Convergence insufficiency with unilateral exophoria at near in schizophrenia and bipolar disorder – a preliminary study

Adrian A. Chrobak¹, Katarzyna Siuda¹, Michał Biela¹, Aleksandra Arciszewska¹, Marcin Siwek², Maciej W. Pilecki³, Dominika Dudek²

¹Students’ Scientific Association of Affective Disorders, Jagiellonian University Medical College
Supervisor: prof. dr hab. n. med. D. Dudek

²Department of Affective Disorders Chair of Psychiatry, Jagiellonian University Medical College
Head: prof. dr hab. n. med. D. Dudek

³Department of Adult Psychiatry, Krakow University Hospital
Acting head of the Department: dr n. med. M.W. Pilecki

Summary

Objectives. The study describes an abnormal convergence symptom, i.e. unilateral exophoria at near, in patients with schizophrenia (SZ) and bipolar disorder (BD). The aim of this paper is to present the symptom and discuss its possible explanations.

Methods. 29 patients with SZ, 15 patients with BD and 20 healthy controls (HC) took part in the study. The neurological assessment was done with International Co-operative Ataxia Rating Scale (ICARS) and Neurological Evaluation Scale (NES).

Results. The abnormal vergence pattern was observed in 12 patients with SZ, 1 patient with BD and 0 HC. Symptom appeared statistically more often in SZ patients than in BD patients and HC. SZ patients with vergence symptom performed significantly worse in oculomotor and dysarthria subscores of ICARS.

Conclusions. The symptom can be linked to disruptions in cortico-ponto-cerebellar network and midbrain. It was the only neurological symptom that differed SZ and BD groups, thus it might be used in differential diagnosis. Further research is needed to obtain a full clinical description of the symptom.

Keywords: convergence insufficiency, eye movement disorders, cerebellum

The study was not sponsored.
**Introduction**

Schizophrenia (SZ) is a complex neurodevelopmental psychiatric illness. Due to its heterogeneous character and subjective methods of diagnosis, growing amount of studies is devoted to the search for the objective signs of SZ [1]. Plenty of neurological impairments, such as imbalanced gait, tremor or frontal release signs have been observed frequently in majority of patients with SZ. Those distinct symptoms have been gathered in the Neurological Evaluation Scale (NES) and called Neurological Soft Signs (NSS) [2]. NSS became an important neurobiological parameter in SZ research. Data suggests that NSS may reflect the general incoordination in sensorimotor processes associated with alterations in the cerebello-thalamo-prefrontal network [3]. Due to their specificity, symptoms measured by NSS hold potential for being SZ endophenotype [4, 5], because of their manifestation from the onset of the disease, in antipsychotic-naïve patients [6] and in healthy subjects with high genetic risk [7, 8]. Moreover, high scores in NSS may be considered as a risk factor of SZ [9].

According to the Andreasen’s Cognitive Dysmetria Hypothesis, impairments in the cortico-cerebellar-thalamo-cortical circuits (CCTCC) may lead to schizophrenic symptoms due to the dysfunctions in coordination of mental processes. This “poor coordination” may be a consequence of impaired timing or sequencing of the flow of information, which affect thinking and verbal processes [10]. There are clinical models that search for neural underpinnings of schizophrenic symptoms in cerebellar structure’s and functions’ deficiency [for review: 11]. Additionally, studies confirm cerebellar engagement in SZ symptoms like hallucinations or delusions [12, 13].

Symptoms that deserve special attention in research on SZ are the abnormalities in eye movements. Chen et al. [14] reported that eye movement abnormalities in SZ patients can be found in tasks that require integrating visual information across space and time with motoroutput, what suggest the CCTC circuits involvement in this symptom. Eye Tracking Dysfunctions (ETD), involving reduced gain in smooth pursuit eye movements and increased compensatory saccades have been widely explored in SZ patients for nearly 30 years. ETD occurring around half of the SZ patients and is likely to have genetic background [15]. The evidence from the eye-tracking studies shows impairments in smooth pursuit and saccadic eye movements in SZ patients and their unaffected relatives [16]. ETD occurrence allows one to distinguish SZ patients from patients with other psychiatric illnesses (depression) and healthy controls. Additionally, the ETD symptoms were observed in patients from different countries, what suggest its intercultural and interracial characteristic [17]. According to Suzuki et al. [18] Eye Tracking Dysfunctions assessed with Exploratory Eye Movement Test might create a diagnostic subtype of SZ. Abnormalities in eye movement are included both in ICARS (International Cooperative Ataxia Rating Scale) and NES scale.

