Non-Criteria or Seronegative Obstetric Antiphospholipid Syndrome

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ABSTRACT: Obstetric antiphospholipid syndrome (Obs-APS) is one of the most commonly identified causes of recurrent pregnancy loss and its accurate diagnosis is a requirement for optimal treatment. Some patients do not fulfill the revised Sapporo classification criteria, the original APS classification criteria, and are considered to be non-criteria Obs-APS. In these patients with non-criteria, there is controversy about their inclusion within the spectrum of APS and eventually their treatment as having Obs-APS. A subset of patients may also have clinical characteristics of Obs-APS even though lupus anticoagulant, anticardiolipin antibodies, and anti-β2 glycoprotein I antibodies are consistently negative. These patients are recognized as seronegative Obs-APS.

We reviewed evidence of non-criteria Obs-APS and discuss a case of a woman with a diagnosis of active systemic lupus erythematosus and non-criteria Obs-APS with four consecutive pregnancy losses. After an accurate diagnosis the patient received prenatal counseling and benefited from the optimal treatment of Obs-APS that led to a successful pregnancy. The applicability of this successful experience about outcomes in women with non-criteria (seronegative) Obs-APS is also evaluated.

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KEY WORDS: non-criteria obstetric APS, seronegative obstetric antiphospholipid syndrome (Obs-APS), pregnancy outcome, prenatal counseling, treatment

Obstetric antiphospholipid syndrome (Obs-APS) is one of the most commonly identified causes of recurrent pregnancy loss and its accurate diagnosis is a requirement for optimal treatment [1]. The international consensus (revised Sapporo) classification criteria for Obs-APS [2] do not include low positive and/or intermittent antiphospholipid antibodies (aPL), such as lupus anticoagulant, anticardiolipin (aCL) and anti-β2-glycoprotein I (aβ2GPI) antibodies. Clinical manifestations such as two unexplained miscarriages, three non-consecutive miscarriages, preeclampsia, placental abruption, premature birth, or two or more unexplained in vitro fertilization failures were not considered as criteria of Obs-APS. In addition, there are women with clinical features of obstetric APS, without serological criteria for APS being recognized as seronegative Obs-APS [3]. However, clinical observations and cohort studies of women with pregnancy morbidity suggest that not taking into account the low and/or intermittent positive aPL (seronegative) may result in understimation of the diagnosis and therefore the patient with non-criteria (seronegative) Obs-APS might not receive the benefit of treatment, which could lead to poor pregnancy outcome [4-6]. In this review we present evidence of non-criteria Obs-APS. In addition, we will discuss a case of a woman with a diagnosis of active systemic lupus erythematosus (SLE) and non-criteria of Obs-APS, and four consecutive pregnancy losses. She benefited from the optimal treatment of Obs-APS that that led to a successful pregnancy pregnancy. The applicability of this successful experience with non-criteria obstetric APS or seronegative Obs-APS is discussed.

Non-criteria or seronegative Obs-APS represents a diagnostic and treatment challenge

PATIENT DESCRIPTION

A 38 year old woman, who was born and living in Mexico City, had been married for 8 years. She presented four failed pregnancies. Her grandmother had rheumatoid arthritis and a niece had juvenile idiopathic arthritis. In 2002 she had her first pregnancy, which was interrupted at week 21 by fetal loss secondary to premature rupture of membranes. In 2003, she had her second pregnancy with unexplained fetal loss at week 21. In 2005, she had her third pregnancy, and at week 31, intrauterine growth retardation was detected. A week later, obstetric ultrasound revealed fetal death. Fetal abnormalities, maternal anatomic, hormonal alterations, and other reasons for fetal loss were ruled out by a gynecologist. Facial erythema, transient wheals

