BIOMARCADORES DE ESTRÉS E INFLAMACIÓN EN LA PSICOSIS TEMPRANA

Alexander Reinaldo Stojanovic Pérez

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TESIS DOCTORAL

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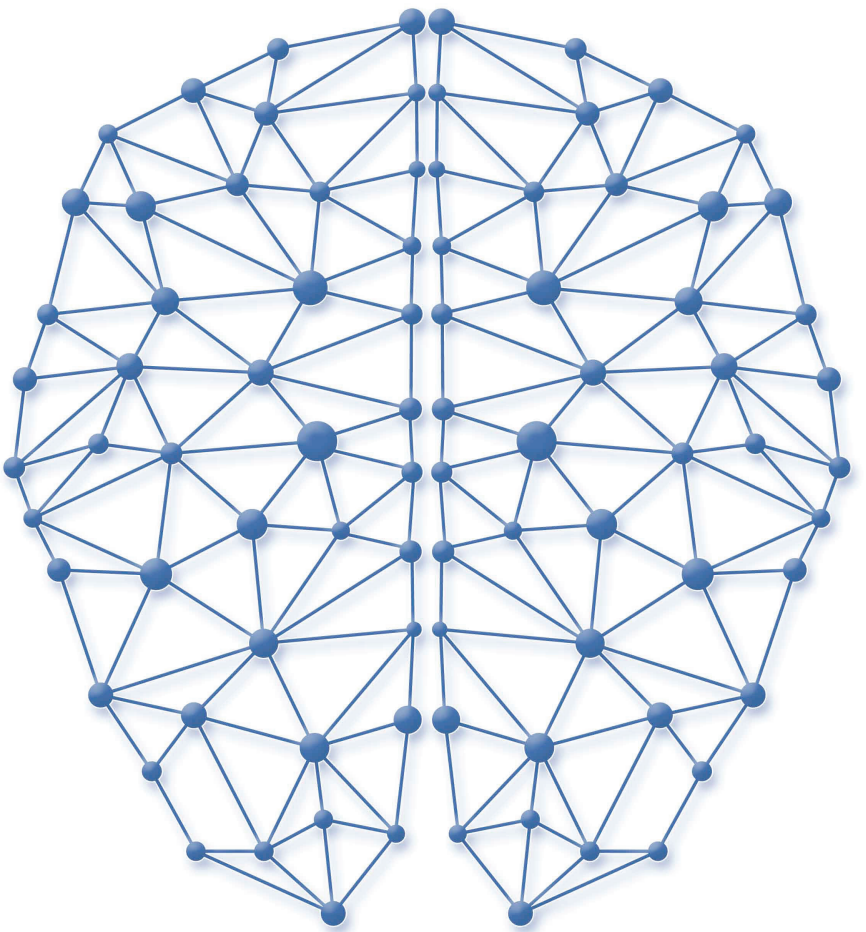

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Dirigida por la Dra. Lourdes Martorell Bonet y el Dr. Javier Labad Arias

Departament de Medicina i Cirurgia

UNIVERSITAT ROVIRA i VIRGILI

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CERTIFICAMOS que este trabajo titulado "Biomarcadores de estrés e inflamación en la psicosis temprana", que presenta Alexander Reinaldo Stojanović Pérez, ha sido realizado bajo nuestra dirección en el Departamento de Medicina y Cirugía de esta universidad y cumple con los requerimientos necesarios para la obtención del título de Doctor.

En Reus, a 26 de junio de 2017

Los directores de la tesis doctoral,

Dra. Lourdes Martorell Bonet

Dr. Javier Labad Arias

1991-2016

A mis ***padres***,
por enseñarme el valor
del esfuerzo y el trabajo.

A los ***amigos,***
que han sido pacientes
en mi afán de escribir
esta tesis doctoral,
tarea que parecía
titánica e interminable.

A ***Cataluña y su gente,***
quienes me recibieron
y me acompañaron
en el camino de enriquecer
mi vida y perfeccionar
mi formación académica.

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- ¿Y el esqueleto?,
- ¿Ya hiciste el esqueleto?, y
- ¡Mira! ¡¿Para cuándo tienes el esqueleto?!
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BIOMARCADORES DE ESTRÉS E INFLAMACIÓN EN LA PSICOSIS TEMPRANA
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ABREVIATURAS

APS	*Attenuated Psychotic Symptoms*; Síntomas psicóticos atenuados
BLIPS	*Brief Limited Intermittent Psychotic Symptoms*; Síntomas psicóticos limitados breves
CAR	*Cortisol Awaking Response*; Respuesta del cortisol al despertar
CAARMS	*Comprehensive Assessment of At-Risk Mental States*; Entrevista para la evaluación general de los estados mentales de alto riesgo
CHR	*Clinical high-risk (CHR) for psychosis*; **Riesgo clínico elevado** de psicosis
CIE-10	Décima edición de la Clasificación Internacional de las Enfermedades
CNVs	*Copy Number Variants*; Variaciones en el número de copias
CRP	C-Reactive Protein; Proteína C reactiva
DSM-5	Manual Diagnóstico y Estadístico de los Trastornos Mentales, quinta edición
DUP	*Duration of Untreated Psychosis*; Duración de la psicosis no tratada
EMAR	**Estado mental de alto riesgo** de psicosis; *At-risk mental state (ARMS) for psychosis*
EMAR-NP	EMAR que no desarrolla un trastorno psicótico
EMAR-P	EMAR que desarrolla un trastorno psicótico
GRD	*Genetic Risk and Deterioration Syndrome*; Síndrome de deterioro y riesgo genético
GWAS	*Genome Wide Association Study*; Estudio de asociación de todo el genoma

HHS	Eje hipotálamo-hipófisis-suprarrenal
hs-CRP	*High-sensitivity C-Reactive Protein*; Proteína C reactiva ultrasensible
IL-1	Interleucina 1 beta
IL6	Gen de la IL-6
IL-6	Interleucina 6
IL-6R	*IL-6 Receptor*; Receptor de la IL-6
ISRS	Inhibidores selectivos de la recaptación de serotonina
LCR	Líquido cefalorraquídeo
OMIM	*Online Mendelian Inheritance in Man*; Herencia Mendeliana en el Hombre en línea
PANSS	*Positive and Negative Syndrome Scale*; Escala de Síntomas Positivos y Negativos
PGC	*Psychiatric Genetics Consortium*; Consorcio de Genética Psiquiátrica
SNC	Sistema nervioso central
SNP	*Single Nucleotide Polymorphism*; Polimorfismo de un solo nucleótido
TDAH	Trastorno por déficit de atención/hiperactividad
TPI	Trastorno psicótico incipiente
TSST	*Trier Social Stress Test*; Prueba de Estrés Social de Tréveris (en alemán, *Trier*)
UHR	*Ultra-high-risk (UHR) for psychosis*; **Riesgo ultra elevado** de psicosis

JUSTIFICACIÓN

La esquizofrenia es un trastorno mental grave, de consecuencias devastadoras, que afecta cómo una persona piensa, siente y actúa. Tiene un gran impacto en la salud de la población, afectando entre 7 a 8 personas por cada 1.000. Más alarmante es el hecho de que en España, los años de vida potencialmente perdidos por muerte prematura o discapacidad atribuible, la sitúan en el primer lugar junto con otras enfermedades neurológicas. En la esquizofrenia se debe intervenir cuanto antes, ya que el tiempo de psicosis que transcurra sin tratar, conduce a la persona hacia una evolución poco satisfactoria. Para cuando un joven reciba tratamiento por un trastorno psicótico incipiente, el daño neurológico y psicosocial ya habrá ocurrido, afectando dominios fundamentales para su desarrollo como persona, que le asegurarán un futuro con peores logros educativos, mayor desempleo y una menor autonomía e independencia.

No se conoce con exactitud cómo se origina la esquizofrenia, pero diversas variantes del genoma, al igual que los factores ambientales, el estrés y la inflamación, juegan un papel relevante. La evidencia acumulada demuestra también que en estos pacientes se encuentran niveles aumentados de marcadores inflamatorios (interleucina 6 [IL-6], proteína C reactiva [CRP] y fibrinógeno) y de prolactina (no asociado al tratamiento antipsicótico), además de un deterioro en la regulación del eje hipotálamo-hipófisis-suprarrenal (HHS).

El diagnóstico de sujetos con alto riesgo de psicosis es eminentemente clínico, siendo perentoria la identificación de posibles biomarcadores que contribuyan a aumentar el valor predictivo de los criterios de riesgo ultra elevado (UHR). Este trabajo de tesis doctoral se centra en el estudio de dichos biomarcadores, integrando el trabajo experimental al estudio de sujetos con estado mental de alto riesgo (EMAR) de psicosis y pacientes con un trastorno psicótico incipiente (TPI) que asisten a un centro de intervención precoz, por lo que nos planteamos como supuesto fundamental, que el estrés ambiental y los biomarcadores relacionados con el estrés (cortisol y prolactina) y la inflamación (IL-6, CRP, fibrinógeno y albúmina), se asocian con el riesgo de desarrollar un TPI en las etapas iniciales de la psicosis.

INTRODUCCIÓN

1.1. Esquizofrenia y fases iniciales de la psicosis

La esquizofrenia (SCHIZOPHRENIA; SCZD [OMIM: #181500], Johns Hopkins University, 2017) es un síndrome multidimensional complejo caracterizado por síntomas positivos, síntomas negativos, síntomas afectivos y alteraciones cognitivas (Stahl, 2008; van Os et al., 2010). Es un trastorno frecuente con una incidencia anual estimada de 15 hombres y 10 mujeres por cada 100.000 habitantes, una prevalencia a lo largo de la vida de 4,0 por cada 1.000 y un riesgo de morbilidad a lo largo de la vida cercano al 0,7% (McGrath et al., 2008; Owen et al., 2016).

Los síntomas positivos son los síntomas típicos de la enfermedad, aquellos que se agregan a la conducta y que por lo general no se observan en personas sanas e incluyen: las alucinaciones, las ideas delirantes, los trastornos formales del pensamiento y la conducta bizarra o desorganizada. A veces son graves mientras que en ocasiones apenas se manifiestan y su presencia dependerá si el paciente está siendo medicado o no. Los síntomas negativos o deficitarios, aquellos que reflejan un empobrecimiento de la conducta normal, están asociados con la interrupción de las emociones y del funcionamiento psicomotor, son más difíciles de reconocer y pueden confundirse con la depresión u otros trastornos neurológicos. Entre ellos se encuentran: la reducción y pobreza del contenido del habla o alogia, la afectividad aplanada, la falta de satisfacción en la vida diaria o anhedonia y la dificultad para iniciar y mantener actividades. Por último, los síntomas cognitivos pueden ser muy heterogéneos, sutiles para algunas personas y graves para otras, y generalmente se detectan cuando se realizan pruebas neurocognitivas específicas. Son característicos de la esquizofrenia los déficits en el funcionamiento ejecutivo, la falta de concentración, de atención y las dificultades en la memoria operativa, conocida también como memoria de trabajo. Las alteraciones a nivel cognitivo se relacionan con un peor desempeño laboral y social (Andreasen and Olsen, 1982; The National Institute of Mental Health, 2016).

Ante la ausencia de pruebas específicas, la evaluación clínica se realiza mediante la entrevista psiquiátrica y la exploración psicopatológica, con dos objetivos claros: realizar un diagnóstico y desarrollar una alianza terapéutica (Thibaut, 2009). Con el fin de identificar los síntomas de la enfermedad, el psiquiatra se sirve de los criterios

operativos y el sistema multiaxial de alguna de las clasificaciones nosológicas más conocidas: la quinta edición del Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM-5) (American Psychiatric Association, 2013) o la décima edición de la Clasificación Internacional de las Enfermedades (CIE-10), siendo la primera de las dos la más comúnmente empleada (Owen et al., 2016).

La esquizofrenia suele iniciarse entre el final de la segunda y principios de la tercera década de la vida, siendo su aparición más precoz en el sexo masculino (Riecher-Rössler, 2017). El inicio puede ser agudo o insidioso, con una larga fase de síntomas atenuados (periodo prodrómico) que anteceden a la aparición del primer episodio psicótico (Fusar-Poli et al., 2013).

En la historia natural de la esquizofrenia pueden establecerse dos grandes periodos: a) la fase de psicosis incipiente, y b) la enfermedad propiamente dicha, en la que se alternan periodos recurrentes de descompensación en los que predomina la sintomatología positiva (fase aguda), con periodos de remisión total o parcial de síntomas en los cuales prevalece la sintomatología negativa (fase estable) (Galletly et al., 2016). La remisión completa no es frecuente y de entre los que permanecen sintomáticos, algunos presentan un curso estable y otros un deterioro progresivo (Owen et al., 2016).

A pesar de los esfuerzos destinados a identificar los factores de riesgo biológico, psicológico y ambiental asociados con la esquizofrenia, las causas precisas de la enfermedad no son bien conocidas. La investigación epidemiológica ha estimado que la heredabilidad (porcentaje de la variación fenotípica atribuible a la variación genética) de esta enfermedad es del ~80% y que hay un conjunto de factores ambientales que también confieren riesgo para su desarrollo (Sullivan et al., 2003). La investigación genética realizada durante los últimos 8 años por el *Psychiatric Genetics Consortium* (PGC; http://pgc.unc.edu) ha cambiado el panorama de la genética psiquiátrica y de forma muy notable el de la esquizofrenia. En 2014, a partir del análisis de 36.989 pacientes y 113.075 controles mediante un estudio de asociación de todo el genoma (GWAS, *Genome Wide Association Study*) identificaron que un tercio del riesgo genético para la esquizofrenia podía atribuirse a un conjunto de variantes comunes (SNPs, *Single Nucleotide Polymorphisms*) que de forma individual tienen

un efecto muy pequeño (Ripke et al., 2014). A pesar de estos resultados, la mayor parte de los factores de susceptibilidad genéticos para desarrollar la enfermedad continúan siendo desconocidos. Parte de esta susceptibilidad puede encontrarse en las variantes de número de copia (CNVs, *Copy Number Variants*) (Kirov et al., 2014) o incluso en cambios de una única base (Genovese et al., 2016) pero su contribución al riesgo de la esquizofrenia se estima muy pequeña por ser estas variantes muy poco frecuentes, a pesar de que pueden tener un gran impacto para el individuo que sea portador de una de ellas (Corvin and Sullivan, 2016). Este es el marco general de lo que conocemos hasta ahora sobre la genética de la esquizofrenia y la hipótesis más aceptada postula que es un trastorno del neurodesarrollo fruto de la interacción de factores genéticos y ambientales en el que la psicosis es una manifestación tardía, y en un futuro potencialmente prevenible, de la enfermedad (Insel, 2010).

Desde hace más de 20 años y bajo la hipótesis de que el abordaje precoz podría mejorar el curso clínico, ha habido un gran interés en el estudio de las fases iniciales de la psicosis (Fusar-Poli et al., 2013). En dichas fases suelen predominar los síntomas negativos o alteraciones prodrómicas, entre los que destacan: los déficits cognitivos (atención y concentración disminuidas), los trastornos del sueño, la ansiedad, la depresión, el retraimiento social y la suspicacia. El estado de ánimo depresivo es el síntoma más prevalente, siendo indistinguible de los síntomas prodrómicos de la enfermedad hasta que emergen los primeros síntomas psicóticos positivos (Häfner, 2015). Los síntomas positivos por lo general responden favorablemente al tratamiento con fármacos antipsicóticos, mientras que los síntomas negativos y cognitivos persisten a lo largo de la vida, siendo generalmente más resistentes al tratamiento farmacológico (Cornblatt et al., 2007; Fusar-Poli et al., 2013).

El concepto de riesgo clínico elevado (CHR, *Clinical High-Risk*) de psicosis hace referencia a aquellas personas que presentan características o factores de riesgo para desarrollar un trastorno psicótico y la investigación en este ámbito pretende esclarecer los procesos patológicos en el pródromo de la esquizofrenia. Se han desarrollado básicamente dos criterios: el riesgo ultra elevado (UHR, *Ultra-High-Risk*) de psicosis y el de síntomas básicos (Fusar-Poli et al., 2013). El más comúnmente empleado es el de UHR, que incluye a las personas con estado mental de alto riesgo (EMAR) de psicosis. Yung y colaboradores han operacionalizado el grupo UHR con la finalidad de

identificar jóvenes de entre 14 y 35 años que buscan ayuda por problemas de salud mental, en tres síndromes clínicos (Alison R Yung et al., 2003):
a) Síntomas psicóticos atenuados (APS, *Attenuated Psychotic Symptoms*),
b) Síntomas psicóticos limitados breves (BLIPS, *Brief Limited Intermittent Psychotic Symptoms*), y
c) Síndrome de deterioro y riesgo genético (GRD, *Genetic Risk and Deterioration Syndrome*) o síndrome de estado-rasgo.

Para reunir criterios de EMAR, según la versión más reciente de la Entrevista para la evaluación general de los estados mentales de alto riesgo (CAARMS, *Comprehensive Assessment of At-Risk Mental States*), una persona debe haber presentado al menos uno de estos síndromes clínicos, acompañado de un deterioro del funcionamiento psicosocial, durante al menos un mes a lo largo del último año (Nieman and McGorry, 2015; Yung et al., 2005).

Dentro del periodo de UHR debemos considerar el concepto de duración de la psicosis no tratada (DUP, *Duration of Untreated Psychosis*), que corresponde al periodo comprendido entre el inicio de los síntomas (primer episodio psicótico) y la administración del primer tratamiento antipsicótico específico. Existen evidencias de que cuanto mayor sea la DUP, peor será la evolución de la enfermedad, dificultando alcanzar la remisión (Marshall et al., 2005). Todos los programas de prevención y atención precoz de la psicosis centran sus objetivos en reducir substancialmente la duración de la enfermedad no tratada, en reducir la gravedad de los síntomas y en evitar la transición a psicosis en sujetos EMAR, que según un reciente metanálisis se ubica en un 18% a los 6 meses, 22% al año, 29% a los 2 años y 36% a los 3 años de haber iniciado el seguimiento en un programa de intervención precoz (Fusar-Poli et al., 2012).

En cuanto al manejo de los sujetos en el periodo de UHR, las recomendaciones actuales indican que deben ser atendidos por equipos multidisciplinares, enfocados hacia la intervención psicosocial intensiva de tipo psicoeducativa, que incorporen el entrenamiento metacognitivo y en cognición social, además del apoyo psicoterapéutico mediante técnicas comprobadamente eficaces (terapia cognitivo-conductual). Además, deben incorporar, en la medida de lo posible, el abordaje familiar, controlar el

abuso de sustancias comórbido y establecer ambientes especializados y mínimamente generadores de estigma a nivel comunitario. El tratamiento con antipsicóticos debe limitarse únicamente cuando aparezcan síntomas psicóticos francos (Galletly et al., 2016).

