The prevalence of neurodevelopmental abnormalities among children of bipolar patients

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Introduction
Bipolar disorder is one of the most distinct syndromes in psychiatry and has been described in numerous cultures over the course of history.

Aim of the work
The aim of the current work was to study the neurodevelopmental abnormalities among children of bipolar disorder patients.

Participants and methods
The participants of the present study were the children of 30 patients diagnosed with bipolar disorder (I or II) according to the DSM-IV criteria.

Results
An overall 1.8% of children of bipolar patients had delayed motor milestones, 3.6% of them had delayed language development and 8.9% of them had nocturnal enuresis.
The mean score of the Waldrop scale among children of bipolar patients was 1.16 ± 1.203, and high arched palate was the most prevalent anomaly (17 out of 56; 30.35%).
As regards intelligence, 76.8% of children were of normal intelligence (between 90 and 110), 5.4% of children were dull-normal intelligence (between 80 and 89), and for the remaining children (17.9%) intelligence was not evaluated as they were younger than 4 years.
No neuromotor abnormalities and neurological soft signs were observed in children of bipolar patients.

Conclusion
It is recommended to follow-up these children to observe any neurological soft signs that may develop in them, as well as any disorder that may develop in them later on during adulthood. However, this subject has to be further studied on a wider scale in the near future. Moreover, a controlled study should be conducted.

Keywords:
bipolar disorder, child, mental health, neurodevelopmental, offspring, soft neurological signs

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Introduction

Bipolar disorder is one of the most distinct syndromes in psychiatry, which affects ~1% of the population worldwide (Merikangas and Yu, 2002). About 50% of patients with bipolar illness have a family history of the disorder. Studies on twins suggest that the concordance for bipolar illness is between 40 and 80% in monozygotic twins and is lower (10–20%) in dizygotic twins, a difference that suggests a genetic component for the disorder (Plomin *et al.*, 1997). Two meta-analyses have been conducted with bipolar genome scan data. The strongest evidence for susceptibility loci was found on 13q and 22q when examining seven published genome scans for bipolar disorder (Craddock *et al.*, 2005). There were also new gene regions containing 'candidate genes' connected to bipolar disorder, specifically the gene '*ADCY2*' on chromosome 5 and the so-called 'MIR2113-POU3F2' region on chromosome 6 (Muhleisen *et al.*, 2014).

Figure 1 shows the regions that have received genome-wide significant support in at least one scan. Of particular note are the 6q16–q25 region and the 12q23–q24 region, which have two genome scans reporting genome-wide significance (Ewald *et al.*, 2002; Shink *et al.*, 2004) and is also supported by linkage analysis in two pedigrees that segregate both bipolar spectrum mood disorder and Darier's disease (an autosomal-dominant skin disease caused by mutations at *ATP2A2*, which maps at 12q23–q24.1) (Craddock *et al.*, 1994; Jones *et al.*, 2002; Green *et al.*, 2005).

Bipolar disorder researchers have been taking an interest in a variety of clinical subtypes and covariates over the recent years as a way of testing subsets of cases with increased clinical (and hopefully genetic) homogeneity. Examples include rapid cycling (illness characterized by a high recurrence rate – at least four distinct episodes per year) (Kirov *et al.*, 1998), lithium responsiveness, bipolar affective and puerperal psychosis (triggering of bipolar episodes in women by parturition) (Jones and Craddock, 2001; Turecki *et al.*, 2001) (Table 1).

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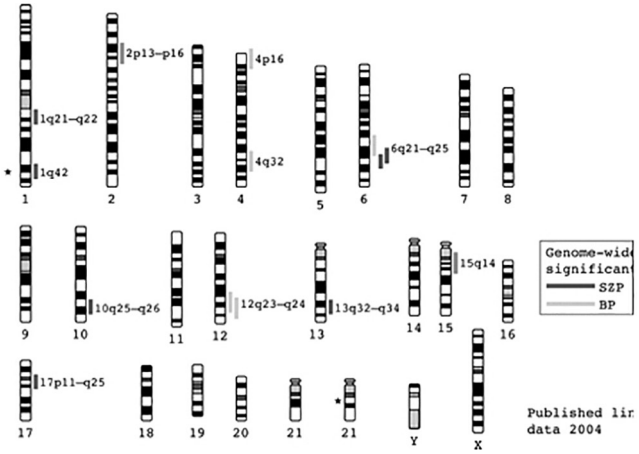
Figure 1



Chromosome ideograms showing locations of genome-wide significant linkages in schizophrenia and bipolar disorder. Asterisks mark the locations of chromosomal abnormalities associated with schizophrenia.

