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Interferon-gamma (+874) T/A genotypes and risk of IFN-alpha-induced depression

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Abstract

Depression is a frequent side effect of interferon (IFN)-alpha therapy of hepatitis C (HCV) and is of great relevance with regard to adherence, compliance, and premature therapy discontinuation. There are no reliable tests to identify patients-at-risk for the development of IFN-alpha induced depression. We retrospectively studied distribution of IFN-gamma (IFNG) (?874) T/A genotypes in 170 Caucasian HCV patients treated by IFN-alpha. Distribution of IFNG (?874) genotypes was different between depressed and not depressed subjects with more TA and less AA carriers among depressed than among not depressed subjects ($P = 0.003$). Carriers with at least one T allele were more frequent among depressed than among not depressed patients ($P = 0.003$). Our results suggest that presence of high producer (T) alleles might be a genetic risk factor for the development of IFN-alpha-induced depression. Assessment of IFNG (?874) genotypes might help to identify patients-at-risk for IFN-alpha-induced depression. IFNG and IFN-alpha transcriptionally induce indoleamine-2,3-dioxygenase (IDO), the rate-limiting enzyme of the kynurenine (KYN) pathway of tryptophan (TRY) metabolism. IFN-induced up-regulation of IDO triggers depression by shifting TRY metabolism from formation of serotonin to production of neuroactive kynurenines. TRY–KYN pathway might be a new target for pharmacological prevention and treatment of IFN-alpha-induced psychiatric complications.

Keywords

Interferon-gamma (+874) polymorphism; Depression; Hepatitis C; Kynurenines

Background

Depression was reported in 25–50% in patients with hepatitis C virus infection (HCV) treated with interferon-alpha (IFN-alpha), and is of great relevance with regard to adherence, compliance, and premature therapy discontinuation (Capuron and Miller 2004). There are no reliable tests to identify patients-at-risk for the development of IFN-alpha-induced depression. Recent studies revealed association of IFN-alpha-induced depression with polymorphisms of inflammation-related genes of IFN-alpha receptor (Yoshida et al. 2005) and interleukin-6 (Bull et al. 2009); and serotonin-related genes: serotonin-1A receptor (Kraus et al. 2007), and serotonin transporter (Bull et al. 2009; Lotrich et al. 2009, Pierucci-Lagha et al. 2010). These findings are in line with the data on cytokines involvement in antidepressant effect (Janssen et al. 2010) and with the hypotheses of serotonin deficiency as a cause of depression (Coppen 1968), and of up-regulation of serotonin transmission as a

determinant of antidepressant effect (Lapin and Oxenkrug 1969). These studies, however, did not consider that serotonin deficiency in depression might be triggered by shunting of tryptophan (TRY) metabolism from serotonin to kynurenine (KYN) pathways (Lapin and Oxenkrug 1969; Oxenkrug 2010a). Up-regulation of TRY–KYN pathway depends on the activation of its rate-limiting enzyme, indoleamine-2,3-dioxygenase (IDO) (Hayaishi 1976). Considering that IFN- α stimulates IDO activity and production of IFN- γ (IFNG), the strongest transcriptional inducer of IDO (Taylor and Feng 1991), it was suggested that IFN- α -induced depression depends upon the up-regulation of IDO (Raison et al. 2006). IFNG production is encoded by polymorphic IFNG (+874) T/A gene (Pravica et al. 2000), therefore, the presence of high (T) or low (A) producer might impact the production of IFNG, the extent of IDO activation, and, consequently, the occurrence of depression associated with IFN- α treatment (Oxenkrug 2007, 2010a). To check this suggestion, we compared IFNG (+874) T/A polymorphisms in HCV patients who have experienced depression while taking IFN- α , and those who did not.

Methods

Study patients

IFNG (+874)T/A polymorphisms were evaluated in a retrospective study of 204 patients treated in the past 2 years with peginterferon alfa-2a (Pegasys® or PegIntron®) administered by subcutaneous injection at doses ranging from 120 to 180 μ g/week, in combination with ribavirin at doses ranging from 1,000 to 1,200 mg/d. Doses were determined by the patients' body weight. Treatment lasted for 6–12 months depending on the virus genotype. Study was approved by Tufts Medical Center and Western Institutional Review Boards. All participants signed the informed consent forms. Patients were evaluated by psychiatrist, and presence/absence of depression was assessed by utilization of SCID for past depression (Structured Clinical Interview for DSM-IV axis 1 Disorders).