Con la aparición del primer episodio psicótico finaliza el periodo premórbido, que en sujetos EMAR se basa en los criterios de Yung y colaboradores, que definen la transición a psicosis como la ocurrencia de al menos un síntoma positivo completo, varias veces por semana, durante más de una semana (A R Yung et al., 2003).

La investigación en este ámbito debe encaminarse a evitar la aparición del primer episodio psicótico y para ello es necesario poder predecir qué factores intervienen en su aparición. Distintos autores proponen que la predicción del riesgo de transición a psicosis puede mejorarse más allá de la evaluación clínica del UHR, siguiendo un modelo de evaluación multinivel o multidominio que incorpore además de los predictores clínicos, la neurocognición, la neuroimagen, la neurofisiología, la genética, la epigenética y el uso de los biomarcadores (Fusar-Poli et al., 2013; Khandaker et al., 2015; Miller and Goldsmith, 2017; Nieman and McGorry, 2015; Pruessner et al., 2017; Riecher-Rössler and Studerus, 2017).

1.2. Biomarcadores de inflamación

En la última década ha habido un gran interés por el estudio del papel potencial de la inflamación en el desarrollo de los trastornos psicóticos, basado en la presencia de anomalías inmunológicas en la esquizofrenia que incluyen la presencia de células activadas de la respuesta inmune innata y adquirida (Smith, 1992) y las consecuentes elevaciones específicas de citoquinas y mediadores inflamatorios tales como la IL-6 y la CRP (Fan et al., 2007; B J Miller et al., 2011; Miller et al., 2014; Potvin et al., 2008). La IL-6 es una citoquina pleiotrópica sintetizada por monocitos activados y linfocitos Th2 (Muller et al., 2000). Induce proteínas de fase aguda y promueve la diferenciación de células B en células plasmáticas productoras de anticuerpos (Kishimoto, 2010). En un reciente metanálisis que exploró la asociación entre las exacerbaciones agudas de la esquizofrenia y la disfunción del sistema inmunológico, se reportó un aumento significativo de la IL-6 en 5 de 6 estudios de pacientes con recaídas agudas y en 4 estudios de pacientes que experimentaron sus primeros episodios psicóticos, en comparación con controles sanos (Brian J Miller et al., 2011).

Estudios previos han sugerido que los niveles de IL-6 pueden estar influenciados por variantes genéticas en el gen de la IL-6 (*IL6*) (Fishman et al., 1998). EL *IL6* se localiza en el brazo corto del cromosoma 7 humano. El polimorfismo funcional rs1800795 del *IL6*, consiste en un cambio de guanina (G) a citosina (C) en la posición –174 de la región promotora del gen. El alelo C se ha asociado con una expresión reducida del *IL6*, en comparación con el alelo G (Fishman et al., 1998). Estudios previos realizados en pacientes con esquizofrenia han mostrado resultados inconsistentes en cuanto a la asociación entre el genotipo y los niveles de la IL-6 (Paul-Samojedny et al., 2013; Zakharyan et al., 2012). En los síndromes o enfermedades en las que la inflamación desempeña un papel fisiopatológico importante (por ejemplo, la resistencia a la insulina, la diabetes mellitus tipo 2 y la artritis crónica juvenil de inicio sistémico), los investigadores han identificado asociaciones entre los niveles séricos de la IL-6 y el SNP rs1800795 (Cardellini et al., 2005; Fishman et al., 1998; Vozarova et al., 2003). Recientemente, también se ha identificado una asociación entre el genotipo del rs1800795 y los síntomas neuropsiquiátricos inducidos por interferón alfa en sujetos con hepatitis C crónica (Udina et al., 2013).

La proteína C reactiva (CRP, C-*Reactive Protein*) y el fibrinógeno son proteínas de fase aguda sintetizadas en el hígado por estimulación directa de la IL-6. Ambas pueden servir como marcadores no específicos de infección e inflamación crónica (Pfafflin and Schleicher, 2009). El fibrinógeno también es un elemento relevante en la cascada de la coagulación (Levy et al., 2012). Se han reportado niveles elevados de CRP sérica y de fibrinógeno plasmático en pacientes con esquizofrenia en comparación con controles sanos (C Garcia-Rizo et al., 2012). Recientemente, un estudio longitudinal que midió la CRP sérica de 6.362 adolescentes entre 15 y 16 años de edad, demostró un aumento de la probabilidad de desarrollar esquizofrenia en la edad adulta, al igual que alguna indicación de su aparición precoz con niveles más elevados de CRP (Metcalf et al., 2017).

Algunos estudios han explorado la relación entre la expresión clínica de la esquizofrenia y los marcadores inflamatorios. Se ha observado que los niveles elevados de la CRP se asocian con síntomas clínicos más severos medidos con las escalas total, negativa y general del PANSS (*Positive and Negative Syndrome Scale*) (Fan et al., 2007) y un peor funcionamiento cognitivo en pacientes con esquizofrenia (Dickerson et al., 2007). Los niveles elevados de IL-6 en suero también se han asociado con una mayor duración de la enfermedad (Ganguli et al., 1994) y un perfil clínico pobre caracterizado por resistencia al tratamiento antipsicótico (Lin et al., 1998). Estas correlaciones podrían indicar una relación entre el proceso inflamatorio y las características clínicas y psicopatológicas de la esquizofrenia.

La mayoría de los estudios que exploran el papel de los marcadores inflamatorios en la psicosis se han llevado a cabo en sujetos con una duración de la enfermedad prolongada, y sólo unos pocos estudios sugieren que las alteraciones en los marcadores inflamatorios están presentes en pacientes con diagnóstico reciente y que aún no han recibido tratamiento con antipsicóticos (Borovcanin et al., 2012; C Garcia-Rizo et al., 2012). Hasta la fecha, ningún estudio había explorado si el aumento de los factores inflamatorios están presentes en pacientes que están en riesgo de psicosis, ni se ha investigado la influencia del genotipo del SNP rs1800795 en los niveles de la IL-6 en pacientes con psicosis temprana.

Finalmente, la albúmina, una proteína circulante abundante en el plasma que puede reducirse en enfermedades físicas graves, podría considerarse otro biomarcador potencial ligado al riesgo de transición a psicosis, ya que tiene propiedades antioxidantes y ejerce una influencia favorable en los procesos de señalización redox que regulan la inflamación (Roche et al., 2008). Diferentes estudios han enfatizado la importancia de la albúmina sérica en los trastornos psiquiátricos. Se han reportado niveles reducidos de albúmina en pacientes con trastorno depresivo mayor (Huang et al., 2005), primeros episodios de esquizofrenia (Pae et al., 2004; Reddy et al., 2003) o esquizofrenia crónica (Huang, 2002; Yao et al., 2000). Los niveles de albúmina sérica se han correlacionado con el procesamiento de la prosodia afectiva en pacientes adultos con trastorno por déficit de atención/hiperactividad (TDAH) (Grabemann et al., 2014). Además, se ha observado una asociación entre niveles bajos de albúmina sérica y psicosis inducida por corticosteroides en pacientes con lupus eritematoso sistémico (Chau and Mok, 2003; López-Medrano et al., 2002).

1.3. Biomarcadores de estrés

Se conoce que las adversidades de la vida y el estrés psicosocial confieren riesgo de morbilidad mental. El estrés es una reacción fisiológica del organismo en la que intervienen distintos procesos neuroendocrinos e inmunológicos que permite afrontar una situación percibida como amenazante. Se cree que el estrés juega un papel relevante en el riesgo de desarrollar un trastorno psicótico, ya que tanto los sujetos con un primer episodio psicótico como aquellos con síntomas prodrómicos de psicosis en comparación con sujetos sanos informan más frecuentemente de eventos de vida estresantes (Beards et al., 2013; Manzanares et al., 2014) y mayor estrés percibido (Pruessner et al., 2011). El modelo neural clásico de estrés-diátesis de la esquizofrenia sugiere que el estrés psicosocial activa el eje hipotalámico-hipófisis-suprarrenal (HHS), induciendo la liberación de cortisol y aumentando la transmisión de dopamina que contribuiría al inicio de la psicosis en individuos vulnerables (Walker and Diforio, 1997).

Esta hipótesis teórica ha sido demostrada recientemente en un estudio de tomografía por emisión de positrones que informa acerca de la liberación de dopamina inducida por estrés en la psicosis (Mizrahi et al., 2012). Los estudios realizados en sujetos con primeros episodios de psicosis también informan una hiperactivación del eje HHS y una respuesta atenuada al estrés en esta fase del trastorno psicótico (Borges et al., 2013). Estudios recientes han explorado igualmente anomalías del eje HHS en sujetos EMAR: el cortisol salival ha sido asociado con una peor tolerancia al estrés (Corcoran et al., 2012) y un riesgo de transición a psicosis (Walker et al., 2013). También se ha reportado una respuesta del cortisol al despertar (CAR) atenuada en sujetos EMAR, cuando se les compara con sujetos sanos (Day et al., 2014) y en las poblaciones de alto riesgo genético, como los hermanos de pacientes con trastorno psicótico no afectivo, los eventos estresantes se asocian con experiencias psicóticas y niveles de cortisol aumentados (Collip et al., 2011).

Sin embargo, aunque la activación del eje HHS es una de las principales respuestas biológicas al estrés, también otros biomarcadores relacionados con el estrés pueden desempeñar un papel. En este sentido, se ha demostrado el aumento de la prolactina

en respuesta al estrés psicosocial en sujetos sanos sometidos a un estrés agudo mediante el TSST (*Trier Social Stress Test*) (Lennartsson & Jonsdottir, 2011), al igual que también se han observado niveles elevados de esta hormona hasta en el 39% de los pacientes con un primer episodio psicótico no tratado (Aston et al., 2010; Clemente Garcia-Rizo et al., 2012; Riecher-Rössler et al., 2013) y en sujetos EMAR (Aston et al., 2010). Estos hallazgos son de interés porque una proporción sustancial de individuos con trastornos psicóticos en etapas tempranas presentan hiperprolactinemia que no es secundaria al bloqueo de receptores D2 por los antipsicóticos. Algunos autores han sugerido que a medida que la prolactina aumenta puede a su vez aumentar la liberación de dopamina a través de un mecanismo de retroalimentación, lo que podría contribuir a explicar cómo el estrés puede desencadenar un brote psicótico (Riecher-Rössler et al., 2013). Sin embargo, no existen estudios prospectivos que exploren si el aumento de la prolactina en sujetos con EMAR puede contribuir al riesgo de desarrollar un trastorno psicótico.

1.4. Antidepresivos y marcadores inflamatorios

Recientemente, se ha propuesto que los antidepresivos pueden poseer propiedades antiinflamatorias a nivel del sistema nervioso central y periférico (Daniele et al., 2015) y que los inhibidores selectivos de la recaptación de serotonina (ISRS) disminuyen los niveles periféricos de mediadores proinflamatorios IL-1β, CRP y posiblemente IL-6 en pacientes con depresión mayor (Hannestad et al., 2011; Hiles et al., 2012). La IL-6 induce la síntesis de proteínas de fase aguda tales como la CRP y el fibrinógeno, y niveles elevados de CRP sérica y de fibrinógeno plasmático han sido descritos tanto en pacientes con esquizofrenia (Wium-Andersen et al., 2013) como en pacientes con trastorno depresivo mayor.

Aunque los síntomas depresivos son frecuentes entre los pacientes con primeros episodios de psicosis (Sönmez et al., 2014), sólo un estudio ha explorado el uso de antidepresivos adyuvantes en pacientes con esquizofrenia en periodo prodrómico, reportando una mejoría en el cumplimiento del tratamiento, una disminución de la sintomatología psicótica positiva, y ninguna transición a psicosis en los pacientes tratados con antidepresivos en comparación con una tasa de transición del 45% en el grupo no tratado con antidepresivos (Cornblatt et al., 2007). Por lo tanto, los antidepresivos pueden ser una estrategia de tratamiento óptima en etapas prodrómicas, reduciendo la vulnerabilidad a la enfermedad a través de la reducción de los estados desencadenantes (por ejemplo, estrés, ansiedad y depresión) a través del mecanismo fisiopatológico de la inflamación.

HIPÓTESIS Y OBJETIVOS

2.1. Hipótesis general

El estrés ambiental y los biomarcadores relacionados con el estrés (cortisol y prolactina) y la inflamación (IL-6, CRP, fibrinógeno y albúmina) se asocian con el riesgo de desarrollar un trastorno psicótico en las etapas iniciales de la psicosis.

2.2. Hipótesis operativas

INFLAMACIÓN

1. Los sujetos EMAR y los pacientes con un TPI mostrarán un aumento de los biomarcadores inflamatorios (IL-6, CRP, fibrinógeno y albúmina) en comparación con controles sanos.

2. Los biomarcadores de inflamación se asociarán con la expresión fenotípica de la enfermedad, es decir, a mayor concentración de marcadores de inflamación mayor gravedad de los síntomas positivos y negativos.

3. La variante genética rs1800795 del *IL6* es un factor de riesgo para desarrollar síntomas psicóticos y se relacionará con un aumento de los niveles séricos de la IL-6 en las primeras etapas de la esquizofrenia.

4. El tratamiento con fármacos antidepresivos se asociará con una reducción en los niveles de marcadores inflamatorios (IL-6, CRP y fibrinógeno) en pacientes con un TPI.

5. Los niveles de marcadores inflamatorios (IL-6, CRP, fibrinógeno y albúmina) serán distintos entre sujetos EMAR que posteriormente desarrollen un trastorno psicótico (EMAR-P) y los que no (EMAR-NP).

ESTRÉS

6. Los sujetos EMAR, en comparación a controles sanos, han experimentado un mayor número de acontecimientos vitales estresantes y, en consecuencia, presentarán mayores niveles de estrés.

PROLACTINA

7. Los sujetos EMAR-P, en comparación a los EMAR-NP y a los controles sanos, mostrarán niveles más elevados de prolactina.

CORTISOL

8. Los sujetos EMAR-P, en comparación a los EMAR-NP y a los controles sanos, mostrarán alteraciones en la respuesta del cortisol al despertar (CAR, *Cortisol Awaking Response*).

2.3. Objetivos

1. Comparar los niveles de moléculas relacionadas con la inflamación periférica (IL-6, CRP y fibrinógeno) entre sujetos EMAR, pacientes con un TPI y sujetos control.

2. Conocer la relación existente entre los marcadores de inflamación periférica y las características sintomatológicas de los sujetos EMAR y los pacientes con un TPI.

3. Comparar las frecuencias genotípicas de la variante rs1800795 del gen de la IL-6 entre sujetos EMAR, pacientes con un TPI y sujetos control.

4. Explorar la posible asociación entre el tratamiento antipsicótico y los marcadores de inflamación periférica.

5. Explorar si los niveles de moléculas relacionadas con la inflamación periférica son distintas entre los sujetos EMAR-P y EMAR-NP.

6. Comparar el número de acontecimientos vitales y el estrés psicológico percibido entre sujetos EMAR y sujetos control.

7. Conocer la relación existente entre el estrés psicológico, los biomarcadores de estrés (cortisol y prolactina) e inflamación (CRP, fibrinógeno y albúmina) y el desarrollo de un TPI.

8. Explorar si el tratamiento antidepresivo está relacionado con los niveles de marcadores de inflamación periférica (IL-6, CRP y fibrinógeno).

RESULTADOS

3.1. Publicación 1 - Artículo Original

Increased serum interleukin-6 levels in early stages of psychosis: associations with at-risk mental states and the severity of psychotic symptoms.

Stojanovic A, Martorell L, Montalvo I, Ortega L, Monseny R, Vilella E, Labad J.

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Antecedentes

La inflamación es la forma de manifestarse de muchas enfermedades y puede estar implicada en el origen de la psicosis. La mayoría de estudios que exploran el papel de los marcadores inflamatorios en la psicosis se han llevado a cabo en sujetos con una larga evolución de la enfermedad.

Se conoce que un 30% de los sujetos EMAR desarrollan un TPI al cabo de un año. Por consiguiente, es prioritario el diagnóstico eficaz más allá del obtenido explorando las características clínicas, mediante la identificación de biomarcadores predictivos que permitan identificar personas con riesgo e implementar posibles estrategias de prevención.

Aportes

Los sujetos EMAR mostraron niveles séricos de IL-6 significativamente más elevados comparados con controles sanos (0,6 pg/mL y 0,3 pg/mL, respectivamente, p=0,003).

Los pacientes con un TPI también mostraron niveles séricos deIL-6 significativamente más elevados, comparados con los controles (0,6 pg/mL y 0,3 pg/mL, respectivamente, p=0,024).

Se identificó una asociación entre los niveles séricos de IL-6 con la sintomatología psicótica positiva y negativa en sujetos EMAR y TPI, no atribuible a variables de confusión.
La variante rs1800795 del IL6 no modula los niveles séricos de IL-6 en sangre periférica.

Aspectos a destacar

Los sujetos EMAR que desarrollaron un TPI, mostraron unos valores medios de IL-6 superiores, pero no significativos, comparados con aquellos que no hicieron la transición. Este resultado sugiere que la IL-6 sérica podría utilizarse como biomarcador en esta etapa de la enfermedad.

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Increased serum interleukin-6 levels in early stages of psychosis: Associations with at-risk mental states and the severity of psychotic symptoms

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KEYWORDS
Inflammation;
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At-risk mental state (ARMS);
rs1800795

Summary Schizophrenia patients experience activated inflammatory responses, but little is known about the presence of such inflammatory processes at or prior to disease onset. We measured interleukin-6 (IL-6) and C-reactive protein (CRP) serum levels and plasma fibrinogen in 17 at-risk mental state (ARMS) subjects, 77 patients with psychotic disorder (PD) and 25 healthy control subjects (HC). ARMS subjects were followed-up, and transition to psychosis was registered. IL6 rs1800795 SNP was genotyped, as IL-6 levels may be influenced by this genetic variant. We did not observe significant differences in the IL6 rs1800795 SNP genotype frequencies between the groups. ARMS subjects exhibited significantly higher IL-6 levels than did controls ($p = 0.019$). In subjects not taking cannabis, we found that patients diagnosed with ARMS or PD exhibited increased IL-6 levels when compared with HC ($p = 0.004$). In both ARMS and PD subjects, IL-6 levels were positively associated with negative symptoms. However, with respect to positive psychotic symptoms, a different relationship was observed in the ARMS and PD groups (positive relationship in ARMS; negative relationship in PD). These findings could not be attributed to confounding variables, including gender, body mass index (BMI), tobacco consumption or the rs1800795 genotype. Six of 17 ARMS subjects (35%) exhibited a transition to psychosis during the follow-up period of 26 months. ARMS subjects who developed psychosis exhibited increased median IL-6 levels compared with those who did not transition (0.61 vs. 0.35 pg/mL). However, this difference was not statistically significant, which could be explained by a lack of statistical power due to the small sample size. Our results suggest that IL-6 may be a biomarker for early psychotic symptoms; however, further studies in larger samples are needed to confirm this result.

