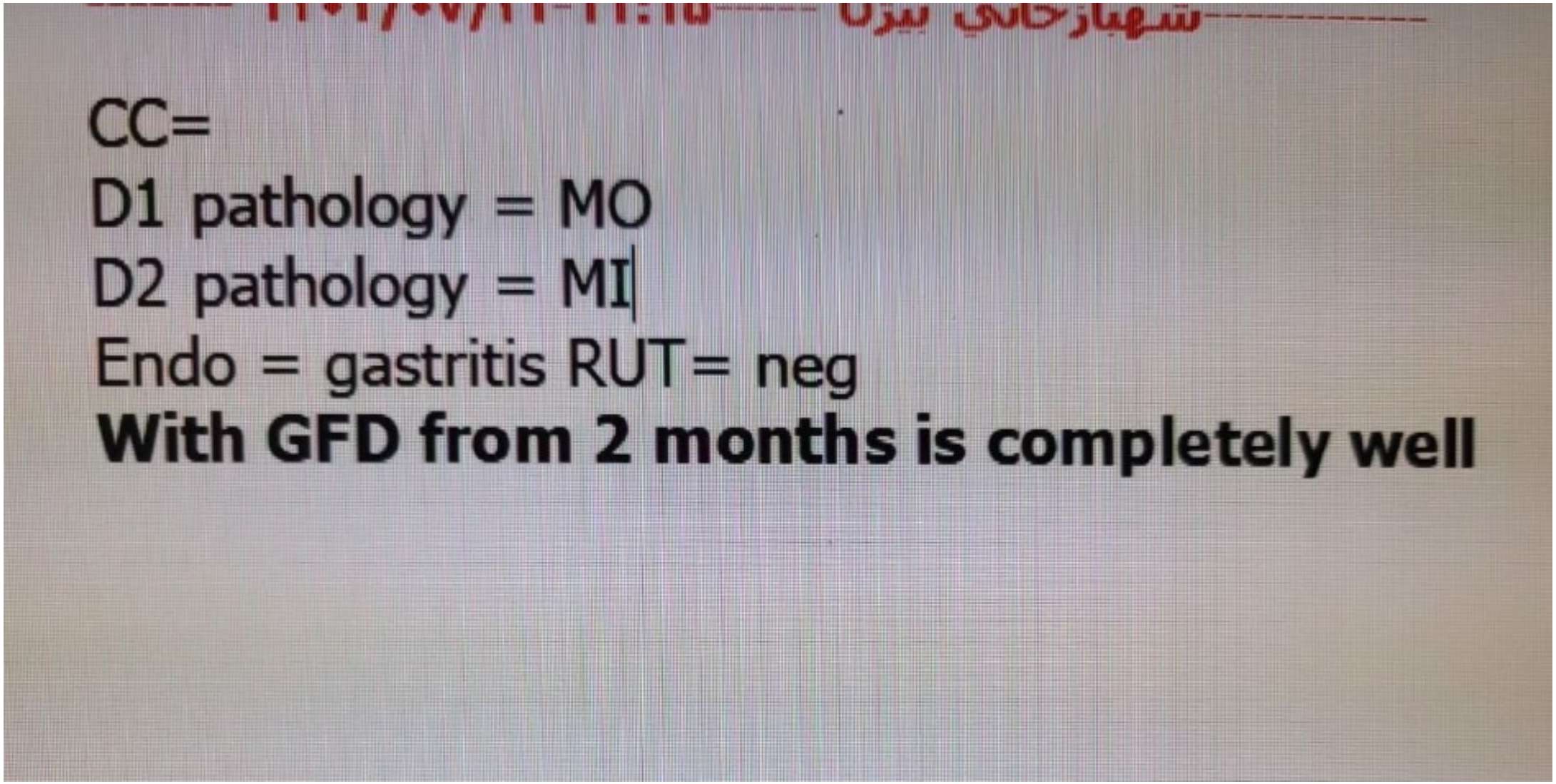
- No major complications of untreated NCGS described unlike CD