in lower extremities and arthralgias were observed during pregnancy. A rheumatologist made the diagnosis of systemic lupus erythematosus (SLE) based on mucocutaneous and articular manifestations and positive antinuclear antibodies 1:640 (Hep2 substrate), positive anti-double-stranded DNA antibody (anti-dsDNA), anti-SSA/Ro (anti-Sjögren's-syndrome-related antigen A) and anti-SSB/La antibodies (ELISA), anti-cardiolipin antibodies immunoglobulin G (IgG) and immunoglobulin M (IgM) (ELISA), and lupus anticoagulant (Russell viper venom) were negative. In May 2006, immunological tests prior to the fourth pregnancy showed anti-nuclear antibodies (ANA) 1:640 homogeneous pattern, anti-dsDNA 306 IU/ml (ELISA, normal value < 200 IU/ml), aCL IgM 17.4 MPL units (normal value < 10MPL Units), anti-SSA/Ro 13.4 IU, and anti-SSB/La 12.4 U (normal value < 8 IU). The patient was asymptomatic. In February 2007, at the onset of the fourth pregnancy, ANA were positive (1:160), although three subsequent determinations were negative in the same laboratory. Of interest, aPL antibodies (IgG and IgM, aCL, LA, and aβ2GPI antibodies) were positive. Treatment with folic acid, acetylsalicylic acid and 20 mg/day of enoxaparine was started at week 14 of gestation. Hydropic placenta was detected during the 16th week of pregnancy. At week 20, 5 mg/day of prednisone were added and the enoxaparine dose was increased to 60 mg/day. In August, she presented erythema and arthralgias. During the 31st week of pregnancy she had premature delivery, the placenta was found to be senescent, and a male was born weighing 580 grams and in serious condition due to severe thrombocytopenia, respiratory insufficiency that required ventilatory assistance, and mesenteric thrombosis. The transfontanellar ultrasound showed venous infarction in fronto parietal region, hemorrhagic infarction of right hemisphere, and thalamic hemorrhagic infarction, according to hospital report. All these previous events were managed at other hospitals.

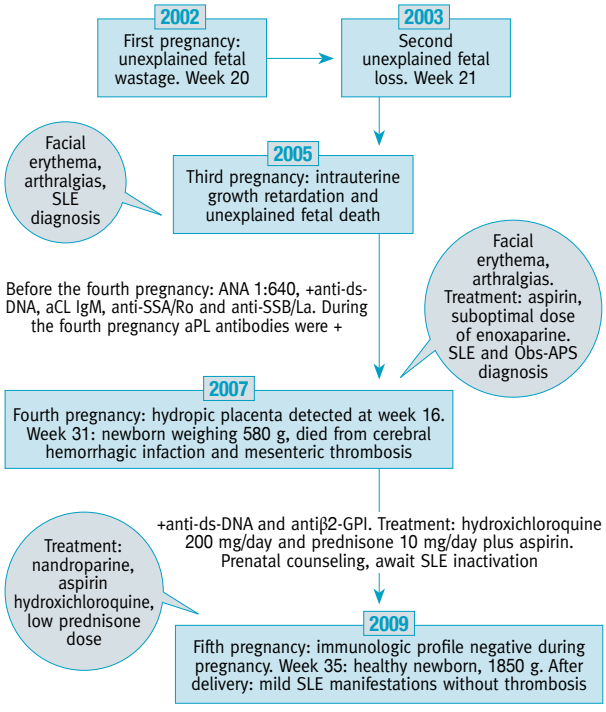
In 2008, at the age of 36 years, the patient was attended by rheumatologist (L.J.J.). She requested counseling about the possibility of attempting a fifth pregnancy. After performing medical history, the rheumatologist made the diagnosis of active SLE and Obs-APS. At that time the patient had intermittent hair loss, arthralgias, facial rash, fatigue, and Raynaud phenomenon. She was being treated with hydroxichloroquine 200 mg/day, prednisone 10 mg/day and acetylsalicylic acid and was advised to avoid pregnancy for at least 6 months until SLE inactivation was reached. In January 2009, new immunologic profile revealed positivity to anti-dsDNA and IgG anti-β2GPI, and complement levels were normal. Other aPL such as LA and IgG and IgM aCL were negative. Clinically SLE was inactive and she continued on hydroxichloroquine 200 mg/day and prednisone 5 mg/day. In November 2009, she became pregnant for the fifth time and she was started on subcutaneous nadroparin (0.6 ml/day, equivalent to 5,700 IU anti-Xa factor) at the 6th week of gestation plus acetylsalicylic acid. During pregnancy, she continued with hydroxichloroquine 200 mg/day and prednisone (5 mg/day). Again, immunologic profile became negative in three determinations throughout pregnancy (anti-dsDNA, normal complement levels, anti-β2GPI, LA and aCL, IgG and IgM). During this pregnancy her SLE remained inactive. Finally, at 35 weeks of gestation she underwent a caesarean section and a female newborn with a weight of 1850 grams was delivered. After delivery she only had mild cutaneous-articular SLE manifestations without thrombosis with negative immunologic profile. Figure 1 shows the clinical course throughout five pregnancies. After 6 years, the patient is asymptomatic and her daughter is healthy.