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1. Introduction

Schizophrenia is a complex multidimensional syndrome characterized by positive symptoms (e.g., delusions, hallucinations), negative symptoms (e.g., motivational impairment), affective dysregulation (e.g., depression, mania or anxiety) and cognitive alterations (van Os et al., 2010). Despite past research efforts that have attempted to identify psychological, biological and environmental risk factors, the precise causes of schizophrenia are not well-known. Inflammation may play a role in the pathogenesis of psychoses, based on the presence of immunological anomalies in schizophrenia that include activated innate and acquired immune response cells (Smith, 1992), and in the consequent elevations of specific cytokines and inflammatory mediators such as IL-6 and CRP (Fan et al., 2007; Potvin et al., 2008; Miller et al., 2011, 2013).

IL-6 is a pleiotropic cytokine synthesized by activated monocytes and Th2 lymphocytes (Muller et al., 2000). It induces acute-phase proteins and promotes differentiation of B cells into antibody-producing plasmatic cells (Kishimoto, 2010). In a recent meta-analysis that explored the association between acute exacerbations of schizophrenia and immune system dysfunction, IL-6 was significantly increased in 5 of 6 studies of acutely relapsed inpatients and in 4 of 4 studies of patients experiencing their first psychotic episodes compared with healthy controls (Miller et al., 2011).

Previous studies have suggested that IL-6 levels may be influenced by genetic variants in the human IL-6 gene (IL6) (Fishman et al., 1998). IL6 is located on the short arm of chromosome 7. The functional IL6 single nucleotide polymorphism (SNP) rs1800795 consists of a G to C change at position −174 in the promoter region. Allele C has been associated with a reduced expression of IL6, in comparison with allele G (Fishman et al., 1998). Previous studies conducted with Polish and Armenian schizophrenia patients have shown inconsistent results in terms of allele frequencies, genotype frequencies and associations between genotype and IL-6 levels (Zakharyan et al., 2012; Paul-Samojedny et al., 2013). In syndromes or diseases in which inflammation plays an important pathophysiological role (e.g., insulin resistance, type-2 diabetes mellitus, and systemic-onset juvenile chronic arthritis), researchers have identified associations between IL-6 serum levels and the IL6 promoter SNP rs1800795 (Cardellini et al., 2005; Fishman et al., 1998; Vozarova et al., 2003). Recently, an association has also been identified between the rs1800795 genotype and interferon alpha-induced neuropsychiatric symptoms in subjects with chronic hepatitis C (Udina et al., 2013).

CRP and fibrinogen are acute-phase proteins synthesized in the liver by direct stimulation of IL-6. Both can serve as non-specific markers of infection and chronic inflammation (Pfafflin and Schleicher, 2009). Fibrinogen also is an important element in the coagulation cascade (Levy et al., 2012). Elevated serum CRP and plasma fibrinogen levels have been reported in schizophrenia patients when compared with healthy controls (Maes et al., 1997; Garcia-Rizo et al., 2012).

A few studies have explored the relationship between the clinical expression of schizophrenia and inflammatory markers. Elevated CRP levels have been found to be associated with more severe clinical symptoms measured by the total, negative and general scales of the PANSS (Fan et al., 2007) and lower cognitive functioning in patients with schizophrenia (Dickerson et al., 2007). Higher serum IL-6 levels have been associated with a longer duration of the illness (Ganguli et al., 1994) and a poor clinical profile characterized by resistance to antipsychotic pharmacotherapy (Lin et al., 1998). The above-mentioned correlations could possibly indicate a relationship between a marked inflammatory process and more severe psychopathology in a subgroup of patients with schizophrenia.

Most studies exploring the role of inflammatory markers in psychosis have been conducted on subjects with long durations of illness, and only a few studies suggest that inflammatory abnormalities are present in newly diagnosed antipsychotic-naïve patients (Borovcanin et al., 2012; Garcia-Rizo et al., 2012). To date, no studies have explored whether increased inflammatory factors are present in patients who are at risk of psychosis, nor have any investigated the influence of the IL6 rs1800795 SNP genotype on IL-6 levels in early-psychosis patients. The ARMS is a clinical construct that attempts to identify individuals with prodromal symptoms of psychosis. Thirty percent of ARMS subjects will develop psychosis at one year after diagnosis (Fusar-Poli et al., 2013). Although ARMS individuals often receive early intervention services, the clinical utility of the diagnosis has been a controversial issue. Interestingly, an attenuated psychosis syndrome has recently been included in Section III of the DSM-V, along with conditions that require further study.

Thus, we hypothesized that ARMS subjects and individuals with a psychotic disorder at early stages of illness would show increased inflammatory markers when compared to healthy controls (HC). Additionally, we hypothesized that inflammation would be associated with the phenotypical expression of the illness (i.e., the severity of positive and negative symptoms).

Finally, as previous association studies of rs1800795 and schizophrenia have produced inconclusive results, we aimed to conduct a case-control association study with a group of early psychosis patients. Furthermore, considering the known influence of rs1800795 SNP on IL6 expression, we hypothesized that rs1800795 could be a risk factor for early psychotic symptoms and could potentially predict the elevations in IL-6 serum levels in the early stages of schizophrenia.

2. Methods

2.1. Participants

We selected 94 male and female patients (18—35 years of age) attending our Early Psychosis Program (HUIPM, Reus, Spain) and 25 healthy individuals. Patients were classified into 2 groups: 17 ARMS subjects with prodromal psychotic symptoms and 77 patients with psychotic disorder (PD) whose durations of illness were less than 5 years. The DSM-IV diagnoses for PD were as follows: schizophreniform disorder (n = 19), schizophrenia (n = 12), schizoaffective disorder (n = 10), and psychotic disorder not otherwise specified (n = 36). Patients diagnosed with substance-induced psychosis, neurological disorders or mental retardation were excluded. The group of healthy control subjects (HC, n = 25) was screened to rule out past or current histories of psychiatric disorders. Recruitment of HC included

Table 1 Demographic data and clinical variables by diagnostic group.

	Healthy controls (HC) $n = 25$	At-risk mental states (ARMS) $n = 17$	Psychotic disorders (PD) $n = 77$	*P* value
Age (years)	27.3 (4.2)	21.4 (2.4)	24.3 (4.8)	<0.001[a,b,c]
Female gender, *n* (%)	13 (52.0)	5 (29.4)	29 (37.7)	0.291
BMI (kg/m^2)	21.6 (2.5)	22.1 (3.2)	24.4 (4.5)	0.004[b]
Inflammatory markers				
IL-6 (pg/mL)	0.3 (1.3)	0.6 (2.1)	0.6 (2.4)	0.019[a]
CRP (mg/L)	0.5 (6.3)	0.5 (4.6)	1.1 (22.9)	0.031
Fibrinogen (mg/L)	257.2 (47.3)	253.0 (55.0)	261.0 (67.2)	0.881
Psychopathology				
PANSS positive score		10.5 (3.6)	11.5 (6.2)	0.615
PANSS negative score		12.5 (6.0)	15.0 (7.6)	0.293
PANSS general score		30.6 (8.0)	29.3 (9.6)	0.372
Psychotic disorder diagnosis				
Schizophreniform disorder			19 (24.7)	
Schizophrenia			12 (15.6)	
Schizoaffective disorder			10 (13.0)	
Psychotic disorder not otherwise specified			36 (46.7)	
Antipsychotic treatment				
Type of antipsychotic drug				
None, *n* (%)	25 (100.0)	9 (52.9)	7 (9.2)	<0.001
Risperidone or paliperidone in monotherapy[d]	0 (0)	3 (17.6)	27 (35.5)	
Olanzapine or quetiapine in monotherapy[e]	0 (0)	1 (5.9)	11 (14.3)	
Aripiprazole in monotherapy	0 (0)	2 (11.8)	8 (10.5)	
Polytherapy	0 (0)	2 (11.8)	24 (31.6)	
Antipsychotic dose (CPZ equivalents in mg/day)	0 (0)	114.9 (163.5)	354.6 (350)	<0.001[a,b,c]
Duration of antipsychotic treatment (months)	0 (0)	7.8 (14.5)	14.5 (15.3)	0.104
Antidepressant treatment	0 (0)	7 (41.2)	12 (15.6)	0.002
Mood stabilizers treatment	0 (0)	2 (11.8)	6 (7.8)	0.268
Substance use				
Smoking, *n* (%)	6 (24.0)	7 (41.2)	53 (68.8)	<0.001
Tobacco consumption (cigarettes/day)	1.2 (3.2)	4.7 (6.9)	10.3 (10.2)	<0.001[b]
Daily alcohol intake, *n* (%)	1 (4.0)	0 (0)	13 (16.9)	0.059
Daily alcohol intake (standard units/day)	0.08 (0.4)	0 (0)	0.8 (2.3)	0.149
Daily cannabis use, *n* (%)	0 (0)	2 (11.8)	20 (26.0)	0.011
Cannabis consumption (joints/day)	0 (0)	0.9 (3.6)	1.7 (4.4)	<0.001[b]

Abbreviations: HC, healthy controls; ARMS, at-risk mental states; PD, psychotic disorders; BMI, body mass index; IL-6, interleukin-6; CRP, C-reactive protein; PANSS, Positive and Negative Syndrome Scale; CPZ, chlorpromazine.
All variables are presented in mean (SD), or *n* (%).
[a] Significant ANOVA post hoc analyses (comparison between groups) with Bonferroni correction: HC vs. ARMS.
[b] Significant ANOVA post hoc analyses (comparison between groups) with Bonferroni correction: HC vs. PD.
[c] Significant ANOVA post hoc analyses (comparison between groups) with Bonferroni correction: ARMS vs. PD.
[d] Of all 30 subjects taking risperidone or paliperidone in monotherapy, 24 received risperidone (3 ARMS, 21 PD) and 6 PD received paliperidone.
[e] Of all 12 subjects taking olanzapine or quetiapine in monotherapy, 11 were taking olanzapina (1 ARMS, 10 PD) and one PD received quetiapine.

patients' friends, non-genetic relatives and university students. The demographic and clinical data summaries pertaining to patients and healthy controls are presented in Table 1.

An additional, population-based sample consisting of 610 Caucasians (290 males and 320 females) without histories of psychiatric disorders, and scoring less than 7 on the 28-item Spanish adaptation of the Goldberg General Health Questionnaire (GHQ-28), was used to compare allele and genotype frequencies of the rs1800795 SNP with the PD patient group (Lobo et al., 1986). The population-based sample was randomly selected from electoral rolls in three municipalities of a geographic region matching that of the patients and has been studied in several genetic studies (Roig et al., 2007; Martorell et al., 2008; Vilella et al., 2008; Soria et al., 2010; Saus et al., 2010). Details regarding the recruitment of this population-based sample are described elsewhere (Aranda et al., 2007).

Approval was obtained from the local ethics committee, and all participants provided written informed consent after having received a full explanation of the study.

2.2. Assessments

The group of healthy control subjects (HC, $n = 25$) was screened to rule out past or current histories of psychiatric disorders by direct interviewing by an experienced psychiatrist as well as scores of less than 7 on the GHQ-28.

All patients were assessed with the Spanish adaptation of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Vazquez-Barquero et al., 1994). The SCAN was administered by a trained psychiatrist in the assessment of this instrument. The following sections were administered: 1, 3—10, 13—20, and 22—24. OPCRIT 4 for Windows was used to generate DSM-IV diagnoses for psychotic disorders (viz., schizophreniform disorder, schizophrenia, schizoaffective disorder and psychotic disorder not otherwise specified). ARMS subjects were also assessed with the Comprehensive Assessment of At-Risk Mental States to ensure that subjects met criteria for any of the three high-risk groups defined by At Risk Mental State criteria (Yung et al., 2005).

The Spanish adaptation of the Positive and Negative Syndrome Scale (PANSS) was used to assess the severity of positive (PANSS-P) and negative (PANSS-N) psychotic symptoms (Peralta and Cuesta, 1994).

Socio-demographic variables, substance use, and antipsychotic treatments were assessed using a semi-structured interview that was administered by a clinician. This interview is an ad-hoc instrument designed by our research team that is regularly used in our Early Psychosis Program. Each antipsychotic dose was transformed into chlorpromazine equivalents expressed in mg/day (Gardner et al., 2010). We also registered the type of antipsychotic drug received by all participants. In our sample, all subjects were treated with atypical antipsychotics (risperidone, paliperidone, olanzapine, quetiapine, or aripiprazole).

As ARMS subjects usually attend at our Early Psychosis Program for at least 5 years with frequent visits (every 2—4 weeks), we have included follow-up data related to psychosis transition. The transition to psychosis was defined as the occurrence of at least 1 fully positive psychotic symptom several times a week for more than 1 week (Yung et al., 2003; Fusar-Poli et al., 2013).

2.3. IL-6, CRP and fibrinogen measurements

A fasting morning (8—10 AM) blood sample was obtained by antecubital needle venipuncture. Morning blood collection was chosen because in clinical practice, patients are regularly monitored at this time of the day for metabolic parameters, including glucose and lipid profiles. High-sensitivity CRP (hs-CRP) levels were quantified by immunoturbidimetry using the A. Menarini Diagnostics Full Range CRP assay (Menarini Diagnósticos, S.A., Badalona, Barcelona, Spain) and fibrinogen using the Clauss method with the Gernon Hemofibrin L Kit (RAL Técnica para el Laboratorio, S.A., Sant Joan Despí, Barcelona, Spain) on the day of the blood sampling. IL-6 levels were measured after storing and freezing aliquots of serum at −80 °C in the Reus Biobank for less than 1 year. The determination of IL-6 was performed using a standard high-sensitivity enzyme-linked immunosorbent assay (ELISA) (IBL International GmbH, Hamburg, Germany) according to the methodology recommended by the manufacturer. The sensitivity of the assay was 0.03 pg/mL, and the calculated overall intra- and interassay coefficients of variation were 4.9% and 6.0%, respectively.

2.4. DNA extraction and IL6 genotyping

Genomic DNA was extracted from peripheral blood mononuclear cells ($n = 610$ HC; $n = 77$ PD patients) using the Puregene Blood Kit (QIAGEN Iberia S.L., L'Hospitalet de Llobregat, Barcelona, Spain) according to the manufacturer's instructions. DNA was genotyped using a custom TaqMan SNP genotyping assay for the rs1800795 SNP (assay ID AH207QX; Life Technologies, Madrid, Spain). Each 5 μL PCR reaction contained 40 ng of DNA, 2.5 μL of TaqMan Universal PCR Master Mix, 0.25 μL of 20X TaqMan SNP Genotyping Assay and 2.25 μL of DNase-free water. PCR conditions were 10 min at 95 °C followed by 40 cycles of 15 s at 95 °C and 1 min at 60 °C. The reactions were carried out on an ABI 7900HT Fast Real-Time PCR System (Life Technologies, Madrid, Spain). Five percent of samples were run in duplicate for quality control with 100% concordance.

2.5. Statistical analysis

Data processing was performed using SPSS 17.0 (SPSS, IBM, USA). We explored the normality of the distribution of all variables using histograms and normality tests (Kolmogorov—Smirnov). Because IL-6 levels and CRP levels were skewed, these variables were log transformed (ln). Chi-square tests were used to compare categorical data among the groups. ANOVA (or Kruskal—Wallis test when needed) was used to compare continuous variables among the groups. Bonferroni correction was used for post hoc analyses in ANOVA. Pearson correlations were used to explore the relationships among the continuous variables. The significance level was set at $p < 0.05$. Considering the cumulative data on immunomodulation by the endocannabinoid system, mediated through CB2 (Pandey et al., 2009; Saito et al., 2012) and CB1 receptor agonism (Kaplan, 2013), we conducted an additional univariate analysis excluding those subjects with daily cannabis use. We also conducted an ANCOVA analysis to compare concentrations in inflammatory markers between groups while adjusting for covariates.

We performed a multiple linear regression analysis to explore the association between the severity of psychotic symptoms and inflammatory markers while adjusting for covariables. Three equations were tested, each one using a different inflammatory marker (IL-6, CRP and fibrinogen) as the dependent variable. PANSS scores were used as independent variables. We also controlled for potential confounders, including gender, BMI, substance use, antipsychotic treatment and genotype. With respect to antipsychotic treatment, we included different variables: total chlorpromazine equivalent doses, duration of antipsychotic treatment and type of antipsychotic treatment. To reduce the loss of statistical power, we grouped all antipsychotics into three variables based on

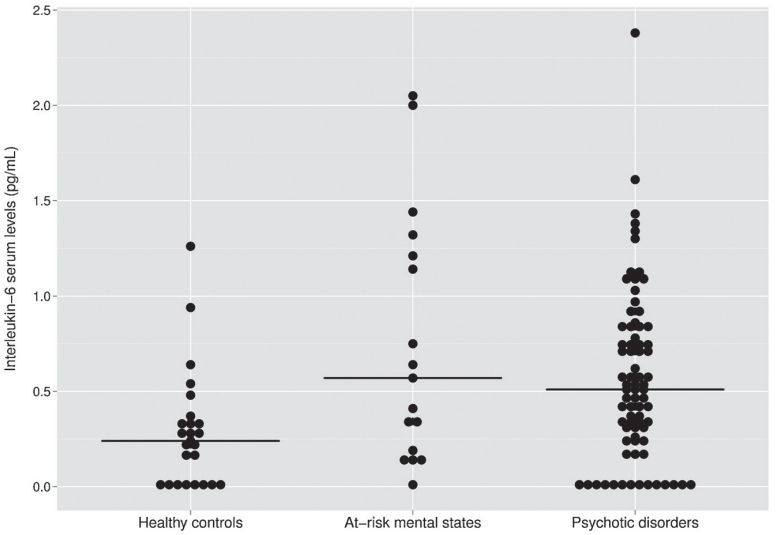

Figure 1 Serum interleukin-6 levels (pg/mL) by diagnostic group. Dots represent individual observations. Lines represent the median value for each subgroup.

their mechanism of action: (1) risperidone or paliperidone, (2) olanzapine or quetiapine, and (3) aripiprazole.

We first conducted a global analysis including both ARMS and PD subjects together. In this analysis, we included diagnosis (PD vs. ARMS) as a covariate and explored the potential interaction between diagnosis and PANSS positive and negative subscales. PD diagnosis was used as the reference category, so we included ARMS diagnosis as an independent variable and created two interaction terms (ARMS by PANSS positive and negative subscales) that were tested in a final step. Only significant interaction terms were kept in the final equation. With this decision, we explored whether there is a differential pattern in the relationship between psychotic symptoms and inflammatory markers by diagnosis.

As it may be controversial whether ARMS diagnosis should be considered a clinical entity distinct from PD (Shrivastava et al., 2011), we conducted an additional analysis only in PD patients. We did not conduct a multiple linear regression analysis only in ARMS subjects to avoid an unstable model, as the sample size for this subgroup was small ($n = 17$).

To test the potential cytokine by gene interaction, we conducted a logistic regression analysis using early psychosis diagnosis (ARMS or PD) as the dependent variable, and IL-6 levels and rs1800795 genotype as independent variables while controlling for other covariates. The interaction term IL-6 by rs1800795 was tested in a last step.