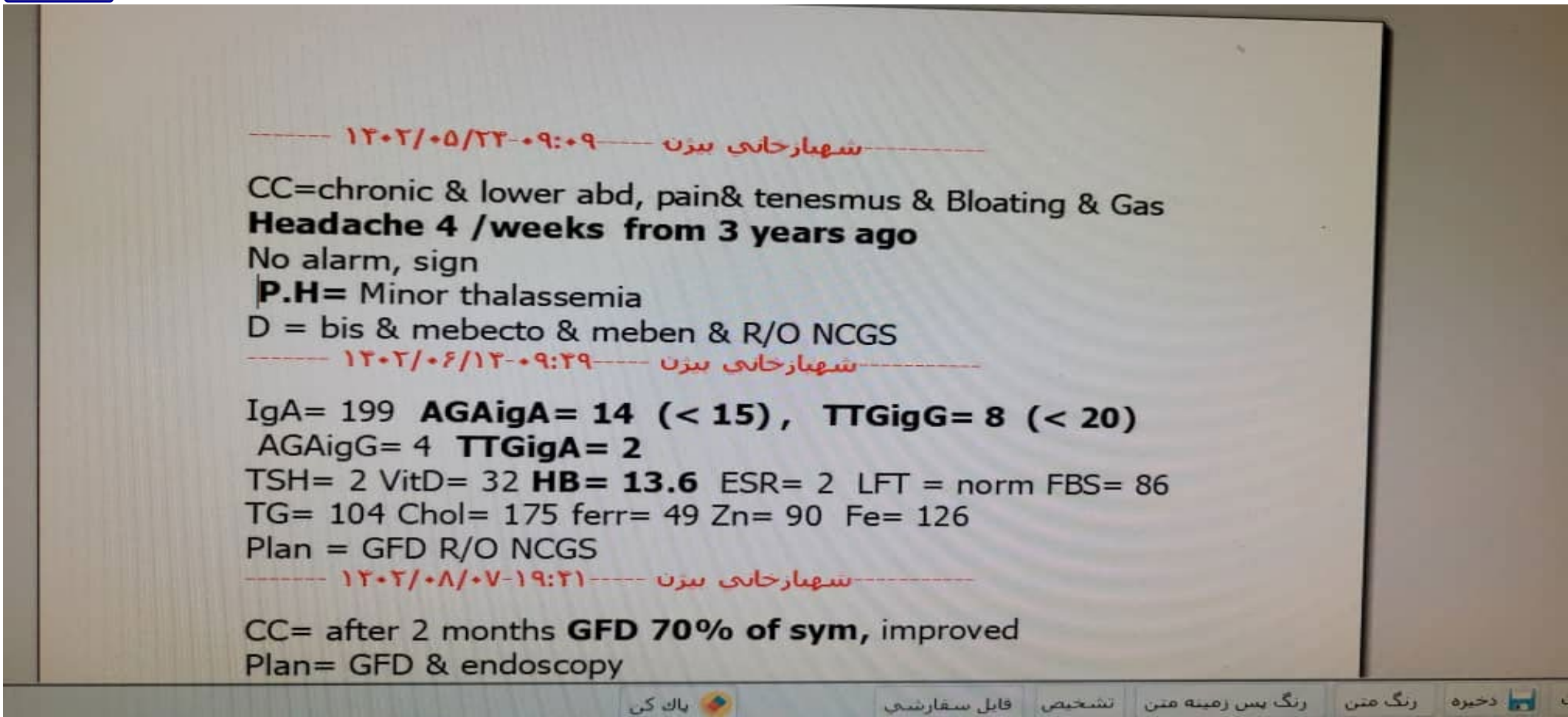
Management

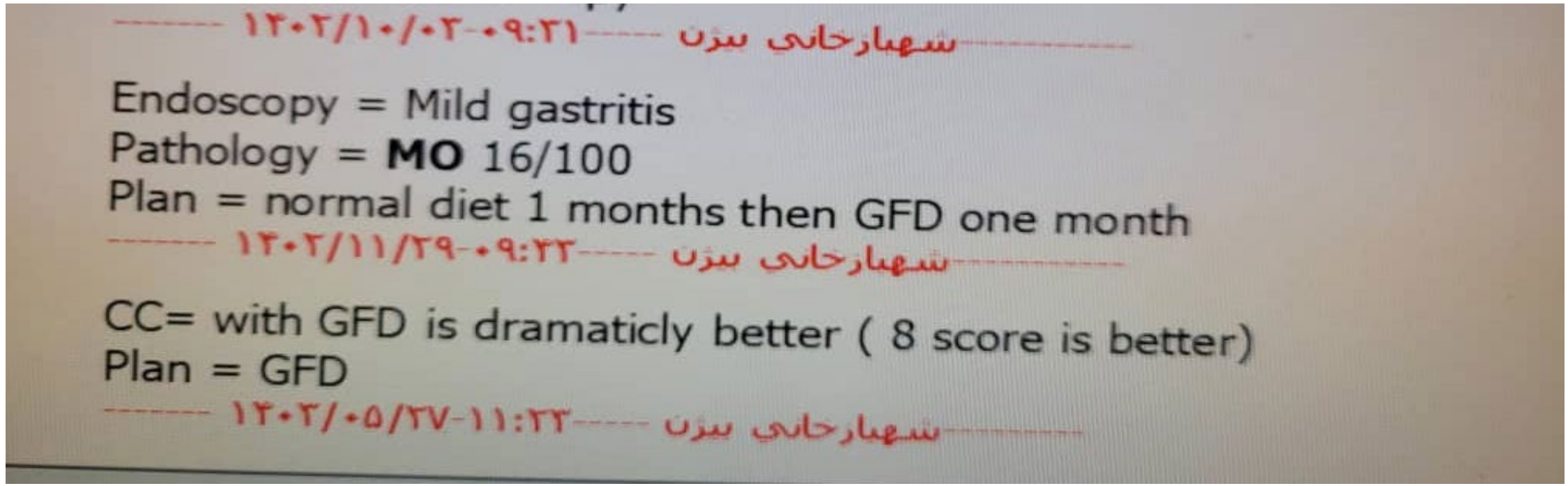
- so strict adherence to a GFD does not appear to be necessary for patients with NCWS based on current data

- Moreover, the levels of gluten required in NCWS to trigger symptoms has been shown to vary significantly between individuals


---------- ۱۴۰۲/۰۵/۰۶-۱۱:۲۶ ---- شهبازخانی بیژن ----------
CC=chronic diarrhea from 6 months ago 4-6 per days
no blood & tenesmus & weakness & 5 kg W.Loss
Allergy to flower
P.H = sjogren syn from 20 years ago (arthralgia & dry eye...) & hypothyriod from 8 years ago
D= ezetinibe & azeram OD & levothy,
HB= 14 FBS = 112 LFT = normal ferr= 65 TSH= 2
Plan = lab R/O celiac
---------- ۱۴۰۲/۰۵/۲۰-۱۲:۲۷ ---- شهبازخانی بیژن ----------
CC=
AGAigA=10.2 > 10
TTGIGg= 7 > 18 TTGigA= 5 >18