Moreover, smooth pursuit deficits that are commonly found in around half of patients with SZ share common neurocorrelates with eye vergence [19]. Therefore, it was proposed that this type of movement will also be impaired in SZ patients. Unfortunately, the data on convergence insufficiency (CI) in SZ patients is limited. Higher rate of intrusive saccades in vergence tracking in patients diagnosed with SZ than
in HC group was reported by Levin et al. [20]. Additionally, in the longitudinal study on children of patients diagnosed with SZ, Schiffman et al. [21] reported a higher rate of eye exam scale and strabismus scale scores in children who later developed a SZ-spectrum disorder, what would imply premorbid characteristic of abnormal vergence movement in SZ. Bolding et al. examined the occurrence of CI in 20 SZ patients and 20 healthy controls [22]. Although no differences in frequency of CI between SZ patients and HC group was noted in this research, 40% of SZ patients reported subjective symptoms associated with CI measured with Convergence Insufficiency Syndrome Survey.

The aim of this paper is to present an abnormal vergence pattern in patients with SZ and BD that occurred during vergence examination included in the NES scale. Our patients presented unilateral exophoria at near, predominantly in the non-dominant eye. Below, we present the symptom and try to analyze its possible explanation and meaning for SZ research. Additionally, we aim at exploring whether the patients presenting the symptom suffer from other neurological deficiencies gathered in the aforementioned scales.

### Methods

#### Patients

29 patients who met DSM-IV-TR criteria for SZ, 14 patients who met DSM IV-TR criteria for BD matched for age, treatment duration and ethnicity and 20 healthy controls were examined (see table 1 for participants’ characteristics). Patients were recruited from Department of Adult Psychiatry of the Krakow University Hospital in Poland. Inclusion criteria for patients were: state of symptomatic remission and treatment with antipsychotic drugs from the group of dibenzoxazepine (olanzapine, clozapine, quetiapine) as monotherapy. This type of medication was chosen due to its comparable profile of generating the potential neurological side effects. Therefore, we have obtained relative pharmacological homogeneity. In case of patients with BD additional treatment with lamotrigine, valproic acid or carbamazepine was also accepted. Exclusion criteria for patients were alcohol or drug abuse, severe, acute and chronic neurological and somatic diseases, severe personality disorders, treatment other than mentioned above, post eye surgery status e.g. cataract surgery. Table 1 contains medication characteristic of the examined groups.

<table>
<thead>
<tr>
<th>Medication</th>
<th>SZ (n = 29)</th>
<th>BD (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOZAPINE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(number of patients, mg, mean daily doses ± SD)</td>
<td>n = 6</td>
<td>n = 2</td>
</tr>
<tr>
<td></td>
<td>341 mg ± 162.5</td>
<td>250 mg ± 70.7</td>
</tr>
</tbody>
</table>

*Table 1. Treatment description of patients within examined groups.*
OLANZAPINE
(number of patients, mg, mean daily doses ± SD)

<table>
<thead>
<tr>
<th>n</th>
<th>15.25 mg ± 5.0</th>
<th>n</th>
<th>13.3 mg ± 5.8</th>
</tr>
</thead>
</table>

QUETIAPINE
(number of patients, mg, mean daily doses ± SD)

| n  | 700 mg ± 100.0 | n  | 437 mg ± 118.8 |

SZ – schizophrenia, BD – bipolar disorder.

Healthy controls

HC group consisted of volunteers and was matched for age and ethnicity with clinical group. Exclusion criteria in the control group were similar to the patients’ groups, no psychiatric condition in the past and no family history of psychiatric and neurological disorders. All of them signed informed written consent to the assessment. The study was approved by the Jagiellonian University Bioethics Committee. Table 2 contains characteristics of the examined groups.