A significant departure from the Hardy—Weinberg equilibrium (HWE) was calculated using chi-square tests (Rodriguez et al., 2009).

3. Results

3.1. Inflammatory markers and diagnostic groups

The clinical data and inflammatory markers for the groups are described in Table 1. We found statistically significant differences among the diagnostic groups with regard to IL-6. The ARMS subjects showed increased IL-6 levels when compared with the HC. The PD patients also had greater IL-6 levels than the HC; however, post hoc analyses using Bonferroni adjustment trended toward significance ($p = 0.054$). With respect to CRP levels, although significant differences were observed between groups in the ANOVA analysis (Table 1), the comparisons were not significant after a post hoc Bonferroni adjustment. We also did not observe significant differences in fibrinogen.

In the ANCOVA analysis adjusted for BMI, age, tobacco, alcohol and cannabis consumption, the differences in the IL-6 levels between diagnostic groups continued to be significant ($p = 0.003$). Post hoc analyses were also significant for the HC vs. ARMS ($p = 0.003$) and HC vs. PD ($p = 0.024$) comparisons, but no significant differences were found between the ARMS and PD groups. The distribution of IL-6 levels among the diagnostic groups is presented in Fig. 1.

In the additional analysis excluding those subjects with cannabis consumption, we also observed significant differences between groups ($p = 0.004$). In the post hoc analyses, both ARMS and PD groups exhibited increased IL-6 levels when compared with HC (ARMS vs. HC, $p = 0.038$; PD vs. HC, $p = 0.001$). There were no significant differences between ARMS subjects and PD patients.

3.2. IL6 promoter polymorphism (rs1800795) genotype frequencies among diagnostic groups

IL6 promoter polymorphism (rs1800795) genotype frequencies in ARMS subjects ($n = 17$) were as follows: C/C = 64.7%, C/G = 23.5%, and G/G = 11.8%; in PD patients ($n = 77$) were as follows: C/C = 49.4%, C/G = 40.3%, and G/G = 10.4%; finally, in the population based sample ($n = 610$), the equivalent frequencies were as follows: C/C = 44.4%, C/G = 42.0%, and G/G = 13.6%. The distribution of the rs1800795 genotypes was consistent with the HWE for all groups. We found no differences in genotype frequencies among the groups ($p = 0.624$).

Table 2 Results of the multiple linear regression analysis exploring the relationship between IL-6 levels and psychotic symptoms in 94 subjects with a psychotic disorder or at risk mental states.

	Model 1 adjusted for gender, BMI and substance use		Model 2 + psychotic symptoms		Model 3 + antipsychotic treatment		Model 4 + SNP rs1800795		Model 5 + interactions	
R^2	0.039		0.156		0.192		0.192		0.237	
	β	p	β	p	β	p	β	p	β	p
Gender (female)	0.040	0.729	−0.014	0.900	0.010	0.931	0.009	0.937	−0.032	0.785
BMI (kg/m^2)	0.158	0.178	0.146	0.201	0.122	0.349	0.119	0.374	0.060	0.652
Tobacco (cigarettes/day)	0.022	0.862	0.052	0.674	0.017	0.896	0.018	0.888	0.028	0.825
Cannabis (joints/day)	−0.047	0.694	0.039	0.741	0.013	0.918	0.011	0.934	−0.043	0.739
Alcohol (standard units/day)	−0.093	0.449	−0.117	0.334	−0.073	0.567	−0.073	0.570	−0.063	0.613
ARMS diagnosis			0.102	0.370	0.029	0.820	0.030	0.815	−0.676	0.075
PANSS positive score			−0.313	0.009	−0.279	0.027	−0.279	0.028	−0.331	0.010
PANSS negative score			0.249	0.031	0.318	0.013	0.317	0.014	0.299	0.018
Risperidone or paliperidone treatment					−0.172	0.238	−0.175	0.237	−0.234	0.115
Olanzapine or quetiapine treatment					−0.166	0.202	−0.166	0.205	−0.229	0.084
Aripiprazole treatment					−0.141	0.312	−0.140	0.320	−0.122	0.376
Chlorpromazine equivalent dose (mg/day)					0.044	0.750	0.046	0.739	0.096	0.489
Duration of antipsychotic treatment (months)					0.021	0.871	0.018	0.895	−0.027	0.840
rs1800795 genotype (CC vs. CG + GG)							−0.019	0.870	−0.042	0.712
Interaction ARMS diagnosis by PANSS-P									0.712	0.049

Log-transformed IL-6 levels were considered the dependent variable.
Abbreviations: BMI, body mass index; PANSS, Positive and Negative Syndrome Scale.

3.3. Gene by cytokine interactions

We also explored the relationship between IL-6 levels and early psychosis diagnosis (defined as either ARMS or PD at the early stage of the illness) and tested the gene by cytokine interaction while controlling for covariates. In this binary logistic regression analysis, which was conducted in 119 participants and was adjusted for age, gender, BMI, tobacco, alcohol, cannabis and rs1800795 genotype, IL-6 levels were positively associated with the diagnosis of early psychosis (OR = 12.0, $p = 0.033$). This result implies that those subjects with an increase of 1 pg/mL in IL-6 levels are 12 times more likely to have an early psychosis diagnosis (ARMS or PD). We did not find a significant interaction between the rs1800795 genotype and IL-6 levels ($p = 0.319$).

3.4. Inflammatory markers and the severity of psychotic symptoms

Univariate analysis exploring the relationship between inflammatory markers and psychotic symptoms found a significant negative correlation between PANSS-P scores and IL-6 levels ($r = -0.255$; $p = 0.028$) in PD patients.

We conducted two multiple linear regression analyses, which allowed adjustments for covariates. In the first analysis, which included both PD and ARMS groups (Table 2), negative symptoms were associated with increased IL-6 levels in both populations. However, in relation to positive symptoms a distinct pattern was observed, as we found a significant positive interaction between ARMS diagnosis and positive psychotic symptoms. This means that in PD patients, positive symptoms were negatively associated with IL-6 levels, whereas in ARMS subjects positive symptoms were associated with increased IL-6 levels. This multivariate analysis was adjusted by gender, BMI, substance use, antipsychotic treatment and genotype. The IL6 rs1800795 SNP genotype was not associated with IL-6 levels.

The relationship between psychotic symptoms and IL-6 levels by diagnosis is also presented with scatter plot graphs (Figs. 2 and 3). In Fig. 2, both PD and ARMS groups show a positive association between negative symptoms and IL-6 levels. However, a different pattern is observed with respect to positive symptoms (Fig. 3): a positive association is observed for ARMS subjects, whereas this relationship is negative in the subgroup of PD patients.

In the multiple linear regression analysis conducted only in PD patients, (Table 1 from Supplementary material), negative symptoms were associated with increased IL-6 levels, whereas an inverse relationship was found for positive symptoms. In all multiple linear regression analyses (Table 2 and Table 1 from Supplementary material), standardized regression coefficients are shown.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2013.12.005.

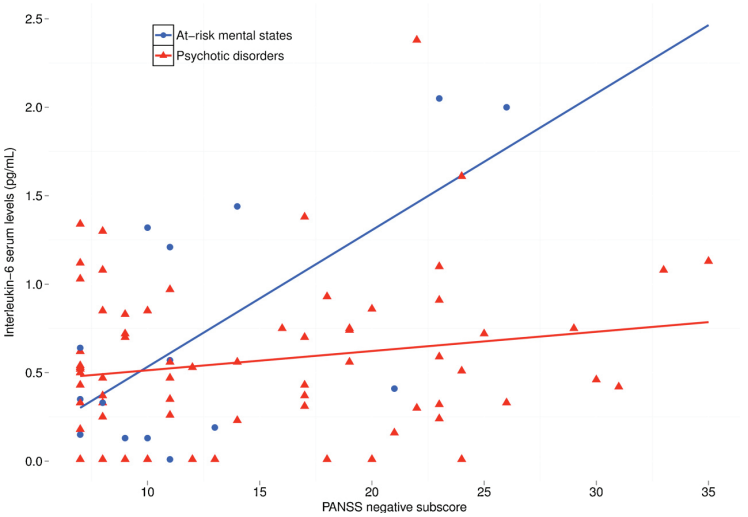

Figure 2 Scatter plot of the relationship between serum IL-6 levels (pg/mL) and the severity of negative psychotic symptoms in ARMS subjects and PD patients. Regression lines for each diagnostic group are presented.

In multiple regression analyses exploring the relationship between psychopathology and CRP or fibrinogen levels, we did not observe an association between the severity of psychotic symptoms and these inflammatory markers (data not shown). In the CRP final model, this inflammatory marker was significantly associated with BMI ($\beta = 0.384$, $p = 0.004$).

3.5. Inflammatory markers and antipsychotic treatment

As described in Table 2 and Supplementary material Table 1, we did not observe a significant association between antipsychotic treatment and IL-6 levels. Of all 94 participants, 16 were antipsychotic-free (9 ARMS and 7 PD). We did not observe statistically significant differences in those subjects that were antipsychotic-free when compared with antipsychotic-treated subjects. In relation to IL-6, the median serum IL-6 level was 0.52 pg/mL for the antipsychotic-free group and 0.49 pg/mL for the antipsychotic-treated group.

3.6. Inflammatory markers and the risk of transition to psychosis

Six of the 17 ARMS subjects (35%) underwent a transition to psychosis during a mean follow-up period of 26.6 months, whereas the remaining 11 did not. The median IL-6 level of those ARMS subjects who developed a psychotic disorder was 0.61 pg/mL, and the median level of the ARMS subjects who

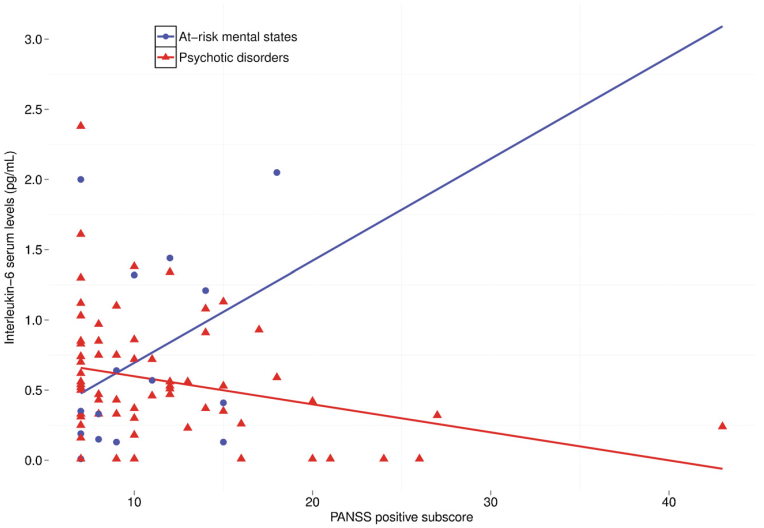

Figure 3 Scatter plot of the relationship between serum IL-6 levels (pg/mL) and the severity of positive psychotic symptoms in ARMS subjects and PD patients. Regression lines for each diagnostic group are presented.

did not transition to psychosis was 0.35 pg/mL. These differences were not statistically significant. We did not observe significant differences in the CRP or fibrinogen levels.

4. Discussion

Our finding of increased IL-6 levels in ARMS subjects suggests that the active inflammatory process that has elsewhere been observed in schizophrenia patients (Potvin et al., 2008; Miller et al., 2011, 2013) may also be present in subjects at high risk for psychosis. To the best of our knowledge, this is the first study to explore IL-6 levels in a sample that included ARMS subjects. This result fits well with previous studies showing increased inflammation in drug-naïve patients experiencing their first episodes of psychosis (Borovcanin et al., 2012; Garcia-Rizo et al., 2012), suggesting that immune abnormalities described in psychotic disorders are present at the early stages of the illness. We also observed increased IL-6 levels in PD subjects when compared to HC, although we did not observe significant differences between the ARMS and PD groups.

In analyses exploring the relationship between psychopathology and inflammatory markers, we found a positive association between IL-6 and negative psychotic symptoms in both ARMS and PD subjects. However, when the relationship between positive symptoms and diagnosis (ARMS vs. PD) was considered, a different pattern was observed, revealing a positive relationship in ARMS subjects and a negative relationship in PD patients. These findings could not be attributed to confounding variables including gender, BMI, antipsychotic treatment, tobacco, alcohol and cannabis consumption, or rs1800795 genotype. The observed association between negative symptoms and IL-6 is in accordance with previous studies linking inflammatory markers to deficit features (Garcia-Rizo et al., 2012). Because negative symptoms are a core feature of deficit schizophrenia, our results suggest that inflammation may be associated with a distinct clinical profile marked by more prominent negative symptoms. Additionally, other studies conducted on subjects with chronic schizophrenia and longer durations of illness have found an association between IL-6 levels and negative symptoms (Kim et al., 2000). Our results, as well as the study by Garcia-Rizo et al. (2012), suggest that this association can be detected before the development of psychosis and the introduction of antipsychotic treatment. The different relationships between positive psychotic symptoms and IL-6 levels between the ARMS and PD groups could be explained by differences in the clinical repercussion of psychotic symptoms. In ARMS subjects, who are less frequently treated with antipsychotics, positive psychotic symptoms may be viewed as prodromal symptoms of the illness, often accompanied by anxiety and stress. However, in PD patients, who have a longer duration of illness and more frequently receive antipsychotic treatment, patients may have 'adapted' to the presence of persistent positive psychotic symptoms. In line with this, a previous study has reported higher stress levels in ARMS subjects when compared with FEP subjects (Pruessner et al., 2011). Although speculative, the positive relationship between positive symptoms and IL-6 levels could be explained by the stressful condition of the prodromal state.

ARMS subjects and PD patients exhibited similar PANSS scores. As our Early Psychosis Program is an outpatient service, some patients who have been previously admitted in the referral Acute Psychiatric Unit are stabilized before attending our service. Moreover, patients need to be informed of the research project and must sign the informed consent; thus in most cases, PD patients are clinically stable at recruitment. As most PD patients have been treated before entering the study, the PANSS scores reflect the psychopathological state at the initial assessment (not at the acute phase of the illness). These characteristics could explain why both groups (ARMS and PD) exhibit similar PANSS scores.

It has been proposed that IL-6 constitutes a state rather than a trait marker for schizophrenia, meaning that IL-6 levels could be affected by a clinical state or treatment. In this respect, our results are in accordance with the most recently published and most thorough meta-analysis regarding cytokine alterations in schizophrenia (Miller et al., 2011), in which a reduction of IL-6 blood levels following antipsychotic treatment was described. We did not observe any influence on IL-6 levels by rs1800795 genotype, as other authors have suggested (Zakharyan et al., 2012). Although previous studies have demonstrated that antipsychotic drugs modulate the production of cytokines and their receptors, such as the suppression of plasma IL-6 levels and IL-6 soluble receptor by typical antipsychotics (Maes et al., 1995; Muller et al., 1997) or the increased production of IL-6 by atypical antipsychotics such as clozapine (Pollmacher et al., 1996), we did not observe significant differences between antipsychotic drugs.

Potential mechanisms for the observed associations have been recently reviewed and summarized into an integrative theoretical framework for immune system dysfunction mediating relapse in a subgroup of schizophrenia patients (Miller and Buckley, 2012). In this paper, the authors proposed that the acute phase response mechanism determining leukocyte, fibroblast, and vascular endothelium activation could be mediating a systemic inflammatory response through pro-inflammatory cytokine production (e.g., IL-6, interleukin-1 beta and transforming growth factor beta). A systemic response involving the hypothalamic-pituitary-adrenal (HPA) axis activation with subsequent cortisol secretion, liver synthesis of acute phase proteins (e.g., CRP, fibrinogen, serum amyloid A), leucocytosis with subsequent additional cytokine and antibodies production, and blood complement system activation with secondary elevations in C3 and C4 constitutes the intermediate player of this immune-mediated mechanism of acute psychosis. Increased serum levels of C3, C4 and ceruloplasmin have been demonstrated in schizophrenia patients and are also significantly positively correlated with PANSS-N scores (Morera et al., 2007). On the other hand, higher cytokine levels could be responsible for the psychopathological changes observed through the enhancement of the tryptophan catabolism at the indoleamine 2,3-dioxigenase (IDO) step. The subsequent elevated production of kynurenic acid, a known N-methyl-D-aspartate receptor antagonist, may modulate glutamatergic neurotransmission, resulting in psychosis (Miller and Buckley, 2012). An additional potential mechanism would consist of the access of circulating inflammatory mediators and antibodies to the central nervous system through the enhanced blood brain barrier (BBB) permeability. BBB increased permeability has been positively associated with negative psychotic symptoms in schizophrenia patients through increased levels of S100 calcium binding protein B (Rothermundt et al., 2001) and a less pronounced decrease in the soluble intercellular adhesion molecule-1 (sICAM-1) levels (Schwarz et al., 2000). These in

turn, could possibly modulate neurotransmission and induce a chronic local inflammatory reaction in the brain of at least a subgroup of schizophrenic patients. In line with the above, Altamura et al. (1999) have proposed that the HPA axis dysfunction observed in schizophrenia could be induced by pro-inflammatory cytokines, and the negative symptom predominant response to atypical antipsychotics may be mediated in part by regulatory effects of these drugs on the HPA axis and inflammatory response system function.

Some limitations of our study need to be addressed. One limitation was the small sample size, particularly for the ARMS group, which limited the study of the relationship between psychopathological features and inflammatory markers in this subgroup of patients. Although we observed increased IL-6 levels in those ARMS subjects who developed psychosis, when compared with those who did not develop psychosis, there was a lack of statistical power due to the small sample size. We did not repeatedly assess inflammatory markers in ARMS subjects that could demonstrate longitudinal changes in inflammation between those ARMS subjects with or without a transition to psychosis. These preliminary results should be considered as exploratory, and further studies with larger sample sizes are needed to confirm this observation. Finally, another potential limitation was not exploring other SNPs that are robustly associated with schizophrenia, such as polymorphisms of the human interleukin-1 beta gene (IL1B) (e.g., rs16944 and rs1143634) (Shi et al., 2008; Xu and He, 2010). IL-1 may directly affect IL-6 levels by activating the IL6 promoter region (Isshiki et al., 1990). Interestingly, IL-1 beta levels have been found to be elevated in acutely relapsed and FEP schizophrenia patients (Miller et al., 2011). Taking into consideration our negative results with rs1800795, these IL1B gene SNPs should be explored in future studies.

In summary, our study confirmed our hypothesis of a possible active inflammatory process in subjects with early psychosis or who are at risk of psychosis, suggesting that IL-6 is a candidate biomarker of psychosis at early stages of the illness, worthy of exploration in future studies.

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Conflicts of interest

All authors declare that they have no conflicts of interest.