Table 1 Summary of current weight of evidence supporting several of the more promising genes implicated in the pathogenesis of schizophrenia and/or bipolar disorder (Craddock *et al.*, 1994)

Gene/locus	Chromosomal location	Evidence in schizophrenia	Evidence in bipolar disorder
Dysbindin	6p22	+++++	–
Neuregulin 1	8p12	++++	+
DISC 1	1q42	+++	+
RGS4	1q23	++	–
COMT	22q11	+	+
DAOA(G72)/G30	13q33	++	++
BDNF	11p13	–	++
DAO	12q23	++	–

More + symbols indicate greater evidence. The scale is relative.

The brain of a bipolar disorder patient shows structural abnormalities on a regional basis, 22, 23, 24 with zones within the cortical, subcortical, limbic, and other regions affected. Best documented is the prefrontal cortex (Sanders *et al.*, 2003).

Neurological soft signs (NSSs) refer to a number of subtle motor and sensory findings elicited through neurological assessment. Sensory integration signs usually include extinction, stereognosis, graphesthesia, and other tasks. Motor coordination signs include rapid alternating signs, finger-to-nose test, and finger–thumb opposition test. The motor sequencing test includes fist-ring and fist-edge-palm test. Primitive reflexes include palmomental, snout, and grasp reflexes (Sanders *et al.*, 2003).

Schwartz *et al.* (1990) found that patients with schizophrenia had greater impairment in perceptual and other parietal neurological examination abnormalities, but not motor tasks.

High levels of neurological abnormality characterize schizophrenic patients, their siblings and their offspring (Walker *et al.*, 1994). This has suggested that some other psychiatric disorders may share similar neurological signs.

Study findings reveal that patients with bipolar I disorder have NSSs, which reflect stable neurological abnormalities that are established at, or before, disease onset (Negash *et al.*, 2004).

As an overlap in findings between bipolar disorder and schizophrenia was noted, as said before, and as NSSs were noted in schizophrenic patients, their siblings, their offspring, and in bipolar patients, does this mean that we can find NSSs in bipolar offspring?

Aim of the work

The aim of the current work was to study the neurodevelopmental abnormalities among children of bipolar disorder patients.

Participants and methods

Participants of this study were offspring of 30 patients diagnosed with bipolar disorder (I or II) according to the DSM-IV criteria, followed up at Hadara University Hospital. Each child had one bipolar parent who met the DSM-IV (*http://www.dsm5.org/Pages/Default.aspx*) criteria for bipolar disorder. At the time of evaluation, none of the children in this study met the diagnostic criteria, and none had ever been evaluated or treated for mental subnormality or any neurological disorder. The parents were subjected to complete psychiatric and mental history and examination with emphasis on family history of mental illness and drug intake during pregnancy or lactation. The offspring were subjected to clinical assessment, assessment of physical developmental abnormalities using the Minor Physical Anomalies scale (Waldrop and Halverson, 1971), evaluation of IQ using the Wechsler Intelligence Scale for Children (WISC-III), assessment of motor abnormalities using the neuromotor rating scale and assessment of NSSs (Chen *et al.*, 2000; Dazzan and Murray, 2002; Schubert and McNeil, 2004), which included sensory integration (stereognosis and graphesthesia), motor coordination (rapid alternating movement, finger–thumb opposition, finger-to-nose test, rhythm tapping-nose test, and rhythm tapping) and primitive reflexes (palmomental, snout, grasp reflexes) (Henriksson and McNeil, 2004).

Results

The present study was carried out on 56 children of 30 bipolar parents; of them, 37 were boys (66.1%) and 19 were girls (33.9%). There were six bipolar fathers (20%) among 11 children and 24 bipolar mothers (80%) among 45 children. None of the studied families had both bipolar parents.