Table 2. Participants’ characteristics.

<table>
<thead>
<tr>
<th>Groups (number of subjects)</th>
<th>Schizophrenia n = 29</th>
<th>Bipolar disorder n = 14</th>
<th>Healthy controls n = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean ± SD)</td>
<td>35.7 ± 11.2</td>
<td>40 ± 13.1</td>
<td>42.3 ± 11.3</td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>20 – 61</td>
<td>21 – 54</td>
<td>22 – 57</td>
</tr>
<tr>
<td>Duration of treatment in years (mean ± SD)</td>
<td>11 ± 9.5</td>
<td>9.7 ± 8.3</td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>0 – 34</td>
<td>1.5 – 25</td>
<td></td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>17/12</td>
<td>1/13</td>
<td>9/11</td>
</tr>
</tbody>
</table>

Research methodology

Neurological impairments level was assessed using the International Co-operative Ataxia Rating Scale (ICARS) [23], and The Neurological Evaluation Scale (NES) [2]. During convergence assessment subjects were instructed to follow the tip of a pen with their eyes as it is moved toward the nose. 5 patients revealing described symptom were recorded. The subjects signed consent for revealing photos of their eyes in this publication. In order to evaluate of dominant eye, patient was asked to form a “lunette” with his both hands, and to look through it. The chosen eye was counted as dominant eye.

Statistical analysis

Statistical analysis was performed using STATISTICA software. In case of normal distribution of data, t-test was applied in order to assess differences between examined
groups. If the data had non-normal distribution, U Mann-Whitney test was used. Additionally, Chi-square test was used to analyze relations between examined variables. Due to low subject count, Yates correction was applied and the adjusted p values are presented.

**Results**

The control group, SZ and BD patients did not differ significantly in age. There was no significant difference between SZ and BD patients in duration of treatment. The abnormal vergence pattern occurred in 12 out of 29 SZ patients (41%), 1 out of 14 BD patients (7%) and 0 healthy controls. Symptom occurred significantly more often in group of SZ patients in comparison with BD patients (\(\chi^2(1, N = 43) = 3.75, p = 0.05\)) and healthy control group (\(\chi^2(1, N = 49) = 3.75, p = 0.003\)). As only one patient with BD presented the abnormal vergence pattern, further analysis will focus on the SZ group with the symptom. This group consisted of 5 women and 7 men with mean age of 33.25 years (SD = 9.13, range 20–52) and mean duration of treatment of 8.59 years (SD = 8.9, range 0-27). The two tailed binomial test revealed that significant majority of SZ patients presenting the symptom revealed exophoria at near of their non-dominant eye (10 out of 12 patients, p = 0.02). Picture 1 presents SZ patient’s eyes in the vergence task.

![Picture 1. One of SZ patients with abnormal vergence symptom before the fixation task, looking at the tip of the pen.](image)

In the picture 2 abnormal vergence pattern is presented with a clear exophoria at near in the left eye. The same patient is presented in both pictures.

![Picture 2. The patient from Photo 1 performing the convergence task. His task was to follow the tip of a pen with his eyes as it is moved toward the nose. The closer to the nose was the pen, the broader exophoria in his left eye was observed.](image)
The analysis of ICARS and NES scores showed that SZ patients presented significantly higher scores in ICARS and NSS scales than HC group in all of their subscales (p < 0.01). There were no significant differences between SZ and BD patients in ICARS, NSS or any of their subscales. SZ patients with abnormal vergence pattern revealed significantly higher scores in ICARS dysarthria (U = 55, z = -2.06, p = 0.04) and oculomotor (t (13.6) = -2.42, p = 0.03) subscales. Table 3 presents the detailed comparison between SZ patients with and without the symptom.