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Supplementary Material Table 1. Results of the multiple linear regression analysis exploring the relationship between IL-6 levels and psychotic symptoms in 77 patients diagnosed with a psychotic disorder

	Model 1 Adjusted for gender, BMI and substance use		**Model 2 + Psychotic symptoms**		**Model 3 + Antipsychotic treatment**		**Model 4 + SNP rs1800795**	
R Square								
	β	P	β	P	β	P	β	P
Gender (female)	0.062	0.629	-0.035	0.781	-0.062	0.643	-0.065	0.632
BMI (kg/m^2)	0.168	0.196	0.134	0.277	0.087	0.539	0.081	0.577
Tobacco (cigarettes/day)	0.002	0.987	0.022	0.868	-0.011	0.937	-0.009	0.946
Cannabis (joints/day)	-0.100	0.452	0.004	0.973	-0.031	0828	-0.032	0.822
Alcohol (standard units/day)	-0.059	0.666	-0.112	0.401	-0.043	0.756	-0.043	0.758
PANSS Positive Score			-0.360	0.008	-0.336	0.016	-0.337	0.016
PANSS Negative Score			0.224	0.076	0.354	0.017	0.354	0.018
Risperidone or paliperidone treatment					-0.296	0.074	-0.302	0.074
Olanzapine or quetiapine treatment					-0.229	0.126	-0.230	0.128
Aripiprazole treatment					-0.163	0.290	-0.160	0.305
Chlorpromazine equivalent dose (mg/day)					0.018	0.903	0.023	0.879
Duration of antipsychotic treatment (months)					-0.037	0.800	-0.041	0.783
rs1800795 genotype (CC vs. CG+GG)							-0.026	0.832

Log-transformed IL-6 levels were considered the dependent variable.

Abbreviations: BMI = Body Mass Index; PANSS = Positive and Negative Syndrome Scale.

3.2. Publicación 2 - Artículo Original

Stress biomarkers as predictors of transition to psychosis in at-risk mental states: roles for cortisol, prolactin and albumin.

Labad J, **Stojanovic-Pérez A**, Montalvo I, Solé M, Cabezas Á, Ortega L, Morenol, Vilella E, Martorell L, Reynolds RM, Gutiérrez-Zotes A.

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Antecedentes

El estrés y algunos biomarcadores relacionados como el cortisol, la prolactina y la albúmina, juegan un papel en el desarrollo de la psicosis. Sin embargo, se desconoce su implicación en el riesgo de desarrollar un trastorno psicótico en sujetos vulnerables.

Aportes

Este es el primer estudio longitudinal que explora el papel del estrés y de biomarcadores relacionados con el estrés y la inflamación, en el riesgo de transición a psicosis en una cohorte de sujetos EMAR.

Aspectos a destacar

Este estudio ha identificado que los sujetos EMAR que desarrollaron un TPI, en comparación a los que no realizaron transición a psicosis, habían experimentado mayor número de acontecimientos vitales estresantes y presentaban mayores niveles de estrés percibido.

Los sujetos EMAR que desarrollaron un TPI mostraron una hiperactividad del sistema del eje hipotálamo-hipófisis-suprarrenal (HHS), especialmente en la pendiente de ascenso del cortisol entre los 0 y 30 minutos del despertar. Además, presentaron niveles más bajos de albúmina y más elevados de prolactina. Estos parámetros podrían ser considerados como posibles biomarcadores de transición a psicosis.

El número de acontecimientos vitales estresantes presentó una asociación positiva con los niveles de cortisol en saliva ($r=0,35$, $p=0,044$) y una asociación negativa con los niveles de albúmina en suero ($r=-0,37$, $p=0,029$).

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Stress biomarkers as predictors of transition to psychosis in at-risk mental states: Roles for cortisol, prolactin and albumin

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ABSTRACT

Stress and inflammation are thought to play a role in the risk of developing a psychotic disorder. We aimed to identify stress-related biomarkers for psychosis transition in help-seeking individuals with an at-risk mental state (ARMS). We studied 39 ARMS subjects who were attending an Early Intervention Service. We included a control group of 44 healthy subjects (HS) matched by sex and age. Stressful life events and perceived stress were assessed. Stress-related biomarkers were determined in serum (cortisol, prolactin, C-reactive protein and albumin), plasma (fibrinogen) or saliva (morning cortisol, cortisol awakening response). All ARMS were followed-up at our Unit for at least one year. We divided the ARMS group into two subgroups based on the development of a psychotic disorder (ARMS-P, $N = 10$) or not (ARMS-NP, $N = 29$). ARMS-P reported more stressful life events and perceived stress than HS and ARMS-NP groups. In relation to baseline stress biomarkers, ARMS-P subjects had increased prolactin and lower albumin levels in serum, when compared to ARMS-NP and HS groups. These results did not change when repeated in a subsample of antipsychotic-naïve ARMS subjects. We also found significant differences between groups in the cortisol secretion after awakening. In a multinomial logistic regression adjusting for age, sex and life stress, prolactin was a predictor of psychosis transition whereas albumin levels had a protective effect. Our study underscores the role of stress and stress-related biomarkers (cortisol awakening response, prolactin and albumin) in the pathogenesis of psychosis.

1. Introduction

Stress is thought to play a role in the risk of developing a psychotic disorder, as both first episode of psychosis and subjects with prodromal symptoms of psychosis report more stressful life events (Beards et al., 2013; Manzanares et al., 2014) and perceived stress (Pruessner et al., 2011), when compared to healthy subjects. The classical neural diathesis-stress model of schizophrenia suggests that psychosocial stress activates the hypothalamic–pituitary–adrenal (HPA) axis, that induces cortisol release and enhances dopamine transmission, contributing to the emergence of psychosis in vulnerable individuals (Walker and Diforio, 1997). This theoretical hypothesis has been recently demonstrated in a positron emission tomography study reporting stress-induced dopamine release in psychosis (Mizrahi et al., 2012). In first episodes of psychosis, hyperactivation of the HPA axis is a common feature (Borges et al., 2013). Recent studies have also explored HPA axis abnormalities in people suffering from potentially prodromal symptoms, also known as at-risk mental states (ARMS) (Fusar-Poli et al., 2013). Salivary cortisol has been associated with impaired stress tolerance (Corcoran et al., 2012) and a risk of psychosis transition (Walker et al., 2013) in ARMS subjects. A blunted cortisol awakening response (CAR) has been also reported in ARMS individuals, when compared to healthy subjects (HS) (Day et al., 2014). In genetically high risk populations, such as siblings of patients with a non-affective psychotic disorder, unpleasant stressful

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events are associated with psychotic experiences and increased cortisol levels (Collip et al., 2011).

However, although the HPA axis is one of the main biological responses to stress, other stress-related biomarkers may also play a role. Prolactin, an anterior pituitary hormone that increases in response to psychosocial stress (Sobrinho, 2003; Lennartsson and Jonsdottir, 2011), has been demonstrated to be increased in up to 39% of drug-naïve individuals with a first episode of psychosis (Aston et al., 2010; Garcia-Rizo et al., 2012; Riecher-Rössler et al., 2013) or with an ARMS diagnosis (Aston et al., 2010). These findings are important, because they underscore that in a substantial proportion of individuals with psychotic disorders at early stages hyperprolactinaemia is not secondary to D2-blockade by antipsychotics. Some authors have suggested that as enhanced prolactin can increase dopamine release through a feedback mechanism, this could contribute to explaining how stress can trigger the outbreak of psychosis (Riecher-Rössler et al., 2013). However, there are no prospective studies exploring whether increased prolactin in ARMS subjects may contribute to the risk of developing a psychotic disorder.

Inflammatory and oxidative stress biomarkers have been also found to be increased in subjects with a first episode of psychosis (Miller et al., 2011; Flatow et al., 2013). In a previous study by our group we also found increased interleukin-6 levels in ARMS subjects, when compared to healthy subjects (Stojanovic et al., 2014). The inflammatory hypothesis of schizophrenia suggests that peripheral inflammation might cause or reflect brain dysfunction in schizophrenia, as cytokines may directly modulate dopaminergic neurotransmission or indirectly modulate glutamatergic neurotransmission through tryptophan metabolism (Kirkpatrick and Miller, 2013). Albumin, an abundant circulating protein in plasma that may be reduced in severe physical illnesses, could be considered another potential biomarker linked to the risk of psychosis transition as it has antioxidant properties and exerts a favorable influence on redox-signaling processes that regulate inflammation (Roche et al., 2008). Different studies have emphasized the importance of serum albumin in psychiatric disorders. Reduced serum albumin levels have been reported in patients with major depressive disorder (Huang et al., 2005), first episodes of schizophrenia (Reddy et al., 2003; Pae et al., 2004) or chronic schizophrenia (Yao et al., 2000; Huang, 2002). Serum albumin levels correlate with the processing of affective prosody in adult male patients with attention deficit hyperactivity disorder (ADHD) (Grabemann et al., 2014). Additionally, an association between low serum albumin levels and corticosteroid-induced psychosis has been reported in patients with systemic lupus erythematosus (López-Medrano et al., 2002; Chau and Mok, 2003). No studies have addressed whether reduced albumin levels may play a role in the risk of transition to psychosis in individuals at risk for psychosis.

The main aim of our study was to assess whether clinical and biological measures of stress could be predictors of psychosis transition in a sample of help-seeking ARMS subjects attending an Early Intervention Service.

2. Material and methods

2.1. Participants

The initial sample consisted of 40 subjects (30% women, mean age: 23.2 years) fulfilling set criteria for ARMS who had attended the Early Intervention Service from Reus (HU Institut Pere Mata, Spain) for at least one year. Exclusion criteria were: pregnancy, mental retardation, severe head injury or neurological disease, active glucocorticoid treatment, oral contraceptive pill use, active substance dependence (other than tobacco or cannabis) and type 1 diabetes mellitus. Of all 40 subjects, one patient was diagnosed of type 1 diabetes after the initial blood analysis and was therefore excluded, leaving a final sample of 39 ARMS subjects. We included a control group of 44 healthy subjects (HS) matched by sex and age. This group was screened to rule out past or current history of psychiatric disorders. Recruitment of HS included young people from the community who were contacted by advertisements. Ethical approval was obtained from the local Ethics Committee. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Clinical assessments

2.2.1. Baseline visit

ARMS subjects were assessed with the Comprehensive Assessment of At Risk Mental States, to ensure that subjects met criteria for any of the three high-risk groups defined by ARMS criteria (Yung and McGorry, 2007): (1) attenuated psychosis ($n = 24$), (2) brief limited intermittent psychotic symptoms (BLIPS) ($n = 7$), and (3) vulnerability group ($n = 8$), that includes subjects with a family history of psychosis in first degree relative or schizotypal personality disorder in identified patient with a 30% drop in GAF score from premorbid level, sustained for 1 month.

Positive, negative and overall psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Stressful life events in the previous 6 months were assessed with the Holmes–Rahe Social Readjustment Scale (Holmes and Rahe, 1967). This scale was initially developed to explore the relationship between social readjustment, stress and susceptibility to illness. It explores 43 life events and gives a 'stress score' for each item, obtaining a final score by adding the scores of all present life events. This scale has been validated and used in Spanish populations (Roca et al., 2013). Previous studies include the use of this scale to explore the relationship between life events and subclinical psychotic symptoms in the general population (Rössler et al., 2007). Perceived Stress Scale (Cohen et al., 1983) was used to assess psychological perception of stress. This instrument is a 14-item self-report questionnaire that was designed to measure the degree to which situations in ones' life are appraised as stressful. Subjects indicate how often they have found their lives unpredictable, uncontrollable, and overloaded in the last month.

As albumin levels may be affected by protein ingestion (Thalacker-Mercer and Campbell, 2008), we assessed dietary habits by means of a clinical interview conducted by a dietician. Food intake was registered by 24 h recall. Specialized software (CESNID, Barcelona University) was used to calculate the daily calorie and protein intake.

Antipsychotic and antidepressant treatment, and other sociodemographic and clinical variables were obtained by semi-structured interview. In our Early Intervention Service, all psychopharmacological treatments (introduction, changes in dosage and retirement) are registered in an electronic clinical record. We verified antipsychotic treatment at assessment by contrasting information obtained during the clinical interview and data included in the electronic health records. Of all 39 ARMS subjects, 7 (17.9%) were taking antipsychotic drugs at baseline assessment (aripiprazole [$n = 4$], risperidone [$n = 2$] and quetiapine [$n = 1$]). Regarding antidepressant treatment, 16 ARMS subjects (41%) were receiving antidepressants (selective serotonin reuptake inhibitors [$n = 12$], venlafaxine [$n = 2$], duloxetine [$n = 1$] and mirtazapine [$n = 1$]).

2.2.2. Follow-up visits: psychosis transition criteria

ARMS subjects that seek treatment usually attend our unit with frequent visits (every 2–4 weeks). We aimed to include longitudinal data in those ARMS subjects who had a follow-up period of at

Table 1
Clinical and biological measures among groups.

	Healthy subjects $N = 44$	ARMS-NP $N = 29$	ARMS-P $N = 10$	p Value[a]
Age (years)	23.2 (4.4)	23.0 (4.9)	20.4 (3.1)	0.209
Female gender	15 (34.9%)	7 (24.1%)	5 (50%)	0.300
PANSS scores				
PANSS positive	–	9.4 (2.8)	11.1 (2.6)	0.093
PANSS negative	–	11.1 (4.5)	13.7 (6.3)	0.182
PANSS general	–	30.9 (10.4)	37.0 (6.0)	0.090
Psychopharmacological treatment				
Antipsychotic treatment	0 (0%)	3 (10.3%)	4 (40%)	<0.001
Antidepressant treatment	0 (0%)	12 (41.4%)	4 (40%)	<0.001
Substance use				
Tobacco (cigarettes/day)	2.3 (5.2)	4.1 (6.1)	7.1 (10.8)	0.096
Cannabis (joint/day)	0.2 (0.6)	1.1 (3.2)	1 (2)	0.161
Alcohol (standard units/day)	0.1 (0.3)	0.1 (0.4)	0 (0)	0.831
Dietary habits				
Calorie intake (kcal/day)	1788.1 (418.4)	2367.7 (787.9)	2739.6 (998.6)	<0.001[A,B]
Protein intake (grams/day)	87.4 (18.4)	93.6 (33.6)	98.0 (35.5)	0.436
BMI (kg/m^2)	22.4 (4.3)	22.1 (3.7)	21.3 (2.9)	0.717
Stress-related measures				
Perceived Stress Scale	19.4 (7.5)	29.7 (10.9)	36.8 (6.5)	<0.001[A,B,C]
Holmes–Rahe (stress score)	113.6 (93.3)	125.0 (69.8)	214.0 (100.7)	0.009[B,C]
Plasma biomarkers				
Total cortisol (nmol/L)	517.7 (146.6)	588.0 (130.4)	576.7 (233.9)	0.141
Prolactin (pmol/L)	700.0 (389.6)	667.4 (597.6)	1572.3 (1215.7)	<0.001[B,C]
C-reactive protein (nmol/L)	22.3 (26.9)	36.7 (96.4)	6.7 (6.7)	0.355
Fibrinogen (μmol/L	7.9 (1.9)	8.0 (1.9)	6.9 (1.2)	0.260
Albumin (g/L)	48.5 (3.8)	48.5 (3.8)	43.9 (4.1)	0.004[B,C]
Morning salivary cortisol (nmol/L)	18.8 (5.3)	21.3 (4.7)	20.9 (8.5)	0.258
Cortisol awakening response				
Awakening time (h:min)	7:56 (0:41)	8:00 (0:31)	8:14 (0:24)	0.572
Cortisol at awakening (nmol/L)	13.0 (9.0)	16.7 (10.0)	9.5 (9.4)	0.193
Cortisol 30′ post-awakening (nmol/L)	23.3 (14.4)	27.4 (14.9)	30.4 (19.2)	0.432
Cortisol 60′ post-awakening (nmol/L)	21.6 (14.6)	19.0 (12.0)	24.6 (13.0)	0.652
Slope (cortisol rise between 0′ and 30′)	0.35 (0.40)	0.35 (40)	0.70 (0.48)	0.144
CAR-AUC$_i$	439.4 (548.1)	350.7 (513.7)	854.2 (512.6)	0.141
Sex hormones[b]				
Estradiol (pmol/L)	214.1 (134.1)	268.6 (212.6)	252.6 (175.5)	0.787
Progesterone (nmol/L)	14.2 (17.2)	23.3 (21.7)	17.9 (16.3)	0.603
Testosterone (nmol/L)	21.4 (5.2)	17.8 (7.6)	17.7 (9.4)	0.141

Data are mean (SD) or N (%).
Abbreviation: ARMS-NP = at-risk mental states without a psychosis transition; ARMS-P = at-risk mental states with a psychosis transition; BMI = body mass index; PANSS = Positive and Negative Syndrome Scale.
Significant ANOVA post-hoc analyses are highlighted: [A]Healthy subjects vs ARMS-NP, [B]Healthy subjects vs ARMS-P, [C]ARMS-NP vs ARMS-P.
[a] One-way ANOVA was used to compare continuous data among groups. Chi-square test was used to compare categorical data among groups.
[b] Estradiol and progesterone concentrations were determined in women; testosterone concentrations were determined in men.

least one year. The transition to psychosis was defined as the occurrence of at least 1 fully positive psychotic symptom several times a week for more than 1 week (Fusar-Poli et al., 2013). Date of psychotic transition was registered in order to conduct a survival analysis. We divided the ARMS group into two subgroups based on the development of a psychotic disorder (ARMS-P) or not (ARMS-NP).

2.3. Blood and salivary stress measures

All blood and salivary samples were obtained at the baseline visit only. A fasting blood sample was obtained in the morning between 8:30 h and 9:30 h at the Early Intervention Service in resting conditions, to determine prolactin, total cortisol, c-reactive protein, fibrinogen, albumin and sexual hormones (estradiol and progesterone in women, testosterone in men). Participants were told to avoid stressful activities (sports, physical exercise) or breast stimulation in the 12 h prior to blood sampling. We also obtained a fasting saliva sample the same day of the blood extraction. Saliva samples for cortisol analysis were obtained using Salivette (Sarstedt AG & Co, Nümbrecht, Germany) containers. Collection of saliva was conducted before venepuncture, in order to avoid the potential stressful component of the needle preparation. This same day 3 Salivettes were given to all participants to collect saliva samples at home when awakening, 30′ and 60′ post-awakening. The return rates for home-collected Salivettes were 80% for HS and 62% for ARMS. Salivary cortisol levels reflect the biologically active or unbound fraction of cortisol and can be collected in a non-invasive, stress-free procedure (Inder et al., 2012). Saliva samples were centrifuged at 3000 rpm during 5 min, aliquoted and frozen at −20 °C until determination of saliva cortisol levels.

The methods for each assay used to determine stress biomarkers are described in Table 1 from the Supplementary material (Table 1SM).