Polymorphism analysis

Genomic DNA was extracted from peripheral blood samples using QIAamp DNA blood mini Kit (Qiagen, Valencia, CA). Polymorphism at position +874 of IFNG gene was identified using allele-specific polymerase chain reaction using specific primer (antisense primer: TCA ACA AAG CTG ATA CTC CA, sense +874T: TTC TTA CAA CAC AAA ATC AAA TCT, and sense +874A: TTC TTA CAA CAC AAA ATC AAA TCA). PCR amplification was performed as described elsewhere (Pravica et al. 2000).

Statistical analysis

The genotype frequencies were tested for Hardy–Weinberg equilibrium using a standard Chi-square test. Comparisons between genotype groups were made by Chi-square test, and *P* values <0.05 were considered as statistical significant.

Results

170 out of 204 patients were Caucasian subjects (121 men and 49 women, median age 53 years). Present report includes data of only these Caucasian patients. 104 of them experienced IFN- α -induced depression. There were almost two times more depressed (35.6%) than not depressed (18.2%) females and almost equal number of depressed and not depressed males (Table 1).

Observed and expected IFNG (+874) genotype distributions were not statistically different, and the allele frequencies for each polymorphism were as expected from the Hardy–Weinberg equilibrium (data not shown).

Distribution of IFNG (+874) genotypes was different between depressed and not depressed subjects with more TA and less AA carriers among depressed than not depressed subjects ($P = 0.01$). There were more carriers of, at least, one T allele among depressed than the not depressed patients ($P = 0.003$; Table 2).

Discussion

This is the first observation of different distribution of IFNG (+874) T/A genotypes between depressed and not depressed HCV patients treated with IFN-alpha. Significant increase of frequency of TA carriers and decrease of AA carriers among depressed patients in comparison with not depressed patients suggests that presence of T alleles represents a genetic risk factor the development of IFN-alpha-induced depression. TA and TT genotypes are associated with higher IFNG mRNA than AA genotypes: mean mRNA levels of IFNG in white blood platelets were not statistically different between TA and TT carriers but 14 times higher than mRNA in carriers of AA genotype ($P < 0.001$) (Biolo et al. 2006). TA and TT carriers had higher blood IFNG levels than AA carriers (Anuradha et al. 2008). Therefore, alternative interpretation of our data as suggestive of protective role of A alleles might be manifested only in AA carriers (but not in TA carriers). The higher frequency of carriers with, at least, one T allele among depressed than not depressed patients might, therefore, suggests the possibility of higher production of IFNG in patients with IFN-alpha-induced depression. This suggestion is in line with the hypothesis that IFN-alpha-induced depression is caused by up-regulation of TRY–KYN metabolism via activation of IDO (Capuron and Miller 2004). It is noteworthy that prolong activation of IDO might decrease TRY content similar to dietary TRY deficiency causing pellagra (first described by 1,735 by Gaspar Casal), that manifested by depression and other psychiatric symptoms (Pitche 2005). There are evidences of anxiogenic (Lapin 1996, 1998, 2003; Dilman et al. 1979, psychomimetic (Erhardt et al. 2004), and cognition impairment (Schwarcz and Pellicciari 2002) effects of KYN and its derivatives that might underline similar psychiatric side effects of IFN-alpha treatment (Oxenkrug 2010a).

Increased risk of developing depression in carriers of T alleles is in line with the finding of association between risk of IFN-alpha-induced depression and IL-6 levels (Bull et al. 2009) since T alleles were associated with the increased production of IL-6 by white blood cells (Biolo et al. 2006). IFNG gene polymorphism might be related to recent finding of association of phospholipase A2 and cyclooxygenase 2 genes with IFN-alpha-induced depression (Su et al. 2010) since phospholipase A2–arachidonic acid–cyclooxygenase 2 cascade is triggered by IFNG-induced production of free radical, superoxide anion, precursor of peroxynitrite, from arginine at the expense of nitric oxide formation (Oxenkrug 2010b, c).

Depression and other psychiatric complications of IFN-alpha therapy are very often (up to 50%). Identification of the risk factors for the development of IFN-alpha-induced depression is important because psychiatric complications may impair patients ability to clear virus; necessitate IFN-alpha dose reduction or even premature discontinuation of therapy; interfere with patients capacity to manage the requirements of everyday life; and have negative impact on families and caregivers (Loftis and Hauser 2004; Raison et al. 2006).