AGAigG= 4 CALP= 2
HB = 14.5
Plan = GFD if needed endoscopy
---------- ۱۴۰۲/۰۷/۰۷-۱۰:۰۲ ---- شهبازخانی بیژن ----------
CC= all GI symptoms improved


CC=
D1 pathology = MO
D2 pathology = MI
Endo = gastritis RUT= neg
With GFD from 2 months is completely well


۱۴۰۲/۰۵/۲۲-۰۹:۰۹ شهبازخانی بیژن
CC=chronic & lower abd, pain& tenesmus & Bloating & Gas
Headache 4 /weeks from 3 years ago
No alarm, sign
P.H= Minor thalassemia
D = bis & mebecto & meben & R/O NCGS
۱۴۰۲/۰۶/۱۲-۰۹:۲۹ شهبازخانی بیژن
IgA= 199 AGAigA= 14 (< 15), TTGigG= 8 (< 20)
AGAigG= 4 TTGigA= 2
TSH= 2 VitD= 32 HB= 13.6 ESR= 2 LFT = norm FBS= 86
TG= 104 Chol= 175 ferr= 49 Zn= 90 Fe= 126
Plan = GFD R/O NCGS
۱۴۰۲/۰۸/۰۷-۱۹:۲۱ شهبازخانی بیژن
CC= after 2 months GFD 70% of sym, improved
Plan= GFD & endoscopy
پاک کن
قابل سفارشی
تشخیص
رنگ پس زمینه متن
رنگ متن
ذخیره