2.4. Statistical analyses

We used SPSS version 19.0 (IBM Corp., Armonk, NY, USA) and R (R Core Team, http://www.r-project.org) for statistical analyses. Continuous variables were compared with Pearson (or Spearman when needed) correlations. Continuous measures by diagnostic groups (HS, ARMS-P, ARMS-NP) were compared by ANOVA. A p-value < 0.05 (two-tailed) was considered to be significant. We also conducted a repeated measures ANOVA to compare cortisol levels after awakening (awakening, 30′, and 60′ post-awakening) between the three diagnostic groups while adjusting for gender, awakening time, BMI and treatments (antipsychotics and antidepressants). Post-hoc contrasts (quadratic) were corrected for sphericity with the Huynh–Feldt correction. In relation to the CAR, we also calculated two different measures: 1) slope of the awakening cortisol rise (between 0 and 30′), 2) area under the curve with respect to the increase (CAR-AUC$_i$) (Pruessner et al., 2003). We compared these measures with an ANCOVA, also adjusting for the same covariates mentioned before.

In order to explore the relationship between life stress and biomarkers in relation to the risk of psychosis transition we conducted a multinomial logistic regression using clinical diagnosis (with three categories: HS, ARMS-NP and ARMS-P) as the dependent variable. HS was considered the reference category, thus this multivariate analysis will show odds ratios (OR) for ARMS-NP and ARMS-P diagnosis, when compared to healthy volunteers. Those biomarkers that were significant in the univariate analysis were included in the analysis as independent variables. As age, gender and stressful life events may have an influence on stress-related biomarkers, we adjusted the final model for these covariates.

We analyzed survival data with a Cox Regression. Transition to psychosis was set as the event of interest. However, as there are sex-differences in prolactin concentrations (greater levels in women), we included sex as a covariate. Cannabis use and antidepressant treatment were also included as covariates in this analysis, as cannabis may precipitate psychosis in vulnerable individuals (Valmaggia et al., 2014) and antidepressants may delay the psychosis onset in some cases (Cornblatt et al., 2007). Because antipsychotic treatment may affect hormone levels (mainly for prolactin), survival analyses were conducted in antipsychotic-naïve ARMS individuals ($n = 32$). All ARMS subjects were followed-up for at least 1 year at our Early Intervention Service. The mean (standard deviation) follow-up period for these 32 subjects was 562.3 (343.3) days.

3. Results

Clinical and biological data of the sample is described in Table 1. The psychosis transition rate over the follow-up period was 25.6% (10 out of 39 ARMS). The mean (SD) time to transition was 167.4 (119.2) days. ARMS-P reported more stressful life events and increased perceived stress than HS and ARMS-NP groups. The ARMS-NP also reported increased perceived stress, when compared to HS. In relation to stress biomarkers, ARMS-P subjects had lower albumin levels in serum, when compared to ARMS-NP and HS groups, as well as increased prolactin levels (Table 1). We repeated these analyses after excluding those subjects on antipsychotic drugs. The results did not change in antipsychotic-naïve subjects (26 ARMS-NP; 6 ARMS-P): increased prolactin levels ($p = 0.028$) were found in ARMS-P subjects (1272.5 [700.3] pmol/L), when compared to ARMS-NP (694.0 [623.4] pmol/L) and HS groups (701.0 [389.7] pmol/L); lower albumin levels ($p = 0.001$) were also found in the ARMS-P group (42.2 [5.1] g/L) when compared to ARMS-NP (48.2 [3.8] g/L) and HS (48.5 [3.8] g/L). Although ARMS-P subjects had increased prolactin levels, hyperprolactinaemia was not associated with hypogonadism because all groups showed similar levels of sexual hormones. No differences were found in relation to morning serum or salivary cortisol, nor in serum CRP or plasma fibrinogen levels. In relation to the CAR, we did not find significant differences in cortisol levels at different time points with an ANOVA, nor with the slope or CAR-AUC$_i$. However, when using an ANCOVA adjusted for awakening time and other covariates, we detected significant differences between ARMS-P and the other two groups for the slope (ARMS-P vs ARMS-NP, $p = 0.037$; ARMS-P vs HS, $p = 0.017$). When using the CAR-AUC$_i$, significant differences were only detected for the comparison between ARMS-P and ARMS-NP groups ($p = 0.043$). We also explored changes in cortisol levels with a repeated-measures ANOVA, within-subjects contrasts showed a significant effect by time ($p < 0.001$) and a significant effect by the interaction between time and diagnostic group ($p = 0.029$). The interaction between time and diagnostic group is represented in Fig. 1. ARMS-P subjects have lower cortisol levels at awakening with a greater increase at 30′, when compared to the other groups.

In ARMS subjects, stressful life events were positively associated with salivary cortisol ($r = 0.35$, $p = 0.044$) and negatively associated with serum albumin levels ($r = -0.37$, $p = 0.029$). Perceived stress was not associated with blood or salivary biomarkers, although a negative relationship with albumin levels was barely significant ($r = -0.33$, $p = 0.051$). In healthy subjects, stressful life events or perceived stress were not associated with any biomarker. Serum albumin levels were negatively correlated with prolactin ($r = -0.38$, $p = 0.017$) only in ARMS subjects. We found a relationship between stressful life events and perceived stress in ARMS subjects ($r = 0.44$, $p = 0.009$) but not in HS ($r = 0.18$, $p = 0.246$). We also conducted a stratified correlation analysis by ARMS diagnosis (ARMS-NP and ARMS-P groups) of stress measures (Table 2).

In the multinomial logistic regression, adjusted for gender, age and stressful life events, prolactin levels at baseline assessment

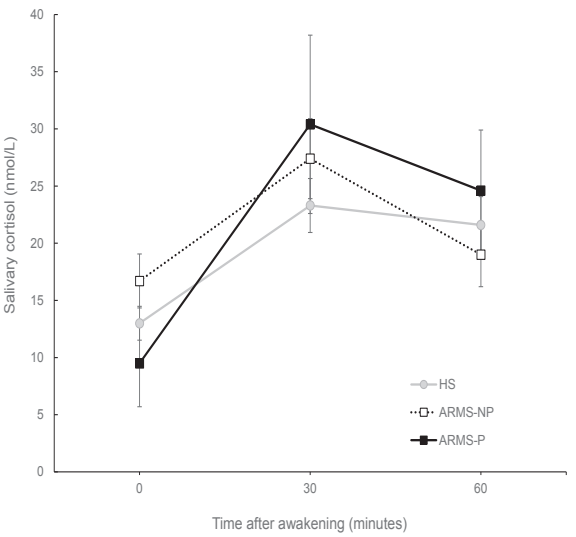

Fig. 1. Mean (±standard error) salivary cortisol levels of the cortisol awakening response for healthy subjects (HS) and at-risk mental states with (ARMS-P) or without (ARMS-NP) a psychosis transition. The ANOVA for repeated measures adjusted for sex, body mass-index, awakening time, antidepressant treatment, antipsychotic treatment and smoking showed a significant interaction between time and diagnostic group ($p = 0.029$).

Table 2
Correlations between psychological stress measures and fasting morning stress biomarkers in At Risk Mental States without (ARMS-NP, $N = 29$) or with a psychosis transition (ARMS-P, $N = 10$).

	ARMS-NP								ARMS-P							
	SLE	PSS	CORTS	CORTP	PRL	CRP	FIBR	ALB	SLE	PSS	CORTS	CORTP	PRL	CRP	FIBR	ALB
SLE		0.31	0.16	0.04	0.08	0.18	0.10	−0.24		0.40	0.41	0.000	0.18	0.46	0.39	−0.31
PSS	0.31		0.05	0.16	0.09	0.10	0.22	−0.24	0.40		−0.43	−0.25	0.36	0.25	0.48	−0.14
CORTS	0.16	0.05		0.54**	−0.02	0.31	0.33	−0.28	0.41	−0.43		0.97**	−0.60	0.32	0.41	0.19
CORTP	0.04	0.16	0.54**		0.42*	0.20	−0.11	−0.31	0.00	−0.25	0.97**		−0.39	0.26	0.50	0.06
PRL	0.08	0.09	−0.02	0.42*		−0.07	−0.24	−0.13	0.18	0.36	−0.60	−0.39		−0.57	−0.32	−0.57
CRP	0.18	0.10	0.31	0.20	−0.07		0.48**	−0.25	0.46	0.25	0.32	0.26	−0.57		0.82**	0.07
FIBR	0.10	0.22	0.33	−0.11	−0.24	0.48**		−0.11	0.39	0.48	0.41	0.50	−0.32	0.82**		0.01
ALB	−0.24	−0.24	−0.28	−0.31	−0.13	−0.25	−0.11		−0.31	−0.14	0.19	0.06	−0.57	0.07	0.01	

Abbreviations: SLE = stressful life events (Holmes–Rahe Stress Score); PSS = Perceived Stress Scale score; CORTS = salivary cortisol (fasting morning levels); CORTP: total cortisol in plasma; PRL = prolactin; CRP = C-reactive protein; FIBR = fibrinogen; ALB = albumin.
*$p < 0.05$; **$p < 0.01$.

were associated with an increased risk of developing a psychotic disorder whereas albumin levels had a protective effect on the transition to psychosis (Table 3). These two biomarkers were not associated with ARMS diagnosis in those subjects who did not convert to psychosis.

In the Cox Regression adjusted for sex, cannabis use and antidepressant treatment, we explored whether albumin or prolactin were associated with the time to psychosis transition. When both biomarkers were included in the equation, albumin showed a protective effect (OR = 0.51, 95% Confidence Interval = 0.31–0.84, $p = 0.009$) but not prolactin.

4. Discussion

Our study has important clinical and theoretical implications identifying biomarkers that may be associated with the psychosis transition in vulnerable individuals. In relation to clinical variables, we found that stressful life events were more frequently reported by ARMS subjects who will develop a psychotic disorder, when compared to those without a psychotic transition or with healthy subjects. This result is in accordance with the scientific literature, as described in a recent meta-analysis that suggests that individuals with psychotic disorder/experiences are 3 times more likely than controls to be exposed to recent life events (Beards et al., 2013). ARMS subjects also reported increased perceived stress. This result replicates previous studies that have also reported increased perceived stress in ARMS subjects, when compared to healthy subjects (Pruessner et al., 2011). The implication of two stress-related biomarkers (increased prolactin; reduced albumin) in the risk of developing a psychotic disorder are novel findings. Although some previous studies have explored these biomarkers in individuals with an ARMS (Aston et al., 2010; Montalvo et al., 2014) or a psychotic disorder (Reddy et al., 2003; Garcia-Rizo et al., 2012; Riecher-Rössler et al., 2013) to our knowledge this is the first longitudinal study in ARMS subjects that explores the role of prolactin or albumin related to the psychosis transition. As the determination of prolactin and albumin concentrations in serum can be determined in most clinical laboratories, our results have important clinical implications, because it may help to identify those ARMS subjects who are at a greater risk of developing a psychotic disorder.

Table 3
Results of the multinomial logistic regression.

	ARMS-NP			ARMS-P		
	OR	CI 95%	*p* Value	OR	CI 95%	*p* Value
Age (years)	0.95	0.84–1.08	0.450	0.66	0.44–0.97	0.035
Female gender	0.34	0.1–1.24	0.102	0.43	0.05–4.0	0.459
Stressful life events (Holmes–Rahe score)	1.01	1.0–1.01	0.553	1.01	1.0–1.02	0.158
Prolactin (pmol/L)	1.00	0.999–1.001	0.806	1.002	1.001–1.003	0.036
Albumin (g/L)	0.95	0.81–1.11	0.510	0.74	0.56–0.98	0.033

Abbreviation: ARMS-NP = at-risk mental states without a psychosis transition; ARMS-P = at-risk mental states with a psychosis transition; OR = odds ratio; CI = confidence interval.

In the last years, several studies conducted in drug-naïve ARMS and first psychotic episodes have shown increased prolactin levels (Aston et al., 2010; Garcia-Rizo et al., 2012; Riecher-Rössler et al., 2013). These results underscore that in some cases, hyperprolactinaemia is not due to dopamine-blockade by antipsychotics. As prolactin is a hormone that can be increased by stress (Lennartsson and Jonsdottir, 2011), hyperprolactinaemia in these cases may reflect the stressful state of experiencing prodromal or psychotic symptoms. Moreover, MRI studies have also demonstrated increased pituitary gland volumes in drug-naïve first episode of psychosis (Pariante et al., 2005) and in ARMS subjects who later will develop a psychotic disorder (Garner et al., 2005; Büschlen et al., 2011; Walter et al., 2014). Although pituitary gland enlargement could be also explained by HPA axis hyperactivity, it may also be secondary to the stimulating effect of stress on lactotroph cells. How could hyperprolactinaemia play a role in the psychosis transition? Some authors like Riecher-Rössler have suggested that as enhanced prolactin can increase dopamine release through a feedback mechanism, this pathway could contribute to explaining how stress can trigger a psychotic episode (Riecher-Rössler et al., 2013). There are different dopamine pathways (mesocortical, mesolimbic, nigrostriatal and tuberoinfundibular) and it is not clear whether hyperprolactinaemia may induce dopamine secretion in other pathways besides the tuberoinfundibular tract. This important question, as increased dopamine in the mesolimbic system has been hypothesized to induce psychosis, may be solved by future animal studies studying this topic, but right now the mechanistic pathways by which hyperprolactinaemia contributes to the risk of developing a psychotic disorder remains a plausible but speculative point.

The contribution of hyperprolactinaemia to the psychosis transition is compatible with the known role of the HPA axis. In fact, it has been suggested that prolactin and cortisol are hormones of two distinct, and alternative, coping strategies to psychosocial stress (Sobrinho, 2003): prolactin linked with the evocation of humiliating experiences, and cortisol related to surprise and shock. The finding of significant differences in baseline cortisol secretion pattern after awakening in those ARMS subjects who later will develop a psychotic disorder is in accordance with

previous reports linking HPA axis abnormalities in ARMS subjects (Sugranyes et al., 2012) and the risk of psychosis transition (Walker et al., 2013). In our study we did not find significant differences in morning salivary cortisol concentrations obtained at the clinical facility, as differences were observed in cortisol levels after awakening. The increase in cortisol levels after awakening is an HPA axis measure that reflects the reactivity of the HPA axis system (Pruessner et al., 2003), that has been suggested to be one of the mechanistic roles linking stress to psychosis (Walker and Diforio, 1997). Clearly, future prospective studies should replicate our findings with larger samples, as the cortisol awakening response, particularly the cortisol rise between 0 and 30′, may be considered a useful biomarker for the prediction of a psychosis transition.

The potential role of reduced albumin levels in the risk of developing a psychotic disorder has received little attention in the literature. Only a few studies have compared albumin levels between subjects with schizophrenia and healthy subjects, finding reduced levels in first episodes of schizophrenia (Reddy et al., 2003; Pae et al., 2004) and chronic schizophrenia (Yao et al., 2000; Huang, 2002). There are no studies addressing whether albumin may be a predictor of psychosis transition in ARMS subjects. For this reason, our results need to be replicated in other samples before drawing definite conclusions. Albumin levels may be influenced by protein intake, but in our sample this was not the case because ARMS-P subjects reported greater calorie intake without lower intake of protein. Oxidative stress and free-radical mediated neurotoxicity are implicated in the pathogenesis of schizophrenia (Prabakaran et al., 2004; Yao et al., 2004). An abnormal metabolic response to oxidative stress has been also reported in early psychosis patients (Fournier et al., 2014). As albumin has free-radical trapping properties and is the major plasma target of oxidant stress (Roche et al., 2008), the reduction of albumin levels in those ARMS individuals who later will develop a psychosis may indicate an impaired antioxidant mechanism in these individuals.

Some limitations of our study need to be acknowledged. The small sample size, particularly in the ARMS-P group, may limit the statistical power to detect small differences in some biomarkers (e.g. morning salivary cortisol) between groups. However, the sample size was adequate for detecting larger differences (e.g. prolactin or albumin levels) or for detecting differences over time with a repeated measures analysis (e.g. CAR). A substantial proportion of ARMS subjects (about 38%) did not return the home-collected Salivettes and the CAR could not be calculated in the whole sample. Only 6 ARMS-P subjects had available data for the CAR. For this reason we did not include CAR in multivariate analysis exploring psychosis transition as the dependent variable (logistic regression or survival analyses). For this same reason in the multinomial logistic regression model we only included three covariates (age, gender, stressful life events) that were theoretically guided. We did not include more covariates because we wanted to ensure the stability of the model, and limit the number of independent variables because the number of ARMS subjects with a psychosis transition was low. In the CAR analysis, BMI was also considered a covariate because obesity is associated with a blunted CAR (Champaneri et al., 2013). Samples were obtained in a clinical setting that may be considered a stressful environment for some participants. However, both clinical assessment and collection of biological samples were conducted at the Early Intervention Service, an outpatient mental health care center where patients had frequent appointments, so this environment is not novel. We decided to include a fasting morning blood sample because in the clinical practice patients are monitored for metabolic parameters that include glucose and lipid profile. We also included a fasting salivary sample because previous studies in ARMS subjects had reported an association between salivary cortisol collected at the clinical setting and the risk of psychosis transition (Walker et al., 2013). We did not repeatedly assess stress biomarkers in ARMS subjects that could demonstrate longitudinal changes in prolactin or albumin between those ARMS subjects with or without a transition to psychosis. However, in spite of these limitations, our study has several strengths, as being the first prospective study to explore the relationship of prolactin or albumin in a cohort of ARMS subjects, controlling for dietary habits (protein intake), or including an age and gender matched control group of healthy subjects. Most ARMS subjects were antipsychotic naïve, and prolactin and albumin results were also found to be significant after excluding those subjects on antipsychotics.

In summary, our study suggests that different stress-related biomarkers (cortisol awakening response, increased prolactin, reduced albumin) are associated with the risk of developing a psychotic disorder in ARMS individuals. Further studies that aim to identify stress-related biochemical parameters that are associated with the risk of psychosis, need to consider these biomarkers as potential candidates.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2014.10.011.

Contributors

Javier Labad and Alfonso Gutiérrez-Zotes designed the study and wrote the protocol. Javier Labad performed the statistical analysis. Javier Labad wrote the first draft of the manuscript, which was supervised by Rebecca M. Reynolds. Irene Moreno and Alexander Stojanovic-Pérez managed the literature searches. Laura Ortega and Alexander Stojanovic-Pérez participated in the collection and processing of biological samples. Alexander Stojanovic-Pérez, Elisabet Vilella and Lourdes Martorell participated in the laboratory procedures and discussion of stress biomarkers. Itziar Montalvo, Montse Solé, Ángel Cabezas and Irene Moreno participated in the recruitment and obtained clinical data including psychiatric interviews. All authors contributed to and have approved the final manuscript.

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Conflict of interest

Javier Labad and Itziar Montalvo have received honoraria for lectures or advisory boards from Janssen-Cilag, Otsuka or Lundbeck. The rest of the authors have no biomedical financial interests or potential conflicts of interest.