In cases with high suspicion of Obs-APS, treatment should be provided even with an inconsistent or negative aPL profile

DISCUSSION AND REVIEW

The case reported in this study highlights the importance of diagnosis, counseling, diligent obstetric, and rheumatologic surveillance as well as prompt treatment leading to a successful pregnancy after multiple previous losses. At the same time, it demonstrates the value of providing treatment despite the inconsistent negative immunologic profile of Obs-APS.

Figure 1. Clinical course throughout 5 pregnancies in a patient with non-criteria obstetric antiphospholipid syndrome (Obs-APS)



SLE = systemic lupus erythematosus ANA = antinuclear antibodies, IgM = immunoglobulin M, SSB = Sjögren's syndrome antigen B, aCL IgM = anticardiolipin antibodies IgM

Spontaneous and recurrent pregnancy loss (RPL) are common complications of an APS pregnancy; therefore, treatment strategies of Obs-APS enhance the possibility of a subsequent successful pregnancy [7]. A study that analyzed the clinical and immunological features of 179 primary and 52 associated APS patients found that 17.8% had recurrent early fetal loss (< 10 weeks) and 54% had late fetal loss (> 10 weeks). As in other studies, LA positivity was the main risk factor in patients with poor obstetric outcome, and late fetal loss was significantly more prevalent in primary APS [8,9]. Our patient had four fetal losses, yet LA, aCL, and anti-β2 GPI were inconsistent.

In this regard, the association of other aPL such as anti-phosphatidylserine/prothrombin (aPS/PT) antibodies in patients with APS and pregnancy complications was investigated. Approximately one-fourth of patients were positive for at least one aPL. The highest prevalence was found for aPS/PT, followed by aCL, LA and anti-β2GPI. Of interest, 11/169 patients with obstetric manifestations had only aPS/PT associated with pregnancy complications such as recurrent early or late abortions and with premature delivery unrelated to other aPL [10]. Patil et al. [11] studied 587 women with no apparent cause of RPL. The risk of RPL was the highest in women with aCL, followed by anti-annexin V antibodies, and LA in 8%. Of note in the present case are the recurrent obstetric clinical features presented by the patient. Other aPL were not investigated so the participation of other aPL such as aPS/PT and anti-annexin V antibodies could be a possible explanation.

Diagnosis, counseling, diligent obstetric, and rheumatologic surveillance, as well as prompt treatment in Obs-APS patients, are necessary to achieve a successful pregnancy

The most frequent cause of RPL in APS is a defective maternal hemostatic response leading to uteroplacental thrombosis. Placenta-mediated pregnancy complications include late pregnancy loss, placental abruption, pre-eclampsia and small-for-gestational-age newborn. These findings suggest the participation of other mechanisms, such as abnormal placental development, placental inflammation, and complement activation by aPL, even more than thrombosis, lead to pregnancy loss [12]. The patient had two mid-trimester pregnancy losses and two late pregnancy losses, the last one with a fetus very small-for-gestational age possibly corresponding to placenta-mediated complications.

There is a debate about aCL and anti-β2GPI titers in patients with fetal loss and recurrent early miscarriage. The results of studies that considered low titers of aPL in pregnancy are controversial, varying from good outcome to poor obstetric results, similar to patients with medium-high titers [13]. Moreover, there is no agreement about cut-offs to consider positive aPL (low vs. medium-high titers) [14].

The variations in aPL during pregnancy have been reported, and some patients with aPS became negative and vice versa [15]. The possible explanations are in the case of positivity to aPL at pregnancy onset, maternal immune response to the antigenic stimuli of placental tissues or aPL negativization because of suppression of autoantibody production, antibody consumption or effect of treatment with hydroxichloroquine that could determine a decrease in antibody titer [16]. In our patient, we observed fluctuations of aPL antibodies. Of interest, in the last and only successful pregnancy, the patient remained aPL negative throughout the pregnancy. This aPL profile, together with optimal treatment, is associated with a favorable outcome [17].