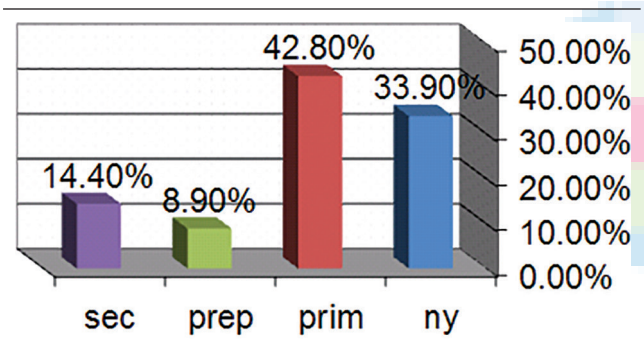
An overall 33.9% of studied children had not attended school yet, 42.8% were attending primary schools, 8.9% were attending preparatory schools and 14.4% were attending secondary school (Fig. 2). None of the children attending school discontinued studying, although some of them had borderline IQ. Delayed motor milestones (1.8%) was reported in one child, delayed development of language in two (3.6%), and nocturnal enuresis in five (8.9%) (Fig. 3). A positive family history of psychiatric illness was reported in the parent of one child (1.8%), whereas the remaining 55 children revealed a negative family history (98.2%). Five children were subjected to drugs during their intrauterine life (8.9%), one of them was subjected to haloperidol, whereas 51 of them were not subjected to any drugs (91.1%) (Fig. 4).

On application of the Waldrop scale, the mean score among children of bipolar patients was 1.16 ± 1.203. High arched palate was the most prevalent anomaly (17 out of 56; 30.35%).

Ten children (17.9%) were not subjected to WISC, as they were younger than 4 years. Forty-three children (76.8%) were of normal intelligence (between 90 and 110) and three (5.4%) were of borderline intelligence (between 80 and 89) (Fig. 5).

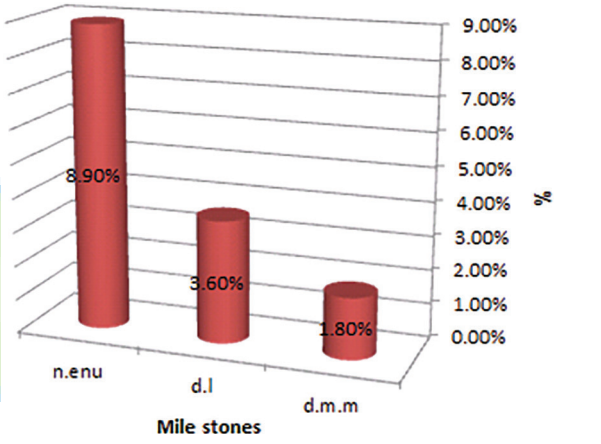
On applying the neuromotor abnormality scale, offspring of bipolar patients reported no abnormality

Figure 2



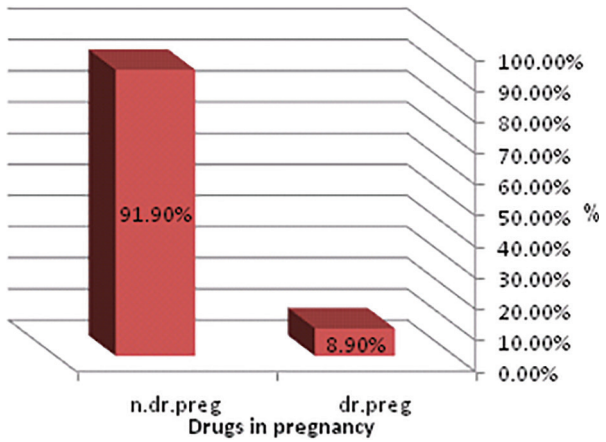
School grades among children of bipolar patients. ny, not yet in school; prim, primary school; prep, preparatory school; sec, secondary school.