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Corrigendum

Corrigendum to "Stress biomarkers as predictors of transition to psychosis in at-risk mental states: Roles for cortisol, prolactin and albumin" [J. Psychiatr. Res. 60 (2015) 163–169]

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The authors regret to inform that in the previously published article there is an error in Table 1. The mean (standard deviation) morning salivary cortisol levels (nmol/L) of the three groups should read: 25.4 (10.9) for healthy subjects, 25.5 (10.9) for at-risk mental states without a psychosis transition (ARMS-NP) and 32.4 (17.9) for at-risk mental states with a psychosis transition (ARMS-P). The p value for the one-way ANOVA comparing morning salivary cortisol levels among diagnostic groups is correct. All other statistical analyses in the article regarding salivary cortisol are also correct. This error does not change the interpretation of the results or conclusions.

The authors would like to apologise for any inconvenience caused.

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Table 1SM. Methodological information of sampling and laboratory determination of plasma and salivary stress biomarkers.

Measure	Fluid	Time of sampling	Location of sampling	Assay information (technique and manufacturer)
Blood measures (fasting conditions)				
Total cortisol	Serum	8:30h - 9:30h	EIS	Maglumi 2000 Analyzer chemiluminescence immunoassay system (SNIBE Co, Ltd, Guandong, China).
Prolactin	Serum	8:30h - 9:30h	EIS	Maglumi 2000 Analyzer chemiluminescence immunoassay system (SNIBE Co, Ltd, Guandong, China). Assay sensitivity: 77 pmol/L.
Albumin	Serum	8:30h - 9:30h	EIS	Photometric colorimetric method using bromocresol green (Human Gesellschaftfür Biochemica und Diagnostica mbH, Wiesbaden, Germany).
Fibrinogen	Plasma	8:30h - 9:30h	EIS	Clauss method; Gernon Hemofibrin L Kit (RAL Técnica para el Laboratorio, S.A., Sant Joan Despí, Barcelona, Spain)
hs-CRP	Serum	8:30h - 9:30h	EIS	Immunoturbidimetry; Menarini Diagnostics Full Range CRP assay (Menarini Diagnostics, S.A., Badalona, Barcelona, Spain)
Salivary measures				
Morning cortisol (fasting conditions)	Saliva	8:30h - 9:30h	EIS	Chemiluminescence immunoassay (IBL, Hamburg, Germany).
Cortisol awakening response	Saliva	Awakening, 30' and 60' post-awakening	Home	Chemiluminescence immunoassay (IBL, Hamburg, Germany).

Abbreviations: EIS= Early Intervention Service; hs-CRP= High-sensitivity C-reactive protein

3.3. Publicación 3 - Research Letter

The relationship between antidepressant treatment and inflammatory markers in early psychosis: preliminary results.

Stojanovic-Pérez A, Martorell L, Montalvo I, Ortega L, Solé M, Moreno I, Vilella E, Labad J.

Psychopharmacology. 2016 Oct;233(19-20):3659-61.
DOI: 10.1007/s00213-016-4413-8

IF: 3,540

Antecedentes

Recientemente se ha propuesto que los fármacos antidepresivos pueden tener un posible efecto antiinflamatorio. Los síntomas depresivos son prevalentes en sujetos con un TPI y el tratamiento adyuvante con antidepresivos es pertinente. Sin embargo, el uso de este tipo de fármacos ha sido escasamente explorado en sujetos con psicosis incipiente, al igual que la asociación entre el uso de fármacos antidepresivos e inflamación.

Aportes

Este es el primer estudio que explora la relación entre biomarcadores de inflamación (IL-6, CRP ultrasensible [hs-CRP] y fibrinógeno) y el uso de antidepresivos en la psicosis temprana.

Aspectos a destacar

Se confirma nuestra hipótesis de que el tratamiento antidepresivo está asociado con niveles reducidos de hs-CRP y fibrinógeno en pacientes con psicosis temprana Sin embargo, la relación causal entre síntomas depresivos e inflamación no pudo ser explorada dado el carácter transversal del estudio.

Psychopharmacology (2016) 233:3659–3661
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LETTER TO THE EDITOR

The relationship between antidepressant treatment and inflammatory markers in early psychosis: preliminary results

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Dear Editor,

Several studies have reported increased blood and CNS concentrations of inflammatory cytokines in patients with schizophrenia (Potvin et al. 2008; Miller et al. 2011). Recently, it has been proposed that antidepressants may possess central and peripheral anti-inflammatory properties (Daniele et al. 2015). Hereof, specific serotonin reuptake inhibitors (SSRIs) decrease peripheral levels of pro-inflammatory mediators IL-1β, CRP, and possibly IL-6 in patients with major depression (Hannestad et al. 2011; Hiles et al. 2012). IL-6 induces acute-phase proteins such as C-reactive protein (CRP) and fibrinogen. In a recent meta-analysis, IL-6 was significantly increased in acutely relapsed inpatients and in patients experiencing their first episode of psychosis, suggesting a possible state and trait-related marker association in schizophrenia (Miller et al. 2011). Likewise, elevated serum CRP and plasma fibrinogen levels have been reported in schizophrenia (Miller et al. 2014; Ding et al. 2015) and major depressive disorder (MDD) patients (Wium-Andersen et al. 2013b). Recently, abnormal hs-CRP levels (>3 mg/L) were associated with antidepressant treatment in non-depressed stable schizophrenia patients, with an illness duration of approximately 10 years (Fond et al. 2016).

Although depressive symptoms are highly prevalent (17–83 %) among first-episode psychosis patients (Sönmez et al. 2014), only one study has explored the use of adjunctive antidepressants in prodromal schizophrenia patients, reporting improved medication compliance, reduced positive symptoms, and no transitions to psychosis in the antidepressant-treated patients compared with a 45 % transition rate in the non-antidepressant-treated group (Cornblatt et al. 2007). Thus, antidepressants may be an optimal treatment strategy in prodromal stages, by lowering the vulnerability to illness through the reduction of trigger states (e.g., stress, anxiety, and depression). There is scarce information about the association between depressive symptoms and inflammatory markers in patients with prodromal schizophrenia. Moreover, it is not known whether antidepressant treatment reduces the levels of inflammatory markers in these patients. Given the hypothesis that antidepressant treatment is associated with a reduction in the levels of inflammatory markers, we explored this relationship in patients with a psychotic disorder at the early stages of the illness.

We conducted a cross-sectional study with 77 clinically stable early psychosis (EP) patients and 25 healthy controls (HC) as described previously (Stojanovic et al. 2014). The DSM-IV diagnoses for EP patients were as follows: schizophreniform disorder (n = 19), schizophrenia (n = 12), schizoaffective disorder (n = 10), and psychotic disorder not otherwise specified (n = 36). EP patients were divided into

Electronic supplementary material The online version of this article (doi:10.1007/s00213-016-4413-8) contains supplementary material, which is available to authorized users.

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Table 1 Demographic and clinical characteristics by diagnostic group

	HC subjects (n = 25)	EP patients without AD (n = 65)	EP patients with AD (n = 12)	Statistic‡	df	ANOVA P value	ANCOVA§ P value
Demographic characteristics							
Age (years)	27.3 (4.2)	23.9 (4.7)	26.6 (4.6)	5.70	3	*0.005*[c]	
Female gender, n (%)	13 (52.0)	25 (38.5)	4 (33.3)	1.72	2	0.425	
BMI (kg/m^2)	21.6 (2.5)	24.6 (4.7)	23.2 (3.2)	4.89	3	*0.010*[c]	
Inflammatory markers							
IL-6 (pg/mL)[a]	0.3 (1.3)	0.5 (2.4)	0.3 (1.0)	3.96	3	*0.037*[c]	0.244
hs-CRP (mg/L)[a]	0.5 (6.3)	1.2 (22.9)	0.3 (1.5)	7.61	3	*0.001*[c,e]	*0.001*
Fibrinogen (mg/L)	257.2 (47.3)	266.2 (68.0)	231.4 (35.1)	1.70	3	0.188	*0.010*
Clinical characteristics							
PANSS positive		10.6 (4.3)	12.9 (7.4)	2.18	2	0.144	
PANSS negative		14.6 (7.6)	16.1 (5.6)	0.39	2	0.534	
PANSS general		27.6 (9.0)	36.7 (9.4)	10.04	2	*0.002*	
YMRS		5.4 (7.5)	5.8 (5.9)	0.02	2	0.876	
HDRS		7.1 (6.9)	16.3 (9.6)	15.48	2	*<0.001*	
CDSS		2.0 (3.8)	4.8 (5.5)	4.57	2	*0.036*	
Psychiatric history							
Duration of antipsychotic treatment (weeks)		16.6 (15.8)	3.0 (2.2)	3.87	2	0.053	
Duration of illness (weeks)		29.3 (30.1)	11.7 (16.2)	8.79	2	*0.004*	
Duration of untreated psychosis (weeks)[b]		12.7 (28.1)	8.7 (16.0)	0.23	2	0.635	
Tobacco consumption (cigarettes/day)	1.2 (3.2)	10.3 (10.0)	13.0 (11.9)	10.61	3	*<0.001*[c,d]	
Daily alcohol intake (standard units/day)	0.08 (0.4)	0.8 (2.3)	1.1 (2.1)	1.39	3	0.254	
Cannabis consumption (joints/day)	0 (0)	1.6 (4.5)	3.6 (4.5)	3.53	3	*0.033*[d]	
Antipsychotic treatment							
None, n (%)		15 (23.1)	1 (8.3)	1.48	2	0.477	
Monotherapy, n (%)		43 (66.2)	9 (75.0)				
Polytherapy, n (%)		7 (10.8)	2 (16.7)				
Antidepressant treatment							
Selective serotonin reuptake inhibitors, n (%)			6 (50)				
Serotonin-norepinephrine reuptake inhibitors, n (%)			3 (25)				
Noradrenergic and specific serotonergic, n (%)			1 (8.3)				
Polytherapy, n (%)			2 (16.7)				

All variables except IL-6 and hs-CRP are presented in mean (SD), or n (%). Significant p values (p<0.05, two-sided) are shown in italics

HC healthy control, *EP* early psychosis, *df* degrees of freedom, *AD* antidepressants, *BMI* body mass index, *IL-6* interleukin-6, *hs-CRP* high-sensitivity C-reactive protein, *PANSS* Positive and Negative Syndrome Scale, *YMRS* Young Mania Rating Scale, *HDRS* Hamilton Depression Rating Scale, *CDSS* Calgary Depression Scale for Schizophrenia

‡ Chi-square (comparison of categorical variables) or F (comparison of continuous variables)

§ An ANCOVA analysis was conducted for all inflammatory markers. This analysis was conducted only in patients (EP without AD vs. EP with AD). The following covariables were included in the ANCOVA analyses: age, gender, substance use (tobacco, cannabis, and alcohol), BMI, duration of antipsychotic treatment

[a] As IL-6 and hs-CRP were skewed, median (range) values are presented. In the ANOVA and ANCOVA analysis, these variables were log transformed (ln)

[b] Duration of untreated psychosis was defined as the time between the onset of psychotic symptoms and the initiation of the first antipsychotic treatment

[c] Significant ANOVA post hoc analyses (comparison between all groups) with Bonferroni adjustment: HC vs. EP without AD

[d] Significant ANOVA post hoc analyses (comparison between all groups) with Bonferroni adjustment: HC vs. EP with AD

[e] Significant ANOVA post-hoc analyses (comparison between all groups) with Bonferroni adjustment: EP without AD vs. EP with AD

two subgroups depending on whether they received antidepressants ($n = 12$ and $n = 65$, respectively). None of the HC subjects were receiving antidepressants. Approval was obtained from the local ethics committee, and all of the participants provided written informed consent. Depressive symptoms were evaluated using the Hamilton Depression Rating Scale (HDRS) and the Calgary Depression Scale for Schizophrenia (CDSS). Finally, we measured serum interleukin (IL)-6, high-sensitivity C-reactive protein (hs-CRP), and plasma fibrinogen following the methodology described earlier (Stojanovic et al. 2014).

The demographic and clinical characteristics for each diagnostic group are presented in Table 1. The antidepressant-treated EP patients had lower hs-CRP levels when compared with the EP patients not treated with antidepressants and the HC subjects (see also Fig. 1 from Supplementary Material). No differences were found in IL-6 levels. We conducted an analysis of covariance in EP patients for all inflammatory markers while adjusting for age, gender, substance use, BMI and duration of antipsychotic treatment. In this multivariate analysis, both hs-CRP and fibrinogen were significantly lower in patients receiving antidepressants. In the correlation analysis exploring the relationship between inflammatory markers and depressive symptoms (HDRS and CDSS scores), no significant associations were found. The adjustment of antidepressant treatment with a partial correlation analysis did not change the results. Depressive symptoms were inversely associated with the duration of treated illness ($r = -0.27$, $p = 0.020$ for CDSS; $r = -0.35$, $p = 0.004$ for HDRS).

Some limitations of our study need to be acknowledged. As our group of antidepressant-treated EP patients was small ($n = 12$) and uneven, we may lack the statistical power for detecting significant differences in IL-6 levels between EP patients treated or untreated with antidepressants. Those EP patients treated with antidepressants showed higher HDRS and CDSS scores and had a shorter duration of illness. A potential selection bias may exist, mainly for those EP patients receiving antidepressants, as dysphoric mood at early stages of the psychotic illness could induce clinicians to prescribe antidepressant treatment. A high risk for psychosocial distress has been associated with elevated levels of hs-CRP in the general population (Wium-Andersen et al. 2013a). Although we would have expected to find an association between mood symptoms and inflammation, that was not the case in our sample. The relationship between mood symptoms and inflammation may be obscured by antidepressant treatment. The cross-sectional design of our study limits the possibility of inferring causal associations and does not allow to explore whether improvement in dysphoria by antidepressants is followed-up by a reduction in inflammatory markers. Future longitudinal studies may address these limitations.

In summary, our study confirmed our hypothesis that low levels of hs-CRP and fibrinogen are associated with antidepressant treatment in EP patients. It remains to be established in future research, which is the possible explanation of the present results.

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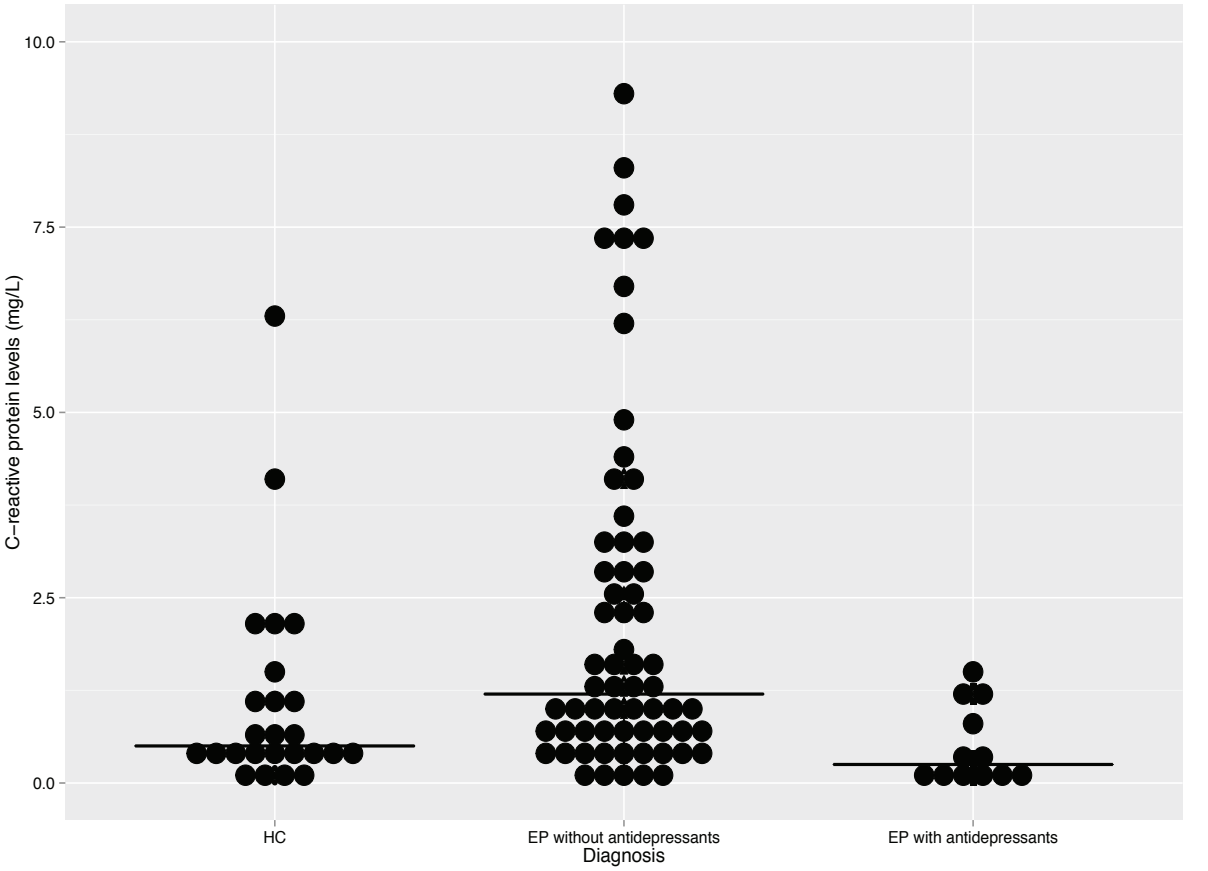
Supplementary Material Figure 1 Serum C-reactive protein levels (mg/L) by diagnostic group.



Dots represent individual observations. Lines represent the median value for each subgroup.

DISCUSIÓN

4.1. Aumento de los niveles séricos de IL-6 en sujetos EMAR

El primer estudio de esta tesis doctoral (Stojanovic et al., 2014) exploró la posible activación del proceso inflamatorio en el inicio de la psicosis. Los sujetos EMAR y los pacientes con un TPI presentaron niveles séricos de IL-6 elevados comparados con los controles sanos. Estos resultados coinciden con los metanálisis publicados por Miller y Potvin (B J Miller et al., 2011; Potvin et al., 2008) y reafirman la hipótesis de que existe un proceso inflamatorio activo en sujetos con psicosis temprana, especialmente en aquellos con alto riesgo para psicosis.

Es interesante destacar que nuestros resultados han sido confirmados por otros autores recientemente. Zeni-Graiff y colaboradores (Zeni-Graiff et al., 2016) han identificado niveles séricos aumentados de IL-6 y reducidos de IL-17 en un grupo de 12 sujetos UHR, comparados con 16 controles sanos. Esto indica que una respuesta inflamatoria activada se asocia con la neurobiología de la psicosis en los sujetos EMAR. Estos autores proponen como posible mecanismo fisiopatológico la activación de células Th17, las cuales promueven un aumento de la permeabilidad de la barrera hematoencefálica y la activación de procesos inflamatorios a nivel del SNC (Kebir et al., 2007).