### Table 3. The detailed comparison of SZ patients with and without the abnormal vergence symptom.

<table>
<thead>
<tr>
<th>SZ patients</th>
<th>with vergence symptom</th>
<th>Without vergence symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 12</td>
<td>n = 17</td>
</tr>
<tr>
<td>Age (mean years ± SD)</td>
<td>33 ± 9</td>
<td>37 ± 12</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>7/5</td>
<td>10/7</td>
</tr>
<tr>
<td>Duration of treatment (mean years ± SD)</td>
<td>8.6± 8.9</td>
<td>12.7± 9.9</td>
</tr>
<tr>
<td>Medication (number of patients, mg, mean daily doses ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLOZAPINE</td>
<td>n = 2</td>
<td>n = 4</td>
</tr>
<tr>
<td>OLANZAPINE</td>
<td>n = 10</td>
<td>n = 10</td>
</tr>
<tr>
<td>QUETIAPINE</td>
<td>n = 0</td>
<td>n = 3</td>
</tr>
<tr>
<td>ICARS results (mean score ± SD, significant differences p &lt; 0.05 in bold)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GENERAL</td>
<td>13 ± 9</td>
<td>12 ± 5</td>
</tr>
<tr>
<td>OCULOMOTOR</td>
<td>3 ± 2</td>
<td>1 ± 1</td>
</tr>
<tr>
<td>DYSARTHRIA</td>
<td>2 ± 2</td>
<td>1 ± 1</td>
</tr>
<tr>
<td>POSTURE</td>
<td>3 ± 3</td>
<td>3 ± 2</td>
</tr>
<tr>
<td>KINETIC</td>
<td>5 ± 4</td>
<td>7 ± 4</td>
</tr>
</tbody>
</table>

### Discussion

In this study 2/5 of examined SZ patients revealed convergence insufficiency (CI) with unilateral exophoria at near. To our knowledge this is the first report indicating a presence of such symptom in this clinical group. The presence of vergence abnormalities in patients with SZ was noted before by Flach et al. [24], however, the symptoms
Convergence insufficiency with unilateral exophoria at near in schizophrenia

did not adopt such a clear form as in case of our patients. Interestingly, Bolding et al. [22] failed to proof differences in CI between SZ patients and healthy controls. Those inconsistencies of results may be caused by relatively small groups of patients examined and different methods of vergence assessment. This indicates the need for further investigation of this issue on a larger sample to reveal significance of this symptom and its potential for being an endophenotype of SZ.

To our knowledge there is no data concerning unilateral exophoria or convergence insufficiency as a side effect of olanzapine, clozapine or quetiapine. There was only one patient with BD, who presented the symptom, even though patients with BD were taking additional normothymic medication which could have potentially influenced the neurological assessment, resulting in e.g. double vision or ataxia. The symptom group in our study comprised two first episode patients and the range of treatment’s duration in SZ group was 0-27 years. Such a wide range of treatment duration and the fact that the onset time of the vergence symptom is not know makes us hypothesize that the observed symptom is more likely associated with the illness rather than the treatment. Notwithstanding, we recommend future evaluation of our findings on neuroleptic naïve groups of patients.

There were no significant differences between scores in NSS and ICARS between patients with SZ and BD. These results are consistent with recent studies indicating that NSS can discriminate SZ from major depression, but not BD [25]. However, in this study the convergence insufficiency presented as unilateral exophoria at near occurred significantly more often in the group of SZ than in the BD, pointing out the possibility of this symptom to be neurological soft sign with a potential to distinguish this two groups in future studies. Basing on that data we assume that this symptom may be etiologically associated with SZ. This finding is also consistent with studies revealing lowered dynamic vergence in SZ [26]. Due to the fact that described symptom occurred only in one patient with BD it is difficult to conclude what characteristics contribute to its occurrence. However it is worth mentioning that this patient obtained the highest score in NSS, compared to the other BD patients.

