European Psychiatry 48 (2018) 20–26

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

The interaction between neurocognitive functioning, subthreshold psychotic symptoms and pharmacotherapy in 22q11.2 deletion syndrome: A longitudinal comparative study

R. Weinberger[a], O. Weisman[a,b], Y. Guri[a], T. Harel[c], A. Weizman[a,d,e], D. Gothelf[a,b,c,*]

[a] Sackler Faculty of Medicine, Tel Aviv University, Israel
[b] The Sagol School of Neuroscience, Tel Aviv University, Israel
[c] The Behavioral Neurogenetics Center, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel-Hashomer, Israel
[d] Felsenstein Medical Research Center, Sackler Faculty of Medicine, Tel Aviv University, Petah Tikva, Israel
[e] Research Unit, Geha Mental Health Center, Petah Tikva, Israel

ARTICLE INFO

Article history:
Received 14 July 2017
Received in revised form 22 October 2017
Accepted 24 October 2017
Available online xxx

Keywords:
DiGeorge Syndrome
Velocardiofacial Syndrome
SIPS
Williams Syndrome
Neurocognitive functioning

ABSTRACT

Background: The 22q11.2 deletion syndrome (22q11DS) is the most common genetic syndrome associated with schizophrenia. The goal of this study was to evaluate longitudinally the interaction between neurocognitive functioning, the presence of subthreshold psychotic symptoms (SPS) and conversion to psychosis in individuals with 22q11DS. In addition, we attempted to identify the specific neurocognitive domains that predict the longitudinal evolution of positive and negative SPS, as well as the effect of psychiatric medications on 22q11DS psychiatric and cognitive developmental trajectories.
Methods: Forty-four participants with 22q11DS, 19 with Williams syndrome (WS) and 30 typically developing (TD) controls, age range 12–35 years, were assessed at two time points (15.2 ± 2.1 months apart). Evaluation included the Structured Interview for Prodromal Symptoms (SIPS), structured psychiatric evaluation and the Penn Computerized Neurocognitive Battery (CNB).
Results: 22q11DS individuals with SPS had a yearly conversion rate to psychotic disorders of 8.8%, compared to none in both WS and TD controls. Baseline levels of negative SPS were associated with global neurocognitive performance (GNP), executive function and social cognition deficits, in individuals with 22q11DS, but not in WS. Deficits in GNP predicted negative SPS in 22q11DS and the emergence or persistence of negative SPS. 22q11DS individuals treated with psychiatric medications showed significant improvement in GNP score between baseline and follow-up assessments, an improvement that was not seen in untreated 22q11DS.
Conclusions: Our results highlight the time-dependent interplay among positive and negative SPS symptoms, neurocognition and pharmacotherapy in the prediction of the evolution of psychosis in 22q11DS.

1. Introduction

22q11.2 deletion syndrome (22q11DS) is a common micro-deletion syndrome with a prevalence of at least 1 to 4,000 live births, and is characterized by high rates of medical and psychiatric comorbidities as well as cognitive deficits [1]. The 22q11DS is currently being considered the most commonly known genetic syndrome associated with schizophrenia, with psychotic illness occurring in about one-third of adults with 22q11DS [2].

Previous studies have shown that some cognitive deficits including lower baseline full-scale IQ, decline in verbal IQ, and deficits in visual memory and executive functioning, predict the later onset of psychotic disorders [3–5]. Thus, it seems that cognitive deficits are endophenotypes involved in the pathways leading to psychosis in 22q11DS.

While positive symptoms like delusions, hallucinations and disorganized speech have traditionally been the focus of schizophrenia research, negative symptoms are another core feature of the disorder, constituting risk factors for the evolution of schizophrenia [6,7]. A large multisite research on clinical high-risk cohort, North American Prodromal Longitudinal Study (NAPLS), showed that early and persistent negative symptoms confer risk for later development of psychotic disorders in non-

* Corresponding author at: The Child Psychiatry Division, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, 5262000, Tel Hashomer, Israel.
E-mail address: gothelf@post.tau.ac.il (D. Gothelf).

http://dx.doi.org/10.1016/j.eurpsy.2017.10.010
0924-9338/

22q11DS individuals [8]. Negative symptoms are often accompanied by cognitive deficits [9] and social impairments [10].

Following the above-mentioned findings in non-22q11DS schizophrenia, greater focus is being given to the identification of negative, in addition to positive subthreshold symptoms in 22q11DS [11–13]. Also, similarly to idiopathic schizophrenia, in previous 22q11DS studies, negative symptoms were associated with neurocognitive deficits [13] and executive dysfunction [14,15]. Recent a large study showed a high prevalence of positive and negative SPS in 22q11DS, 33% and 28%, respectively, with highest rates manifested during adolescence and young adulthood [16].

To date, only a few studies investigated the association between cognitive deficits and subthreshold psychotic syndrome (SPS) in 22q11DS individuals. One study, found that both positive and negative SPS are more common in individuals with lower IQ scores [16]. Another study reported that lower verbal skills increase the likelihood of prodromal or overt psychotic symptoms [17].