Nuestro estudio ha identificado un aumento de los niveles de IL-6 en suero y es destacable que las alteraciones en los niveles de IL-6 también han sido descritas a nivel central en un estudio que analizó el líquido cefalorraquídeo (LCR) 15 sujetos EMAR, 46 pacientes con esquizofrenia y 35 controles sanos, evaluando más de 90 moléculas relacionadas con el sistema inmune y la inflamación, además de la presencia de anticuerpos contra el *Toxoplasma gondii* (TG) y el virus del herpes simple (Hayes et al., 2014). Identificaron una reducción en los niveles de fibrinógeno y del receptor de la IL-6 (IL-6R) en los pacientes con esquizofrenia y una reducción aún más pronunciada en el grupo de sujetos EMAR comparados con los controles sanos, lo que sugiere posibles cambios de tipo rasgo asociados con la psicosis en general. Por otro lado, observaron un aumento substancial en los niveles de IL-6R en los pacientes con esquizofrenia y una reducción discreta en los sujetos EMAR, en comparación con

los controles sanos. Todas las diferencias observadas fueron significativas. Los cambios moleculares (fibrinógeno e IL-6R, entre otros) específicos para el grupo de sujetos EMAR y pacientes con esquizofrenia, comparados con controles sanos, constituyen posibles biomarcadores de rasgo. En cambio, otros podrían servir para identificar a los sujetos en periodo prodrómico de la enfermedad, es decir, serían específicos para sujetos EMAR. Curiosamente, la reducción de los niveles de IL-6R en sujetos EMAR se correlacionó con la presencia de anticuerpos contra el TG en LCR. El descenso del IL-6R es un indicio de la producción activa de IL-6 dentro del SNC. Su disminución en los sujetos EMAR nos señala de manera indirecta la presencia de un proceso inflamatorio activado de mayor intensidad.

Aunque se observó un aumento estadísticamente no significativo de los niveles de IL-6 en los sujetos EMAR-P en comparación con los EMAR-NP, posiblemente producto del pequeño tamaño de la muestra (escaso poder estadístico), dicha observación nos permitiría proponer este aumento de la IL-6 como un posible marcador de transición a psicosis. Por otro lado, a pesar de que los niveles de IL-6 en el grupo EMAR-P son más elevados que los del grupo EMAR-NP, dichos niveles son cuantitativamente muy bajos (no muy diferentes de los observados en controles sanos) y representan quizás un estado pro-inflamatorio de bajo grado en los sujetos con alto riesgo de psicosis.

En este sentido, varios autores han intentado identificar marcadores de transición a psicosis en sujetos UHR, como en el estudio doble ciego, randomizado y controlado con placebo durante 12 semanas de Föcking y colaboradores, en el que investigaron un grupo de 39 sujetos EMAR, a fin de valorar el posible efecto de los ácidos grasos poliinsaturados de cadena larga omega-3 sobre distintos marcadores de inflamación y su capacidad de prevenir la transición a psicosis (Föcking et al., 2016). Estos investigadores identificaron que la IL-12/23 es como un potencial biomarcador de transición a psicosis en sujetos con alto riesgo, pero no confirmaron los cambios observados en nuestro estudio en la IL-6 ni observaron diferencias en otros 39 marcadores de neuroinflamación.

Cabe destacar también un estudio longitudinal prospectivo, con una cohorte de 4500 niños, que evaluó si los niveles elevados de IL-6 y CRP en la infancia se asociaban con un

aumento del riesgo futuro de desarrollar depresión o psicosis (Khandaker et al., 2014). Para ello midieron los factores inflamatorios a los 9 y a los 18 años de edad, además de determinar la presencia de depresión, experiencias psicóticas o un trastorno psicótico al final del periodo de estudio. Encontraron que el riesgo de desarrollar experiencias psicóticas o un trastorno psicótico en la edad adulta se incrementó con niveles elevados de IL-6 en la infancia en forma dosis dependiente.

Niveles séricos elevados de IL-2 e IL-6 han sido descritos en un grupo de TPI sin tratamiento antipsicótico comparados con sujetos control. Se ha propuesto que estos cambios podrían estar relacionados con la sensibilización dopaminérgica, reducción del volumen del hipocampo y alteraciones en la neurotransmisión glutamatérgica; mecanismos fisiopatológicos propuestos en la esquizofrenia (Petrikis et al., 2015).

En cuanto a la relación entre los biomarcadores de inflamación y las características clínicas de los sujetos, nuestro estudio observó que los niveles aumentados de IL-6 se correlacionaron positivamente con la sintomatología psicótica negativa en EMAR y TPI, de igual manera con la sintomatología psicótica positiva en EMAR y se correlacionaron negativamente con los síntomas positivos en TPI. Un estudio reciente también ha identificado que los niveles de ARN mensajero en leucocitos polimorfonucleares de sangre periférica presentaban una correlación positiva con la sintomatología psicótica positiva, en pacientes con esquizofrenia (Chase et al., 2016).

Diversos estudios, incluido el nuestro, han identificado que la IL-6 está aumentada en las fases iniciales de la psicosis. En la búsqueda de posibles mecanismos de intervención se ha propuesto que los ácidos grasos poliinsaturados omega-3 podrían disminuir los niveles de marcadores inflamatorios (Smesny et al., 2017). Finalmente, también cabe destacar la vía del ácido quinunérico, producto del metabolismo del triptófano que actúa como agente antiexcitotóxico y modulador de las vías colinérgica y dopaminérgica, puesto que su expresión está críticamente regulada por citoquinas pro-inflamatorias entre las cuales destaca la IL-6, cuya reducción a nivel del SNC se propone como una posible aproximación terapéutica a explorar en futuras investigaciones, que en la actualidad solo tienen soporte experimental (Erhardt et al., 2017).

4.2. Biomarcadores de estrés e inflamación y transición a psicosis

En la segunda publicación que integra esta tesis doctoral (Labad et al., 2015a, 2015b) nos propusimos conocer la relación que existe entre el estrés psicológico, los biomarcadores de estrés e inflamación y la transición a un TPI en una muestra de sujetos EMAR.

Encontramos que los sujetos EMAR reportaron más frecuentemente eventos vitales estresantes al igual que manifestaron un aumento del estrés percibido, lo cual está en concordancia con la literatura científica (Beards et al., 2013; Pruessner et al., 2017).

Es un hallazgo novedoso el hecho de demostrar la participación de biomarcadores relacionados con el estrés (prolactina) y la inflamación (albúmina) en el riesgo de desarrollar un TPI, especialmente por sus implicaciones clínicas, pues nos permitirían identificar aquellos sujetos EMAR con mayor riesgo de transición a psicosis. Adicionalmente, en los análisis de regresión logística multinomial, los niveles de prolactina inicial se asociaron con un aumento del riesgo de desarrollar un TPI, mientras que los de albúmina mostraron un efecto protector. Finalmente, el análisis de supervivencia ajustado por género, uso de cannabis y tratamiento antidepresivo, después de incluir a la albúmina y la prolactina en la ecuación, demostró que la albúmina a diferencia de la prolactina, mostró un efecto protector. Dicho de otra manera, la albúmina se asoció con una transición tardía a psicosis.

El mecanismo mediante el cual la prolactina contribuye al riesgo de transición sigue siendo un punto de controversia en la literatura. Sin embargo, un reciente artículo de revisión (Riecher-Rössler, 2017) propone que nuestros hallazgos refuerzan la hipótesis del estrés-prolactina-dopamina. Esta hipótesis, altamente especulativa, lleva a Riecher-Rössler a afirmar que el aumento de la prolactina en respuesta al estrés, podría estimular la liberación de dopamina, a través de un mecanismo de retroalimentación positiva que involucra la vía dopaminérgica tuberoinfundibular, promoviendo la aparición de síntomas psicóticos, al menos en un subgrupo de sujetos susceptibles (Riecher-Rössler and Studerus, 2017).

Con relación al cortisol, nuestro estudio no identificó diferencias significativas en los niveles de cortisol basal, tanto en suero como en saliva. Dicha observación no está en concordancia con un reciente metanálisis en el cual se analizaron ocho estudios independientes con un total de 1060 participantes (504 sujetos UHR y 457 controles sanos), entre los cuales se incorporó nuestro estudio. El metanálisis reveló un aumento significativo de los niveles de cortisol en saliva basales entre sujetos con UHR comparados con controles sanos, pero no entre pacientes con primeros episodios psicóticos y controles sanos (Chaumette et al., 2016).

Por otro lado, en relación a los niveles de cortisol en saliva y la CAR, la interacción observada entre tiempo y grupo diagnóstico reveló que los sujetos EMAR que hicieron la transición a psicosis (EMAR-P) presentaron niveles basales de cortisol más bajos y un incremento mayor al minuto 30 del despertar, comparados con los EMAR-NP o los controles sanos. Estos resultados manifiestan una clara hiperactividad del eje HHS en los EMAR-P, en concordancia con estudios previos que relacionan alteraciones del eje HHS con el riesgo de transición a psicosis en sujetos EMAR (Sugranyes et al., 2012; Walker et al., 2013).

Sin embargo, a pesar de que existen controversias con relación a estas observaciones, nuestros hallazgos coinciden con un reciente metanálisis que incluyó 11 estudios y 879 participantes (entre los que se encontraba nuestro grupo de estudio), y demostró la existencia de una CAR atenuada en pacientes con esquizofrenia y primeros episodios psicóticos, mas no sujetos EMAR (Berger et al., 2016). Estas alteraciones diferenciales en la función del eje HHS podrían reforzar el valor de la CAR como biomarcador con valor predictivo, aunque otros estudios no repliquen esta observación (Day et al., 2014), debido quizás a diferencias individuales, situacionales y metodológicas, como por ejemplo: a) la naturaleza de los eventos estresantes, b) el diseño del estudio, c) el tratamiento psicofarmacológico (especialmente los antipsicóticos atípicos y los antidepresivos), d) los factores sociodemográficos (por ejemplo, ser de raza negra y nivel socioeconómico bajo), y e) el género de los participantes (Pruessner et al., 2017).

En este sentido, en nuestro estudio la proporción de mujeres fue del 24,1% en los EMAR-NP, 50% en los EMAR-P y 34,9% en los controles sanos. En el caso de Day y colaboradores, la proporción de mujeres fue del 46,2% en sujetos UHR y 40,5% en controles sanos. La hipótesis del estrés-prolactina-dopamina (Riecher-Rössler, 2017) propone que las diferencias de género podrían explicar la asociación entre el inicio/ recaída de las psicosis en mujeres y aquellos periodos en los cuales la mujer presenta grandes fluctuaciones en las hormonas sexuales o la prolactina (adolescencia, postparto y perimenopausia).

Además de los mencionados, existen otros factores que posiblemente expliquen las diferencias existentes entre estudios tales como: el momento de la toma de muestras (matutina o a lo largo del día), el patrón y frecuencia de las determinaciones (única o repetida), el lugar de obtención de la muestra (domicilio o laboratorio), procedencia de la muestra (saliva o sangre), la toma adecuada de muestras, o las características fenotípicas de los sujetos (grupo de riesgo genético, estadio de la enfermedad o género) (Pruessner et al., 2017).

Cabe destacar que recientemente se ha revisado el modelo de estrés-diátesis de la esquizofrenia, con implicaciones importantes en cuanto al estudio adecuado de la función del eje HHS, siguiendo guías de consenso para la mejor valoración de estos marcadores. De igual manera, este modelo ampliado plantea la normalización del funcionamiento del eje HHS como una interesante aproximación terapéutica en poblaciones con UHR. Finalmente, exhorta al diseño de estudios de intervención no farmacológica especialmente orientados hacia la reducción del estrés y la normalización de la función del eje HHS, a través de terapia cognitivo-conductual, psicoeducación familiar, entrenamiento en el auto-manejo de la enfermedad y el entrenamiento en habilidades sociales (Pruessner et al., 2017).

4.3. Marcadores inflamatorios y tratamiento antidepresivo

Los procesos inflamatorios no han sido descritos únicamente en el inicio de los trastornos psicóticos. Durante los últimos años se ha acumulado evidencia a favor, también, de la existencia de un proceso inflamatorio activado en la depresión y que posiblemente los antidepresivos podrían ejercer su acción terapéutica a través de mecanismos antiinflamatorios (Kohler et al., 2016; Więdłocha et al., 2017). En el tercer trabajo de esta tesis (Stojanovic-Pérez et al., 2016) hemos propuesto que los síntomas psicóticos positivos, tratados con antipsicóticos en pacientes con TPI, frecuentemente se acompañan de depresión y ansiedad. Sin embargo, el uso de antidepresivos ha sido escasamente explorado en pacientes con TPI, al igual que tampoco la posible asociación entre tratamiento antidepresivo e inflamación.

Nuestro estudio confirmó la hipótesis de que niveles reducidos de hs-CRP se asocian con el tratamiento antidepresivo en pacientes con TPI. En el análisis multivariable, tanto la hs-CRP como el fibrinógeno presentaron niveles significativamente más bajos en pacientes TPI que recibieron tratamiento antidepresivo. Finalmente, los síntomas depresivos se asociaron negativamente con la duración de la enfermedad tratada.

Es necesario mencionar algunas de las limitaciones de nuestro estudio: en primer lugar dado el reducido tamaño de la muestra, los resultados están influidos por una reducción del poder estadístico. Sería interesante abordar el estudio de estas variables con una muestra lo suficientemente amplia que nos permita valorar distintos grupos fenotípicos dentro del espectro de pacientes con un TPI, pues es posible que los antidepresivos sean utilizados más frecuentemente en etapas más tempranas de los trastornos psicóticos cuando la ansiedad y la disforia pueden coexistir. Sin embargo, en nuestro estudio hemos ajustado los análisis en función de la duración del tratamiento antipsicótico, sin observar cambios significativos en nuestros hallazgos.

Por otro lado, se sabe que el tratamiento antipsicótico puede suprimir al sistema inmune y modificar perfiles de citoquinas específicas en pacientes con un TPI (Borovcanin et al., 2013), por lo que se podría hipotetizar que los niveles aumentados

de CRP en el grupo de pacientes que no recibían tratamiento con antidepresivos podría deberse al uso de antipsicóticos. Sin embargo, en el grupo de pacientes con tratamiento antidepresivo había más pacientes que recibían tratamiento con antipsicóticos (92%) que en el grupo de pacientes sin tratamiento antidepresivo (77%). Por consiguiente, podemos afirmar que la reducción en los niveles de CRP no estaba influida por el posible uso de antipsicóticos. Es interesante resaltar que un metanálisis reciente reafirma esta última observación, es decir, que los niveles de CRP en pacientes con esquizofrenia o un primer episodio psicótico no aumentan tras el inicio del tratamiento antipsicótico (Köhler et al., 2017).

Probablemente, nuestro estudio es el único en este ámbito por lo reciente de su publicación, pero los resultados ponen de manifiesto que es necesario realizar más investigación en esta dirección.

En este sentido, un diseño longitudinal podría resolver algunas de estas limitaciones observadas en el estudio de pacientes con TPI y síntomas depresivos. Además, la relación entre síntomas depresivos e inflamación podría ser estudiada previo al inicio del tratamiento con antidepresivo, y la reducción de los marcadores inflamatorios por los antidepresivos podría ser explorada mediante un diseño prospectivo.

CONCLUSIONES

1. Los sujetos EMAR y los pacientes con un TPI presentan niveles elevados de IL-6 compatible con la existencia de un proceso inflamatorio en las fases prodrómicas e incipientes de los trastornos psicóticos.

2. Existe una asociación entre la sintomatología psicótica negativa y los niveles séricos de IL-6 tanto en sujetos EMAR como en pacientes con un TPI. Los niveles séricos de IL-6 se correlacionan positivamente con los síntomas negativos.

3. Existe una asociación negativa entre la sintomatología psicótica positiva y los niveles séricos de IL-6 en pacientes con un TPI, mientras que dicha asociación fue positiva en sujetos EMAR. Los niveles séricos de IL-6 y la sintomatología positiva se correlacionan negativamente en pacientes con un TPI y positivamente en sujetos EMAR.

4. La variante genética rs1800795 no influye en los niveles séricos de IL-6, ni es un factor de riesgo para el desarrollo de psicosis.

5. La IL-6 es un posible candidato a biomarcador de transición a psicosis en los periodos iniciales de la enfermedad.

6. Los niveles bajos de hs-CRP y fibrinógeno se asocian con el tratamiento antidepresivo en pacientes con un TPI.

7. La presencia de eventos estresantes vitales y el nivel de estrés percibido es mayor en los sujetos EMAR-P que en sujetos EMAR-NP y sujetos control.

8. Los niveles de prolactina son mayores en sujetos EMAR-P que en sujetos EMAR-NP y sujetos control.

9. Diferentes biomarcadores relacionados con el estrés (CAR, aumento de la prolactina y reducción de la albúmina) se asocian con el riesgo de transición a psicosis en sujetos EMAR.

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La esquizofrenia es un trastorno mental grave, de consecuencias devastadoras, que afecta cómo una persona piensa, siente y actúa. Tiene un gran impacto en la salud de la población y se debe intervenir cuanto antes, ya que el tiempo de psicosis sin tratar conduce a peor evolución. Se desconoce su origen preciso, pero estos pacientes muestran marcadores inflamatorios y prolactina aumentados, además de desregulación del eje hipotálamo-hipófisis-suprarrenal. Frente al diagnóstico fundamentalmente clínico, es perentoria la identificación de biomarcadores que optimicen los criterios de riesgo en sujetos susceptibles.

Esta tesis doctoral pretende identificar biomarcadores en sujetos con estado mental de alto riesgo (EMAR) de psicosis y pacientes con un trastorno psicótico incipiente (TPI). Se cuantificó IL-6, CRP, albúmina, cortisol y prolactina en suero, fibrinógeno en plasma, cortisol basal y respuesta del cortisol al despertar (CAR) en saliva. Se genotipó el rs1800795. Finalmente, se valoró los pacientes mediante la adaptación española del SCAN obteniendo diagnósticos DSM-IV, se valoró los sujetos EMAR mediante la CAARMS y en todos los pacientes se midió la severidad de los síntomas psicóticos (PANSS), el estrés percibido (SRRS), la percepción psicológica del estrés (PSS), y los síntomas depresivos (HDRS y CDSS).

Se demostraron niveles aumentados de IL-6 en sujetos EMAR frente a controles, la asociación positiva entre IL-6 y síntomas negativos (EMAR y TPI), y una relación positiva (EMAR) y negativa (TPI), entre IL-6 y síntomas positivos. Los EMAR que hicieron la transición a psicosis (EMAR-P) presentaron un aumento no significativo de IL-6 frente a quienes no la hicieron (EMAR-NP). También, se demostró niveles aumentados de prolactina y bajos de albúmina en EMAR-P frente a EMAR-NP y controles, además de diferencias significativas en la CAR. Confirmamos que el tratamiento antidepresivo se asocia con niveles bajos de CRP y fibrinógeno en TPI.