Figure 3



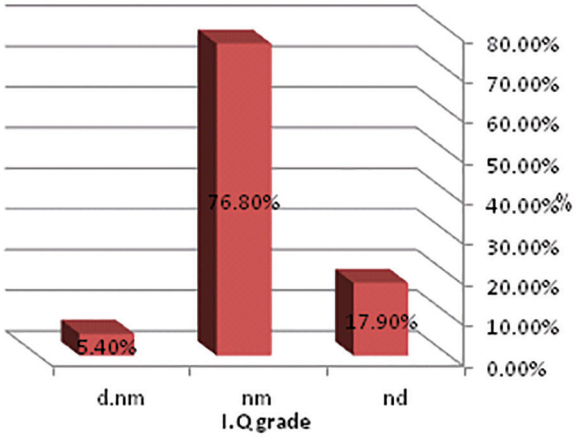
Frequency of delayed milestones (motor, language, and sphincteric) among children of bipolar patients. d.m.m., delayed motor milestones; d.l., delayed language development; n.enu, nocturnal enuresis.

Figure 4



Drug intake during pregnancy. dr.preg, drug intake during pregnancy; n.dr.preg, no drug intake during pregnancy.

Figure 5



IQ grades among children of bipolar patients according to the Wechsler Intelligence Scale for Children. nd, not done (<4 years); nm, normal (90–110); br, borderline (80–89).

as regards abnormal hand posture, abnormal orofacial movement, bradykinesia, dysmetria, dysmorphic features, hypotonicity, intentional tremors, rest tremors and tics. No NSSs were reported among offspring of bipolar patients as regards sensory integration, motor coordination, motor sequencing and primitive reflexes.

Discussion

In the present study, 1.8% of children of bipolar patients reported delayed motor milestones, and 3.6% reported delayed language development. Henriksson and McNeil (2004) stated that offspring of mothers with affective psychosis showed only a significantly increased rate of delayed walking compared with controls (Henriksson and McNeil, 2004). As regards sphincter control, nocturnal enuresis was reported in 8.9% of children in the present study. All of the affected children were female, and this may be attributed to poor toilet training and negligence by their bipolar mothers.

As regards the minor physical anomalies, the mean score of the Waldrop scale among children of bipolar patients was 1.16 ± 1.203. High arched palate was the most prevalent anomaly (17 out of 56; 30.35%). However, in another study it was observed (Trexiler *et al.*, 2001) that in patients with bipolar disorder, furrowed tongue was significantly more common compared with controls.

In the present study, 76.8% of children were of normal intelligence (between 90 and 110), 5.4% of children were of dull-normal intelligence (between 80 and 89), and the remaining children (17.9%) were not subjected to WISC as they were younger than 4 years. The results of this study support an association between bipolar disorder and creativity and contribute to a better understanding of possible mechanisms of transmission of creativity in families with genetic susceptibility for bipolar disorder.

Osher *et al.* (2000) stated that offspring of bipolar parents, similar to bipolar patients themselves, show significantly increased incidence and severity of thought disorder, lower numbers of cognitively mediated affective responses, and fewer responses indicating conventional perceptions.

No neuromotor abnormalities and NSSs were observed in children of bipolar patients (Negash *et al.*, 2004).

Study findings revealed that patients with bipolar I disorder have NSSs, which reflect stable neurological abnormalities that are established at, or before, disease onset (Negash *et al.*, 2004).

On assessment with the Neurological Evaluation Scale (Buchanan and Heinrichs, 1989), bipolar I disorder patients performed significantly worse on two Neurological Evaluation Scale items from the sensory integration subscale – audio–visual integration and graphesthesia – and on the finger–thumb opposition of the motor coordination subscale. They also showed impaired performances on four items of the 'others' subscale – rhythm tapping test A, tremor, gaze impersistence, and glabellar reflex (Negash *et al.*, 2004).

Conclusion

(1) In 1.8% of children of bipolar patients delayed motor milestones was reported, in 3.6% of them delayed language development was reported and 8.9% of them nocturnal enuresis was reported.
(2) The mean score of the Waldrop scale among children of bipolar patients was 1.16 ± 1.203, and high arched palate was the most prevalent anomaly (17 out of 56; 30.35%).
(3) As regards intelligence, 76.8% of children were of normal intelligence (between 90 and 110), 5.4% of children were of dull-normal intelligence (between 80 and 89), and the remaining children (17.9%) were not subjected to WISC as they were younger than 4 years.
(4) No neuromotor abnormalities and NSSs were observed in children of bipolar patients.

Conflicts of interest

There are no conflicts of interest.

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