The pathway controlling convergence includes brainstem, subcortical, and cortical structures. Animal studies revealed that pre-motor neurons encoding convergence are localized in the mesencephalic reticular formation, dorsal and lateral to the motor nuclear complex [27, 28]. Parietal-occipital cortex of monkeys comprise recognized group of neurons that fire prior to the maximum velocity of ocular convergence [29]. It is also believed that in humans CI associated with brain injury express permanent damage of cortical brain structures and the mesencephalic [30, 31]. Due to the fact that patients with SZ reveal reduced midbrain volume [32] it cannot be ruled out that the structures of mesencephalic reticular formation may also be disrupted. Additionally, it is possible that the observed syndrome is a consequence of enlarged cerebral ventricles, especially the cerebral aqueduct, as this structure contains the oculomotor nuclei. The enlargement of ventricles is one of the most replicated findings in research on biological background of SZ [33]. Moreover, the eye movement abnormalities as a consequence of enlarged ventricles have been reported in patients with hydrocephalus [34].
Interestingly we revealed that patients with SZ presenting unilateral exophoria at near also presented significantly higher scores in both Oculomotor and Dysarthria subscales of ICARS compared to SZ without the symptom. Searching for the common causal component of these symptoms leads us to the hypothesis of cerebellar involvement. Medial part of nucleus reticularis tegmentipontis, which receives inputs from the frontal eye field, contains neurons discharging during the vergence. Those neurons project to the dorsal vermis and the nucleus interpositus in the cerebellum of monkeys – regions corresponding to the emboliform and globose nuclei in humans. The dorsal vermis projects to the fastigial nucleus, containing neurons which are active during a near response. This nucleus projects also to the mentioned mesencephalic reticular formation. Lesions of the oculomotor region of fastigial nucleus result in eye exodeviation [35]. Acoustic analysis and instrumental measurement of patients with cerebellar dysfunction and ataxic dysarthria have revealed that the prolongation of vowel duration correlated with cerebellar eye movement abnormalities. Authors concluded that cerebellar midline structures, such as vermis and fastigial nucleus may also play a role in the coordination of motor speech [36]. The vermis was infrequently reported in the context of the dysarthria before [37], however, speech disturbances were reported to accompany congenital oculomotor apraxia associated with vermal abnormalities [38]. More recent studies suggest that ataxic dysarthria is most commonly associated with bilateral or generalized cerebellar disease, and it is also associated with focal lesions of paravermal, lateral hemispheres and posteromedial regions [39].

Growing number of research indicate the role of the cerebellum in psychiatric illnesses [40]. Numerous studies have reported various abnormalities of structure of the vermis [41] and other parts of cerebellum [3, 40] and its significance in SZ. Interestingly, the vermis and its fastigial nucleus are part of the limbic cerebellum [42], which impairment may cause affective alterations [43]. Its abnormalities have been observed in several psychiatric disorders e.g. SZ and autism [40, 44-46]. It was found that patients with BD also show these abnormalities [41]. In our study, no significant differences between the SZ and BD in cerebellar symptoms were observed. However, the comparison of the cerebellar grey matter reduction of patients with BD and SZ revealed that this reduction is less pronounced in psychotic patients with BD compared to SZ [47]. Basing on this data we suggest that observed symptom may reflect possibly greater disruption of cortico-ponto-cerebellar pathways in SZ than in BD. Unilateral character of this symptom may, in our opinion, refer to stronger networks of dominant eye, which is consistent with observation that during physiological vergence, nondominant eye start diverge slightly faster than dominant eye, reflecting the eyedness of the patient [48].

A small subject sample, lack of broader psychiatric assessment of examined patients and an amateur, non-standardized measurement of convergence constitute strong limitations of our study. Small size of examined group made it impossible to analyze the possible treatment influence on observed vergence pattern. Moreover, we were not able to match participants for gender due to low number of participants with BD and the domination of females in this group (13 females, 1 male). Additionally, more
detailed description of the observed symptom was not possible due to non-standardized method of measuring the vergence.

The above study has a preliminary character and its most important aim is to present observed vergence pattern to a broader spectrum of specialist and to call attention on the convergence insufficiency issue in the research of SZ. This phenomenon may be explained by the impairments in the midbrain, cortico-ponto-cerebellar pathways including fastigal nucleus. The evaluation of presented symptom is short and accessible in everyday clinical practice; therefore, it can be easily replicated in future studies. It may be possible that this abnormal vergence pattern will help reducing heterogeneity of SZ patients in genetic studies, support differencing patients with SZ from BD in neurological assessments, or will help recognize patients with potentially higher component of the cerebellar signs.

References


Address: Adrian Chrobak
Students’ Scientific Association of Affective Disorders,
Jagiellonian University Medical College
31-501 Kraków, Kopernika Str. 21a