However, identification of patients-at-risk is a difficult task considering the absence of reliable tests. Genetic factors might be considered along with environmental (stress) modifiers (Leonard and Myint 2009). The presence of T alleles of IFNG (+874) gene (if replicated in larger cohort of different genetic background) along with the other reported genetic polymorphisms (Bull et al. 2009; Kraus et al. 2007; Lotrich et al. 2009; Su et al. 2010; Yoshida et al. 2005) might be helpful for the identification of individuals-at-risk for

the development of depression and other psychiatric side effects of IFN- α treatment for HCV, multiple sclerosis and certain malignancies (Patten 2006) and for implementation of appropriate therapeutic interventions (Molina-Hernández et al. 2008).

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References

- Anuradha B, Rakh SS, Ishaq M, et al. Interferon-gamma Low producer genotype +874 overrepresented in Bacillus Calmette-Guerin nonresponding children. *Pediatr Infect Dis J*. 2008; 27:325–329. [PubMed: 18379373]
- Biolo G, Amoroso A, Savoldi S, et al. Association of interferon-gamma +874A polymorphism with reduced long-term inflammatory response in haemodialysis patients. *Nephrol Dial Transplant*. 2006; 21:1317–1322. [PubMed: 16410273]
- Bull SJ, Huezo-Diaz P, Binder EB, et al. Functional polymorphisms in the interleukin-6 and serotonin transporter genes, and depression and fatigue induced by interferon- α and ribavirin treatment. *Mol Psychiatry*. 2009; 14:1095–1104. [PubMed: 18458677]
- Capuron L, Miller AH. Cytokines and psychopathology: lessons from interferon- α . *Biol Psychiatry*. 2004; 56:819–824. [PubMed: 15576057]
- Coppen A. Depressed states and indolealkylamines. *Adv Pharmacol*. 1968; 6(Pt B):283–291. [PubMed: 5301640]
- Dilman, VM.; Lapin, IP.; Oxenkrug, GF. Serotonin and aging. In: Essman, W., editor. *Serotonin in health and disease*. Vol. vol 5. Spectrum Press; NY: 1979. p. 111-123.
- Erhardt S, Schwieler L, Emanuelsson C, Geyer M. Endogenous kynurenic acid disrupts prepulse inhibition. *Biol Psychiatry*. 2004; 56:255–260. [PubMed: 15312813]
- Hayaishi O. Properties and function of indoleamine 2,3-dioxygenase. Properties and function of indoleamine 2,3-dioxygenase. *J Biochem (Tokyo)*. 1976; 79:13P–21P.
- Janssen DG, Caniato RN, Verster JC, Baune BT. A psychoneuroimmunological review on cytokines involved in antidepressant treatment response. *Hum Psychopharmacol*. 2010; 25:201–215. [PubMed: 20373471]
- Kraus MR, Al-Taie O, Schäfer A, Pfersdorff M, Lesch KP, Scheurlen M. Serotonin-1A receptor gene HTR1A variation predicts interferon-induced depression in chronic hepatitis C. *Gastroenterology*. 2007; 132:1279–1286. [PubMed: 17408646]
- Lapin IP. Kynurenines and anxiety. *Adv Exp Med Biol*. 1996; 398:191–194. [PubMed: 8906265]
- Lapin IP. Antagonism of kynurenic acid to anxiogens in mice. *Life Sci*. 1998; 63:231–236.
- Lapin IP. Neurokynurenines (NEKY) as common neurochemical links of stress and anxiety. *Adv Exp Med Biol*. 2003; 527:121–125. [PubMed: 15206724]
- Lapin IP, Oxenkrug GF. Intensification of the central serotonergic processes as a possible determinant of the thymoleptic effect. *Lancet*. 1969; 1:32–39. [PubMed: 4178772]
- Leonard BE, Myint A. The psychoneuroimmunology of depression. *Hum Psychopharmacol*. 2009; 24:165–175. [PubMed: 19212943]
- Loftis JM, Hauser P. The phenomenology and treatment of interferon-induced depression. *J Affect Disord*. 2004; 82:175–190. [PubMed: 15488246]
- Lotrich FE, Ferrell RE, Rabinovitz M, Pollock BG. Risk for depression during interferon- α treatment is affected by the serotonin transporter polymorphism. *Biol Psychiatry*. 2009; 65:344–348. [PubMed: 18801474]
- Molina-Hernández M, Tellez-Alcántara NP, Pérez-García J, et al. Antidepressant-like actions of minocycline combined with several glutamate antagonists. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008; 32(2):380–386. [PubMed: 17933448]
- Oxenkrug GF. Genetic and hormonal regulation of the kynurenine pathway of tryptophan metabolism: new target for clinical intervention in vascular dementia, depression and aging. *Ann N Y Acad Sci*. 2007; 1122:35–49. [PubMed: 18077563]

