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Predictors of longer-term outcome in the Vienna omega-3 high-risk study

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ABSTRACT

Longer-term data on ω-3 polyunsaturated fatty acids (PUFA) for prevention of psychosis in (ultra high risk) UHR individuals have initially shown promising results.
This analysis aimed to assess clinical predictors of longer-term outcome in UHR individuals treated with ω-3 PUFAs versus placebo.
Data derived from an RCT in 81 UHR individuals treated with ω-3 PUFAs versus placebo for 12 weeks and follow-up assessment after a median of 6.7 years.
Baseline GAF, baseline PANSS global score, pre-to-post-intervention change in EPA (Eicosapentaenoic acid) level were significant predictors of transition to psychosis, PANSS negative score and baseline MADRS reached trend-levels. In the final multivariate Cox regression analysis change in EPA levels remained the only significant predictor.
Taking into account all other significant predictors, changes in EPA levels were found to be the single most significant predictor for transition to psychosis in a longer term observation of UHR individuals.

1. Introduction

Early psychosis research in the last 15 years has established criteria for the definition of high risk groups for the development of psychotic illnesses, therewith proposing a prospective concept for the originally retrospective "prodrome" idea (Nelson et al., 2013). According to meta-analytical data, these ultra-high risk criteria are associated with transition rates of around 22% to 36% after 1, respectively 3 years (Fusar-Poli et al., 2012).

Since transition rates have been reported as being in decline in specialized early intervention centres (Yung et al., 2007), additional potential clinical outcome predictors could serve to further stratify risk groups. Recently, isolated predictors for transition have been established by different groups in similar samples, amongst others: baseline global functioning (Cannon et al., 2008; Nelson et al., 2013; Thompson et al., 2011), decline in functioning alongside a genetic risk (Cannon et al., 2008; Thompson et al., 2011), history of substance abuse (Cannon et al., 2008), duration of symptoms (Nelson et al., 2013), sex (Walder et al., 2013), age (Amminger et al., 2006), attenuated psychotic symptoms (Ziermans et al., 2014), especially unusual thought content (Cannon et al., 2008; Thompson et al., 2011), paranoid ideations (Cannon et al., 2008) and formal thought disorder (Thompson et al., 2013), as well as negative symptoms (Lin et al., 2011). Low levels of nervonic acid were previously described by our group as being associated with a higher risk of transition to psychosis (Amminger et al., 2012). Other non-clinical predictors, such as neurocognitive- and related variables (Nieman et al., 2014; Seidman et al., 2016; Ziermans et al., 2014) have also shown good discrimination potential regarding transition status in young individuals. A staged probabilistic model approach performed in this sample using history of drug use, positive and negative and global symptoms, psychosocial functioning, total omega-3 levels and nervonic acid improved the prediction of transition within one year to over 70% (Clark et al., 2016).

Several early intervention strategies of indicated prevention have been investigated, amongst others low-dose antipsychotics, CBT

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(cognitive behavioural therapy) and ω-3 polyunsaturated fatty acids (PUFA) (Schmidt et al., 2015). The latter have provided promising results in one double-blind placebo-controlled study performed by our group (Amminger et al., 2010), while first results of the recent NEURAPRO multi-site replication trial did not replicate the original findings, notabene with generally low transition rates and substantial improvements in both group with high quality psychosocial treatment, which might at least partly have led to a ceiling effect (McGorry et al., 2016). As described in Amminger et al. (2010), treatment with ω-3 PUFAs over a period of 12 weeks proved to be effective in reducing 12-months transition rates in a UHR population compared to placebo. Transition rates in the ω-3 PUFAs were 4.9% at 12-months follow-up compared to 27.5% in the placebo group. A longer-term follow-up of the same population has shown sustained protective effects after a median of 6.7 years with transition rates of 9.8% in the ω-3 PUFAs and 40% in the placebo group (Amminger et al., 2015b). These results remain remarkable, and questions have arisen on the generalizability of the sample and its findings.

However, RCTs with ω-3 PUFAs bear the difficulty of controlling for non-study intake of ω-3 PUFAs, such as increases in fish and seafood consumption, or use of non-study ω-3 PUFAs supplements (James et al., 2014). Furthermore, tissue and erythrocyte levels of ω-3 PUFA can vary significantly between individuals. These potential pitfalls can be accounted for by analysing outcome independent of group allocation at baseline but with respect to changes in cell membrane ω-3 PUFA levels, which reflect all ω-3 intake regardless of its source.

Thus, the aim of this analysis was to test whether baseline levels or changes in ω-3 PUFA levels during the initial 12-week intervention phase of the study were predictive of longer-term outcome (i.e. transition to psychosis) while taking into account previously reported clinical predictors in a population of UHR individuals.

2. Methods

2.1. Sample

The initial sample was previously described in Amminger et al. (2010) and consisted of individuals between the ages of 13 and 25 with an increased risk for psychosis, meeting at least one of three operationally defined criteria (i.e., attenuated psychotic symptoms, brief limited intermittent psychotic symptoms, or a genetic risk with decreased functioning). Exclusion criteria were a previous history of a psychotic disorder or manic episode, a substance-induced psychotic disorder, acute suicidal or aggressive behaviour, a current substance dependence except for cannabis dependence, neurological disorder, relevant structural brain changes, IQ of <70, previous antipsychotic or mood-stabilizing treatment for longer than one week, previous supplementation with ω-3 PUFAs within 8 weeks of inclusion in the trial, abnormal laboratory values for transaminases, thyroid hormones, C-reactive protein, bleeding parameters or any other severe intercurrent illness that may have put the person at risk.