۱۴۰۲/۱۰/۰۲-۰۹:۳۱ شهیارخانی بیژن
Endoscopy = Mild gastritis
Pathology = MO 16/100
Plan = normal diet 1 months then GFD one month
۱۴۰۲/۱۱/۲۹-۰۹:۲۲ شهیارخانی بیژن
CC= with GFD is dramaticly better (8 score is better)
Plan = GFD
۱۴۰۲/۰۵/۲۷-۱۱:۲۲ شهیارخانی بیژن

Role of NCGS in Refractory Functional dyspepsia

A Randomized Double-Blind, Placebo-Controlled Trial

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Dyspepsia

Dyspepsia is a common symptom (**25 %** of general population)

In about **75%** of patients with dyspepsia, we don’t find a structural pathology to identify the patient s symptoms.

Rome IV Criteria for Functional Dyspepsia

B1. Functional dyspepsia
Diagnostic criteria¶
1. One or more of the following:
a. Bothersome postprandial fullness
b. Bothersome early satiation
c. Bothersome epigastric pain
d. Bothersome epigastric burning
AND
2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

¶ Criteria fulfilled for the last three month s with symptom onset at least six months before diagnosis.

Refractory Functional Dyspepsia

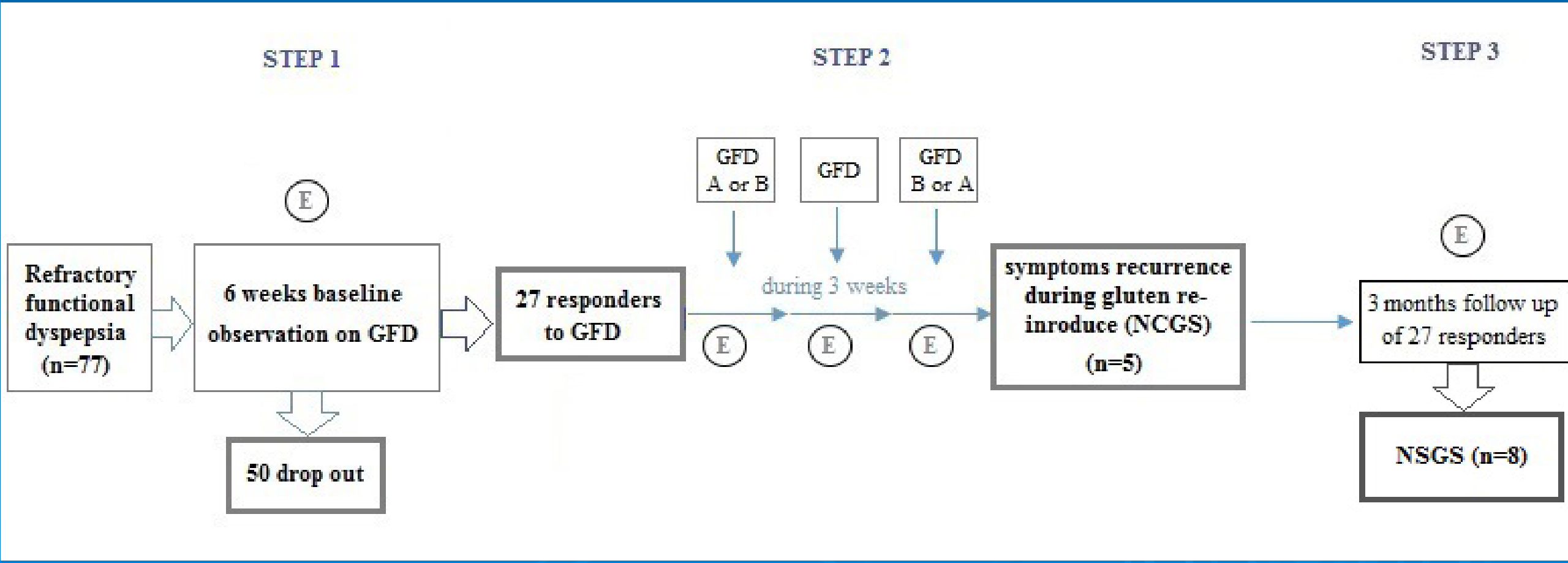
Refractory FD is defined as FD in patients with continuous symptoms for **at least 6 months** that has been unresponsive to at least two medical treatments, such as H. pylori eradication and PPIs, prokinetics or TCA