A diagnosis of non-criteria Obs-APS is considered to be present if the patient has a combination of non-criteria clinical manifestations with international consensus laboratory criteria or international consensus clinical criteria with a non-criteria laboratory manifestation (low positive aCL or anti-β2GPI present between the 95th and 99th percentiles) or presence of intermittent aPL in women with classical clinical manifestations of Obs-APS [3]. Our patient had one or more unexplained deaths of a morphologically normal fetus beyond the 10th week of gestation, (international consensus clinical criteria) with low aPL levels or intermittent aCL, anti-β2GPI, and LA in patients with classical clinical manifestations of Obs-APS (non-criteria laboratory manifestation). A recent study did not find differences in the frequency of thrombotic or obstetric manifestations of APS between patients with low to medium levels of aCL and/or high vs. lower levels of anti-β2GPI antibodies, suggesting that diagnosis and further APS treatment should not be excluded because of low titer of aPL [18].

In addition, there are women with a high suspicion of having Obs-APS, revealing the classical clinical features but persistently negative for common laboratory tests for aPL. Some studies have described this phenomenon as seronegative APS. This condition cannot assure that there are no other antibodies that have not been detected previously. In some of the women in this subset of patients, antibodies to zwitterionic phospholipid (e.g., phosphatidylethanolamine) or various phospholipid-binding plasma proteins or phospholipid-protein complexes as well as anionic phospholipids could be detected [3]. However, clinical significance of these antibodies remains unclear. It is important to mention that the same patient may show a negative aPL profile in a determination and during follow-up may have positivity to traditional or non-traditional aPL. Therefore follow-up of serological profile is mandatory to decide the course of treatment.

However, cases of thrombosis have rarely been reported in the neonates of mothers with APS or aPL. Children born to mothers who have aPL acquire these antibodies passively, and occurrences of thrombosis appear to be extremely unusual [19]. A study that reviewed 21 patients with neonatal thrombosis found stroke as the most prevalent arterial clinical manifestation, occurring in 12 patients along with impairment of the middle cerebral artery in 10 neonates. The aorta, mesenteric,

and femoral arteries were involved in two cases and the renal artery in one case [20]. In the fourth pregnancy our patient gave birth to a neonate who had a cerebral hemorrhagic infarction and mesenteric thrombosis. Unfortunately, aPL was not determined, although the clinical picture could correspond to neonatal APS (data not shown).

Another important aspect is the prenatal advice, which is one of the keys to successful pregnancy in patients with autoimmune or systemic diseases such as SLE and APS. This matter has been frequently forgotten. Among its purposes is the right time to plan the pregnancy in relation to inactivity of the disease prior to pregnancy, to anticipate some problems, to adapt treatments and minimize risks for both mother and fetus, and to improve the prognosis of these high risk pregnancies [21]. In the present case prenatal counseling in the last pregnancy was crucial to achieve a successful pregnancy after several fetal losses. Previously, the patient did not receive prenatal counseling and a clear explanation about the diagnosis of Obs-APS and mild clinical SLE activity were not offered.

Traditional and novel treatments have been tried in women with APS to improve the result of gestation and to reduce obstetric complications [22]. The American College of Chest Physicians (ACCP) guidelines recommend that women with Obs-APS should be treated with prophylactic or intermediate dose unfractionated heparin or with prophylactic dose or low molecular weight heparin (LMWH) combined with low dose aspirin (75 to 100 mg/daily) in the antepartum period as soon as pregnancy is confirmed [23]. Present day treatment of special cases with recurrent obstetric morbidity considers:

- Starting low-dose aspirin even before conception
- Combining with LMWH starting as soon as possible after conception and maintaining it throughout the pregnancy
- Switching from prophylactic to full-dose LMWH, together with hydroxychloroquine and low prednisone dose if necessary

Because of the lack of available studies, the strength of these recommendations are based on clinical judgment [23,24]. Retrospective and prospective cohort studies in patients with non-criteria laboratory manifestations of Obs-APS suggest the possibility of similar pregnancy outcomes with standard treatment for Obs-APS as women who fulfill international consensus criteria. [3,25-27]. Our patient benefited from the full treatment considering the diagnosis of Obs-APS despite intermittent titers of autoantibodies.