In a previous study, we compared, cross-sectionally, the rates of SPS among individuals with 22q11DS, typically developing (TD) controls and individuals with Williams syndrome (WS) [12]. We found that both 22q11DS and WS had similarly higher rates of positive subthreshold symptoms compared to TD. In addition, the 22q11DS had higher rates of negative SPS than WS and TD, despite having higher mean IQ scores than the WS group.

There are only a few published longitudinal studies that looked at the evolution of SPS in 22q11DS individuals [18,19]. In Schneider et al. [19], 89 individuals with 22q11DS were evaluated twice in a 32 months interval. Transition rate to full-blown psychosis was 27% in those with ultra-high risk (UHR) condition.

In the current study, we wished to evaluate longitudinally the psychiatric and neurocognitive functioning of individuals with 22q11DS and to identify the neurocognitive deficits that predict the emergence of positive and negative SPS. We used a relatively short evaluation interval of 12-20 months to be able to detect immediate changes and response to treatment. In addition to TD controls, we also included the WS group in the current longitudinal follow-up study, since our previous studies suggested the importance of including a control group with another neurogenetic syndrome in the attempt to identify the specific phenotypical features of 22q11DS, that are beyond the nonspecific effect of having intellectual disability [12,20].

Specifically, we formulated the following main aims and hypotheses:

1. The 22q11DS group will show higher conversion rates to either psychotic disorders or more severe SPS over time, compared to WS; 2. General cognitive deficits as well as specific deficits in the executive and social cognition domains would be associated with the presence of negative SPS in 22q11DS, but not in WS; 3. In individuals with 22q11DS, both baseline global neurocognitive performance (GNP) scores and scores of neurocognitive subdomains of the Penn Computerized Neurocognitive Battery (CNB)will predict the presence and severity of negative but not positive SPS at follow-up. Similarly, GNP scores at baseline will predict the emergence and persistence of negative SPS. 4. Finally, we wished to investigate the potential effect of psychiatric medications on 22q11DS trajectories. We assumed that 22q11DS individuals treated with psychiatric medications will demonstrate more robust improvement in SPS and neurocognitive functioning relative to 22q11DS individuals not treated with psychiatric medications.

2. Methods and measures

2.1. Participants

In a previous publication [12] we described the recruitment procedure and baseline evaluation of 102 individuals- 22q11DS (n = 50), WS (n = 20) and TD (n = 32) controls at the Behavioral Neurogenetics Center, Tel Aviv. Of the 102 individuals, 93 (88.2%) returned for follow-up- 22q11DS (n = 44), WS (n = 19) and TD (n = 30) and were included in the final longitudinal analyses. The mean interval between the baseline and follow-up visits was 15.2 months (SD = 2.1, range 12-20 months) (Table 1). The study was approved by the Institutional Review Board of Sheba Medical Center. After providing a complete description of the nature of the study, informed consent was obtained from all participants and from the parents of minors. Additional details on the participants' characteristics and their recruitment are listed in Table 1 and Appendix A in Supplementary material.

2.2. Measures

2.2.1. Psychiatric evaluation

All individuals with 22q11DS and WS and their main caregivers were interviewed by a trained psychologist using the Hebrew version with the Structured Interview for Prodromal Symptoms (SIPS) version 4 [21]. The Scale of Prodromal Symptoms (SOPS) is composed of 19 items, each representing a different possible SPS, divided into four groups: positive, negative, disorganized and general symptoms. Each item on the SIPS was rated on a seven-point scale (0 - absent, 1- questionably present, 2 - mild, 3 - moderate, 4 - moderately severe, 5 - severe but not psychotic, 6 - severe and psychotic/extreme) [22]. A participant was considered both at baseline and at follow-up assessments to have "positive

Table 1
Demographics, intelligence and adaptive functioning of the study groups at baseline.

	22q11DS (n = 44)	WS (n = 19)	TD (n = 30)	Statistics
Sex (male %)	52.3	36.8	46.6	$\chi 2(2) = 1.27$, $P = 0.529$[a]
Age at baseline [mean(SD)]	20.7(6.0)	21.9(6.2)	20.0(6.6)	F (2,90) = 0.56, $P = 0.569$[b]
Age range (years)	12-33	12-35	12-34	
Interval between assessment in months [mean(SD)]	16.2(2.2)	14.7(1.2)	14.8(2.1)	$\chi 2$ (2) = 1.42, $P = 0.065$[c]
Parents years of education [mean(SD)]	13.4(3.2)	14.1(2.1)	14.7(2.3)	$\chi 2(2) = 6.04$, $P = 0.058$[c]
FSIQ [(mean(SD)]	77.2(11.0)	68.8(9.5)	106.4(9.8)	F (2,90) = 108.99, $\boldsymbol{P < 0.001}$[b,d]
VABS ABC at baseline [(mean(SD)]	75.1(6.9)	71.5(9.7)	n.a	F (1,54) = 2.60, $P = 0.112$[b]

22q11DS: 22q11.2 deletion syndrome; ABC: Adaptive behavioral composite; FSIQ: Full-scale IQ; n.a: Not available; Paternal years of education: Average parents number of years in a formal educational setting; TD: Typically developing; VABS: Vineland Adaptive Behavior Scale; WS: Williams syndrome.

[a] Pearson chi square test.
[b] Analysis of variance.
[c] Kruskal–Wallis test.
[d] On post-hoc tests WS<22q11DS <TD.