First step

- **Gluten-free regimen was introduced to all patients for six weeks.**

- After 6 weeks GFD, patients whose **symptoms improved** more than 3 score , were **entered** into the second step

Study protocol according saleno criteria



Results

- The prevalence of NCGS was 6.5% among patients with RFD

- With follow up the responder for more three months, increase the NCGS prevalence to 10.3%

Results

- The age range 31 to 40 years old (80%)
- NCGS was more frequent in women than men (4:1)
- The most common GI symptoms was postprandial fullness (in all patients) and epigastric pain (80%)

Results

- The most common extra-gastrointestinal symptoms was

- Headache/ fatigue 80%

- And musculoskeletal pain (fibromyalgia) 60%

Conclusions

- In addition to five patients 6.5% who was diagnosed as NCGS by Salerno's Expert criteria

- Three more patients were categorized as NCGS during extra follow up (overall 10.3%)

Conclusions

- This study confirmed that due to significant prevalence of NCGS among patients with RFD **(6.5 % - 10.3%)**

- **We recommend 6-weeks GFD in patients with RFD**

SCIENTIFIC REPORTS
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OPEN

Prevalence of Non-Celiac Gluten Sensitivity in Patients with Refractory Functional Dyspepsia: a Randomized Double-blind Placebo Controlled Trial

Bijan Shahbazkhani[1], Mohammad M. Fanaeian[1*], Mohammad J. Farahvash[1], Najmeh Aletaha[1], Foroogh Alborzi[1], Luca Elli[2], Amirhossein Shahbazkhani[1], Jayran Zebardast[3] & Mohammad Rostami-Nejad[4]

Refractory functional dyspepsia (RFD) is characterized by symptoms persistence in spite of medical treatment or *H. pylori* eradication. No study has yet investigated the presence of gluten-dependent RFD as a clinical presentation of Non-Celiac Gluten Sensitivity (NCGS). Patients with RFD, in whom celiac disease, wheat allergy and *H. pylori* infection had been ruled out, followed a six weeks long gluten-free diet (GFD). Symptoms were evaluated by means of visual analogue scales; patients with $\geq$30% improvement in at least one of the reported symptoms after GFD underwent a double-blind placebo controlled gluten challenge. Subjects were randomly divided in two groups and symptoms were evaluated after the gluten/placebo challenge. GFD responders were further followed on for 3 months to