CONCLUSIONS

Patients with non-criteria (seronegative) Obs-APS should be closely monitored by a multidisciplinary team to receive full treatment for Obs-APS, which could lead to a successful pregnancy outcome.

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References

1. Kutteh WH, Hinote CD. Antiphospholipid antibody syndrome. *Obstet Gynecol Clin North Am* 2014; 41: 113-32.
2. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; 4: 295-306.
3. Arachchillage DR, Machin SJ, Mackie IJ, Cohen H. Diagnosis and management of non-criteria obstetric antiphospholipid syndrome. *Thromb Haemost* 2015; 113: 13-9.
4. Mekinian A, Loire-Berson P, Nicaise-Roland P, et al. Outcomes and treatment of obstetrical antiphospholipid syndrome in women with low antiphospholipid antibody levels. *J Reprod Immunol* 2012; 94: 222-6.
5. D'Ippolito S, Meroni PL, Koike T, Veglia M, Scambia G, Di Simone N. Obstetric antiphospholipid syndrome: a recent classification for an old defined disorder. *Autoimmun Rev* 2014; 13: 901-8.
6. Ruffatti A, Calligaro A, Del Ross T, et al. Risk-based secondary prevention of obstetric antiphospholipid syndrome. *Lupus* 2012; 21: 741-3.
7. De Jesús GR, Rodrigues G, de Jesús NR, Levy RA. Pregnancy morbidity in antiphospholipid syndrome: what is the impact of treatment? *Curr Rheumatol Rep* 2014; 16: 403.
8. Singh NK, Behera DR, Agrawal A, et al. Hospital based prospective longitudinal clinical and immunologic study of 179 patients of primary anti-phospholipid syndrome. *Int J Rheum Dis* 2013; 16: 547-55.
9. Jara LJ, Pacheco-Reyes H, Medina G, Angeles U, Cruz-Cruz P, Saavedra MA. Prolactin levels are associated with lupus activity, lupus anticoagulant, and poor outcome in pregnancy. *Ann N Y Acad Sci* 2007; 1108: 218-26.
10. Žigon P, Perdan Pirkmajer K, Tomšič M, et al. Anti-phosphatidylserine/prothrombin antibodies are associated with adverse pregnancy outcomes. *J Immunol Res* 2015: 975704.
11. Patil R, Ghosh K, Vora S, Shetty S. Inherited and acquired thrombophilia in Indian women experiencing unexplained recurrent pregnancy loss. *Blood Cells Mol Dis* 2015; 55: 200-5.
12. Viall CA, Chamley LW. Histopathology in the placentae of women with antiphospholipid antibodies: a systematic review of the literature. *Autoimmun Rev* 2015; 14: 446-71.
13. Levy RA, Dos Santos FC, de Jesús GR, de Jesús NR. Antiphospholipid antibodies and antiphospholipid syndrome during pregnancy: diagnostic concepts. *Front Immunol* 2015; 6: 205.
14. Gardiner C, Hills J, Machin SJ, Cohen H. Diagnosis of antiphospholipid syndrome in routine clinical practice. *Lupus* 2013; 22: 18-25.
15. Donohoe S, Quenby S, Mackie I, et al. Fluctuations in levels of antiphospholipid antibodies and increased coagulation activation markers in normal and heparin-treated antiphospholipid syndrome pregnancies. *Lupus* 2002; 11: 11-20.
16. Broder A, Putterman C. Hydroxychloroquine use is associated with lower odds of persistently positive antiphospholipid antibodies and/or lupus anticoagulant in systemic lupus erythematosus. *J Rheumatol* 2013; 40: 30-3.
17. Sciascia S, Hunt BJ, Talavera-Garcia E, Lliso G, Khamashta MA, Cuadrado MJ. The impact of hydroxychloroquine treatment on pregnancy outcome in women with antiphospholipid antibodies. *Am J Obstet Gynecol* 2016; 214: 273.e1-8.
18. Ofer-Shiber S, Molad Y. Frequency of vascular and pregnancy morbidity in patients with low vs. moderate-to-high titers of antiphospholipid antibodies. *Blood Coagul Fibrinolysis* 2015; 26: 261-6.
19. Tincani A, Rebaioli CB, Andreoli L, Lojacono A, Motta M. Neonatal effects of maternal antiphospholipid syndrome. *Current Rheum Rep* 2009; 11: 70-6.
20. Peixoto MV, de Carvalho JF, Rodrigues CE. Clinical, laboratory, and therapeutic analyses of 21 patients with neonatal thrombosis and antiphospholipid antibodies: a literature review. *J Immunol Res* 2014: 672603.