- Oxenkrug GF. Tryptophan–kynurenine metabolism as a common mediator of genetic and environmental impacts in major depressive disorder: serotonin hypothesis revisited 40 years later. *Isr J Psychiatry*. 2010a; 47(1):56–63.
- Oxenkrug GF. Metabolic syndrome, age-associated neuroendocrine disorders and dysregulation of tryptophan–kynurenine pathway metabolism. *Ann N Y Acad Sci*. 2010b; 1199:1–14. [PubMed: 20633104]
- Oxenkrug GF. Interferon-gamma-inducible kynurenines/pteridines inflammation cascade: implications for aging and aging-associated medical and psychiatric disorders. *J Neural Transm*. 2010c epub ahead of print.
- Patten SB. Psychiatric side effects of interferon treatment. *Curr Drug Saf*. 2006; 1:143–150. [PubMed: 18690925]
- Pierucci-Lagha A, Covault J, Bonkovsky HL, et al. A functional serotonin transporter gene polymorphism and depressive effects associated with interferon-alpha treatment. *Psychosomatics*. 2010; 51:137–148. [PubMed: 20332289]
- Pitche PT, Pellagra. *Sante*. 2005; 15:205–208. [PubMed: 16207585]
- Pravica V, Perrey C, Stevens A, et al. A single nucleotide polymorphism in the first intron of the human INFG gene: absolute correlation with a polymorphic CA micro marker of high INF-g gene. *Hum Immunol*. 2000; 61:8333–8366.
- Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol*. 2006; 27:24–31. [PubMed: 16316783]
- Schwarcz R, Pellicciari R. Manipulation of brain kynurenines: glial targets, neuronal effects, and clinical opportunities. *J Pharmacol Exp Ther*. 2002; 303:1–10. [PubMed: 12235226]
- Su KP, Huang SY, Peng CY, et al. Phospholipase A2 and cyclooxygenase 2 genes influence the risk of interferon-alpha-induced depression by regulating polyunsaturated fatty acids levels. *Biol Psychiatry*. 2010; 67:550–557. [PubMed: 20034614]
- Taylor MW, Feng GS. Relationship between interferon-gamma, indoleamine 2,3-dioxygenase, and tryptophan catabolism. *FASEB J*. 1991; 5:2516–2522. [PubMed: 1907934]
- Yoshida K, Alagbe O, Wang X, et al. Promoter polymorphisms of the interferon-alpha receptor gene and development of Interferon-induced depressive symptoms in patients with chronic hepatitis C: preliminary findings. *Neuropsychobiology*. 2005; 52:55–61. [PubMed: 15990456]

Table 1

Subject characteristics overall and stratified by depression status-Caucasians only

Characteristic	All (<i>n</i> = 170)	Depressed (<i>n</i> = 104)	Not depressed (<i>n</i> = 64)	<i>P</i> value*
Age, mean $\pm$ SD (<i>n</i>)	53.3 $\pm$ 7.7 (166)	53.1 $\pm$ 7.2 (102)	53.6 $\pm$ 8.5 (64)	0.65 (<i>t</i> test)
Age, median (25th–75th percentiles)	55 (49–58)	55 (49–58)	55 (49–57.5)	
Gender, % (<i>n</i>)				
Female	28.8 (49/170)	35.6 (37/104)	18.2 (12/66)	0.0147
Male	71.2 (121/170)	64.4 (67/104)	81.8 (54/66)	

Table 2

Distribution of genotypes overall and stratified by depression status

	All (<i>n</i> = 170) (%)	Depressed (<i>n</i> = 104) (%)	Not depressed (<i>n</i> = 64) (%)	<i>P</i> value*
Genotype (among Caucasians)				0.0106
AA	29.4 (50)	21.2 (22)	42.4 (28)	
TA	45.3 (77)	51.9 (54)	34.8 (23)	
TT	25.3 (43)	26.9 (28)	22.7 (15)	
At least one "T" allele, % (<i>n</i>)	70.6 (120/170)	78.8 (82/104)	57.6 (38/66)	0.0030

P values are from comparisons of depressed versus not depressed. *P* values are from Chi-square tests unless noted otherwise in the table