If you look for NCGS disease you will find it

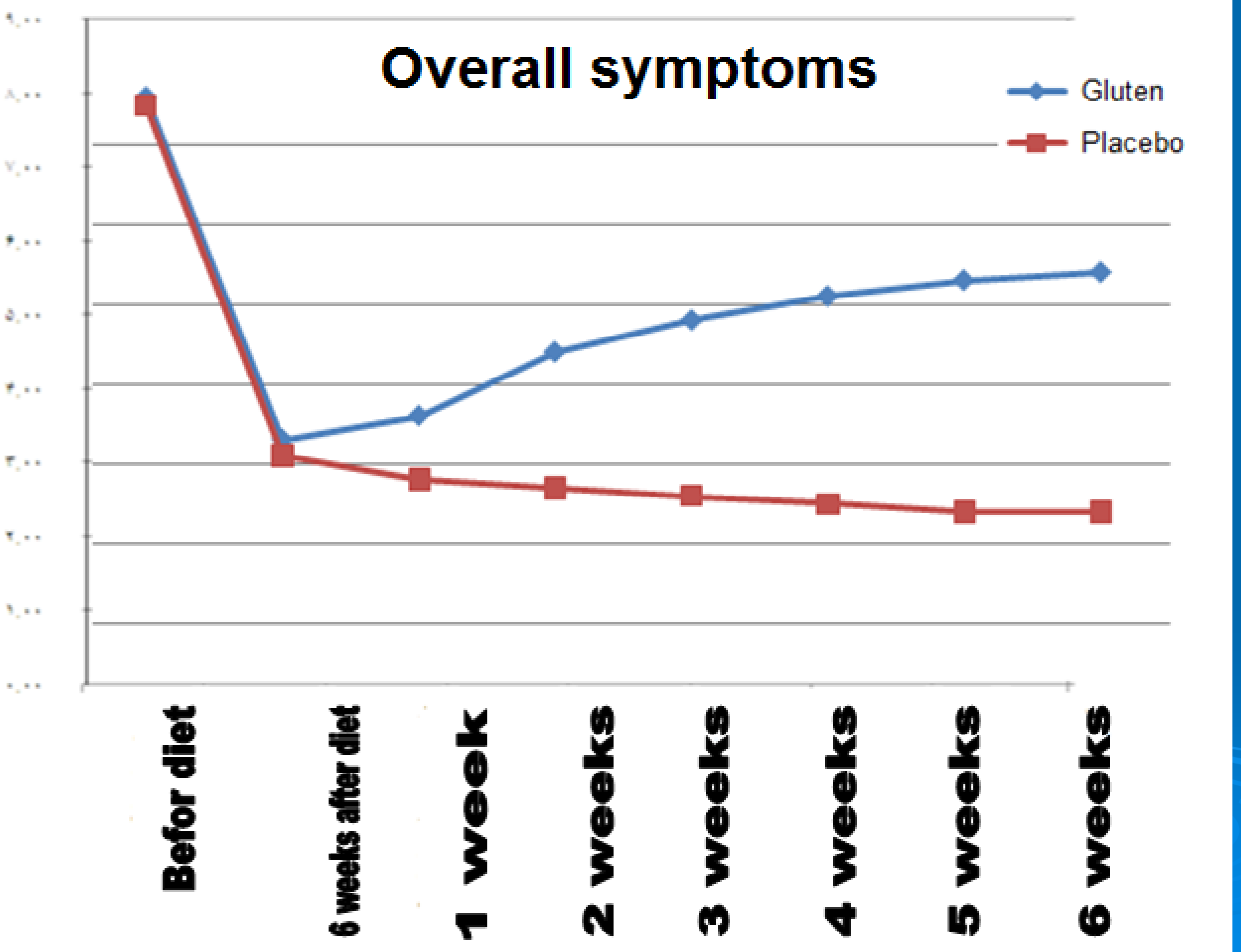
Methods

- During the study , **148 patients** with IBS diagnosis were enrolled , after 6 weeks GFD **80 patients respond to GFD**

- Finally, only **72 patients:**

  35 patients in the gluten(GCD) group ,

  37 patients in the placebo(GFD) group were enrolled


Overall symptoms
Gluten
Placebo
Befor diet
6 weeks after diet
1 week
2 weeks
3 weeks
4 weeks
5 weeks
6 weeks

Result

- **symptomatic improvement was statistically different in the gluten-containing group compared with placebo**

➢ **GCD group in 9 (25.7%)**

➢ **GFD 31 (83.8%) patients** **($p < 0.001$)**

Conclusion

- **Gluten-free diet** is recommended

In patients with refractory IBS, without celiac disease

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Article

Non-Celiac Gluten Sensitivity Has Narrowed the Spectrum of Irritable Bowel Syndrome: A Double-Blind Randomized Placebo-Controlled Trial

Bijan Shahbazkhani [1,2,3], Amirsaeid Sadeghi [1,*], Reza Malekzadeh [2,3], Fatima Khatavi [4], Mehrnoosh Etemadi [4], Ebrahim Kalantri [5], Mohammad Rostami-Nejad [6] and Kamran Rostami [7]

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