21. Le Guern V, Guettrot-Imbert G, Costedoat-Chalumeau N. The pre-pregnancy counseling. *Rev Med Interne* 2015; 36: 151-3.

22. Xiao J, Xiong J, Zhu F, He L. Effect of prednisone, aspirin, low molecular weight heparin and intravenous immunoglobulin on outcome of pregnancy in women with antiphospholipid syndrome. *Exp Ther Med* 2013; 5: 287-91.

23. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO; American College of Chest Physicians. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 41: e691S-736S.

24. Saavedra Salinas MÁ, Barrera Cruz A, Cabral Castañeda AR, et al. Clinical practice guidelines for the management of pregnancy in women with autoimmune rheumatic diseases of the Mexican College of Rheumatology. Part II. *Reumatol Clin* 2015; 11: 305-15.

25. Espinosa G, Cervera R. Current treatment of antiphospholipid syndrome: lights and shadows. *Nat Rev Rheumatol* 2015; 11: 586-96.

26. Cohn DM, Goddijn M, Middeldorp S, Korevaar JC, Dawood F, Farquharson RG. Recurrent miscarriage and antiphospholipid antibodies: prognosis of subsequent pregnancy. *J Thromb Haemost* 2010; 8: 2208-13.

27. Keeling D, Mackie I, Moore GW, Greer IA, Greaves M. British Committee for Standards in Haematology. Guidelines on the investigation and management of antiphospholipid syndrome. *Br J Haematol* 2012; 157: 47-58.

Capsule

Common antibiotic hurts bee survival

Several factors have been identified that could be responsible for the collapse of honeybee populations. However, Raymann et al. have identified an antibiotic that appears to reduce bee survival by changing the bee microbiome. Hives are frequently treated with tetracycline to prevent infections. When bees were fed tetracycline for 5 days in a laboratory and reintroduced to their hives, half as many survived after 3 days, relative to controls. Antibiotic treatment decreased the number and relative abundance of the bacteria living in the bee gut. After treatment, bees were more sensitive to infection by a *Serratia* species of bacterial pathogen. Bees that were germ-free showed no changes after tetracycline treatment, suggesting that tetracycline was acting on the microbiome and not directly on the bees.

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Eitan Israeli

Capsule

Metastatic cells feed off a complement

Cancer patients with metastases in the cerebrospinal fluid (CSF) have a poor prognosis. How cancer cells survive in the CSF has been an enigma because this microenvironment is devoid of mitogens and nutrients required for cell growth. Studying mice and patient samples, Boire and colleagues showed that cancer cells metastasizing to the CSF over-express a protein called "complement component 3" (C3). C3 activates a specific receptor in the choroid plexus epithelium, a barrier system in the brain that prevents cells and molecules in the blood from entering the CSF. This activation disrupts the blood-CSF barrier, allowing circulating growth factors into the CSF. A drug that blocks this activation suppressed metastasis to the CSF in mice.

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Eitan Israeli

Capsule

Viruses compound dietary pathology

Reoviruses commonly infect humans and mice asymptomatically. Bouziat and colleagues found that immune responses to two gut-infecting reoviruses take different paths in mice. Both reoviruses invoked protective immune responses, but for one reovirus, when infection happened in the presence of a dietary antigen (such as gluten or ovalbumin), tolerance to the dietary antigen was lost. This result occurred because this strain prevented the formation of tolerogenic T cells. Instead, it promoted T helper 1 immunity to the dietary antigen through interferon regulatory factor 1 signaling. Celiac disease patients also exhibited elevated levels of antibodies against reovirus.

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Eitan Israeli

"No human being is illegal"

Elie Wiesel (1928–2016), Romanian-born American Jewish writer, professor, political activist, Nobel Laureate and Holocaust survivor. He was the author of 57 books written mostly in French and English