After the median follow-up of 6.7 years 20 of the 81 individuals (24.7%) had transitioned to psychosis (Amminger et al., 2015b).

2.2. Study design

The trial was initially designed as a double-blind, placebo-controlled RCT consisting of a 12-week intervention period of 1.2 g/d ω-3 PUFAs vs. placebo and a 6- and 12-months follow-up (Trial registration: clinical trials.gov Identifier: NCT00396643). A total of 81 patients were included in the trial after having given written informed consent. The study was approved by the local ethics committee. The main outcome criterion was transition to psychosis using the criteria defined by Yung et al. (1998) with severity thresholds assessed with the PANSS (Positive and Negative Syndrome Scale (Kay et al., 1987) (score of ≥4 on hallucinations, ≥4 on delusions, or ≥5 on conceptual disorganization, for at least 1 week (Morrison et al., 2004)). Additional assessments of psychopathology were performed using the PANSS, the Montgomery Asberg Depression Rating Scale, MADRS (Montgomery and Asberg, 1979) and the Global Assessment of Functioning, GAF (Association, 1994).The Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I/P (First et al., 2002)) was done at baseline and at 12-months follow-up to assert operationalized psychiatric diagnoses. A follow-up assessment was done after a median of 6.7 years in 71 of the original 81 participants; last observation at 12-months follow-up was used for the survival analysis in the remaining 10 individuals.

The dose of 1.2 g/d ω-3 PUFAs were adapted on the basis of information drawn from previous studies in patients schizophrenia (Emsley et al., 2002; Peet et al., 2001) and in first episode psychosis (Berger et al., 2007). The capsules in the intervention group were 0.5-g yellow gelatin capsules containing concentrated marine fish oil. The daily dose of 4 capsules added up to 700 mg of eicosapentaenoic acid (20:5n3), 480 mg of docosahexaenoic acid (22:6n3), and 7.6 mg of mixed tocopherol (vitamin E). The study medication also provided a daily dose of 220 mg of other omega 3 fatty acids (18:3n3, 18:4n3, 20:4n3, 21:5n3, and 22:5n3). Placebo capsules contained coconut oil, which is free of PUFAs and has no influence on ω-3 PUFA metabolism; they also contained 1% fish oil for flavor-matching, as well as the same amount of vitamin E. Participants were asked to refrain from taking additional supplements during the study period. See Amminger et al. (2010, 2015b) for further details.

2.3. Laboratory analyses

The baseline quantification of fasting erythrocyte fatty acid composition was done using capillary gas chromatography as follows (see Smesny et al., 2014 for further details): Plasma and erythrocytes were separated from blood samples and centrifuged in order to analyse the fatty acid composition in the phospholipids of the phosphatidylethanolamine fraction of erythrocyte membranes. An extracting agent (methanol:chloroform (1:2) + 50 mg/l BHT) was used to dissolve fatty acids from erythrocyte membranes; a separating funnel (method according to Folch et al., 1957) was used for the separation of the lipid phase from the water-soluble phase. Subsequent to resolving fatty acid methyl esters in hexane and injecting these into the gas-phase chromatograph, the following fatty acids were analysed: saturated FAs (SFAs: 14:0, 16:0, 17:0, 18:0), monounsaturated fatty acids (MUFAs: 18:1ω-9, 20:1ω-9, 20:3ω-9, 22:1ω-9, 24:1ω-9), trans fatty acids (TFAs: 18:1ω-7tr, 18:1n-9tr), and PUFAs (18:2ω-6, 18:3ω-6, 20:3ω-6, 20:4ω-6, 22:2ω-6, 22:4ω-6; 18:3ω-3, 20:5ω-3, 22:5ω-3, 22:6ω-3). See Fig. 1 for synthesis cascade of essential fatty acids.

2.4. Data analysis

This is a secondary analysis of the data described in Amminger et al. (2010, 2015b). Cox regression analyses were conducted with the entire sample, ignoring treatment group allocation (omega-3 or placebo), to provide an estimate on the effects of PUFA levels and their changes and previously established outcome predictors on outcome after a median of 6.7 years. The choice of a priori predictor variables for this analysis follows the results of Clark et al. (2015)'s probabilistic model in our sample, where a combination of history of drug use, PANSS positive, negative and global scores, omega 3 and nervonic acid levels increased the probability of prediction of transition to psychosis. Furthermore, the most commonly replicated predictive clinical variables with respect to specific psychopathology, i.e. delusions and conceptual disorganization were also accounted for. Thus, individual baseline predictor variables, i.e. age, sex, previous and current or previous illicit substance use, positive symptoms, negative symptoms, general symptoms (according to PANSS scores), delusions (PANSS P1 item), formal thought disorder (PANSS P2 item), depressive symptoms (MADRS scores), baseline levels of EPA, nervonic acid and global psychosocial functioning

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