Original Article

Psychosocial Functioning of Persons Who Develop Serious Mental Illness after Exhibiting a Somatic Prodrome in Adolescence

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ABSTRACT

Background: Adolescents who present with medically unexplained somatic symptoms and subsequently develop serious mental illness (SMI) are often seen in psychiatric practice. We investigated the characteristics of somatic symptoms, development of psychiatric symptoms, and psychosocial functioning in such patients.

Methods: We retrospectively reviewed the medical records of patients seen in the psychiatric outpatient clinic of 2 university hospitals in Tokyo. All patients who exhibited a medically unexplained somatic prodrome and later experienced onset of an SMI were included in the analysis. We used the Children's Global Assessment Scale (CGAS) to evaluate level of psychosocial functioning at 3 time points: when the first medically unexplained somatic symptom appeared, when the first psychiatric symptom appeared, and at psychosis onset (definitive diagnosis).

Results: Eighteen patients met the study inclusion criteria. Headache (33.3%) was the most common somatic symptom preceding an SMI. Hypobulia (44.4%) was the most common first psychiatric symptom, followed by impaired concentration (38.9%). Analysis of CGAS scores for psychosocial functioning when the first medically unexplained somatic symptom appeared, when the first psychiatric symptom appeared, and at psychosis onset showed that CGAS scores were lower than those for healthy people when the first somatic symptom appeared, and significantly decreased thereafter, *i.e.*, when the first psychiatric symptom appeared and at psychosis onset.

Conclusion: Physicians examining adolescents with medically unexplained somatic symptoms should obtain a comprehensive history and examination findings and pay careful attention to psychosocial functioning, with the risk of mental illness in mind. In addition, such patients should be evaluated over time for changes in psychosocial functioning.

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The importance of early intervention in psychoses, including schizophrenia, has been stressed in recent years,

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and great importance has been attached to early detection and early treatment, to shorten the duration of untreated psychosis (DUP) and provide support.[1–4] During development of psychosis, a prodromal phase may occur during which patients exhibit a variety of nonspecific symptoms before the onset of psychotic symptoms.[5–7]

Somatic symptoms are 1 category of such nonspecific symptoms.[8, 9] Some children and adolescents with medically unexplained somatic complaints eventually develop a serious mental illness (SMI), such as schizophrenia or bipolar disorder, during long-term follow-up in psychiatric practice.[10, 11] Pediatricians and primary care physicians frequently encounter patients who present only with medically unexplained somatic symptoms. However, physicians who are not specialists in psychiatry frequently fail to recognize the process by which a patient who exhibits such somatic symptoms later develops psychiatric symptoms and, gradually, full-blown psychosis. Although it is extremely important from a clinical standpoint to recognize prodromal somatic symptoms and initiate psychiatric treatment, when necessary, previous studies have not identified somatic symptoms significantly associated with psychosis.[12] To facilitate early detection and early treatment of mental illness it is necessary to identify prodromal symptoms, including somatic complaints and somatic symptoms, determine the characteristic course of such symptoms, and inform psychiatrists, pediatricians, primary care physicians, school nurse-teachers, public health nurses, and parents of the salient findings.

We retrospectively reviewed medical charts to investigate (1) the characteristics of medically unexplained somatic symptoms in patients that exhibited such symptoms in adolescence and subsequently developed an SMI and (2) changes in psychiatric symptoms and psychosocial functioning in such patients.

Methods

Patients

We reviewed the medical charts of patients aged 35 years or younger who had attended the outpatient clinic of Toho University Omori Medical Center Mental Health Center or Toho University Ohashi Medical Center Department of Neuropsychiatry during the 12-month period from April 2014 through March 2015. We included patients who presented to the psychiatry department with medically unexplained somatic symptoms before age 18 years but had no evidence of objective abnormal findings in evaluations conducted in other departments. In total, 68 patients fulfilled these criteria (30 males and 38 females). Mean (SD) age was 17.9 (4.3) years. Those who had continued to attend the clinic for at least 6 months and, on the basis of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) codes,[13] had subsequently received a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or attenuated psychosis syndrome (APS) were included in the analysis.

APS is a condition associated with a very high risk of subsequent psychosis, such as schizophrenia, and has attracted considerable recent attention.[14] It was therefore included among the conditions of interest in this study, even though it is listed in the "Conditions for Further Study" in Section III of the DSM-5.[15] Patients who received a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder were included in the psychosis group and analyzed separately from patients with APS.

Methods

The methods of the present study were similar to those used in previous studies. First, we systematically collected data for items (1) to (13) below from medical records and other sources, such as referral letters from previous physicians. The data were classified by consensus after discussions between two authors (H.H. and T.F.), as follows: (1) time and age when the first medically unexplained somatic symptom appeared, (2) somatic symptoms, (3) level of psychosocial functioning when the first medically unexplained somatic symptom appeared, (4) pathway to psychiatric care, (5) age when first examined in a psychiatry department, (6) time and age when the first psychiatric symptom appeared, (7) the first psychiatric symptom, (8) level of psychosocial functioning when the first psychiatric symptom appeared, (9) interval between the appearance of the first medically unexplained somatic symptom and appearance of the first psychiatric symptom, (10) time and age when onset of psychosis was confirmed, (11) definitive diagnosis of psychosis, (12) level of psychosocial functioning at psychosis onset (definitive diagnosis), (13) interval between the appearance of the first medically unexplained somatic symptom and psychosis onset.

Somatic symptoms were carefully distinguished from symptoms that were clearly due to physical illness, and the time when they appeared was determined. The first psychiatric symptom was carefully distinguished from lifelong behavior patterns and symptoms associated with a longstanding condition that had begun in childhood, and

Table 1 Brief summary of the Children's Global Assessment Scale (CGAS)[16]

80-71	No more than slight impairment in functioning at home, at school, or with peers; some disturbances of behavior or emotional distress may be present in response to life stresses, but these are brief and interference with functioning is transient; such children are not considered deviant by those who know them.
70-61	Some difficulty in a single area, but generally functioning pretty well and with some meaningful interpersonal relationships; most people who do not know the child well would not consider him/her deviant, but those who do know him/her well might express concern.
60-51	Variable functioning, with sporadic difficulties or symptoms in several social areas; disturbance would be apparent to those who encounter the child in a dysfunctional setting or time.
50-41	Moderate degree of interference in functioning in most social areas or severe impairment of functioning in one area, such as might result from suicidal preoccupations, school refusal, and other forms of anxiety, with some preservation of meaningful social relationships.

the time when it occurred was determined. The time of psychosis onset was determined by carefully ascertaining the time when the DSM-5 diagnostic criteria were fulfilled.

We used the Children's Global Assessment Scale (CGAS)[16] to evaluate level of psychosocial functioning (Table 1). The CGAS is a scale used to evaluate children aged 4 to 16 years and was developed by using the Global Assessment Scale (GAS), which was designed for adults.[17] We performed global evaluations of psychosocial functioning, using a score range of 1 to 100. The CGAS reflects the social functioning of patients whose social functioning has been impaired by various mental illnesses. The CGAS has been used in many studies as an evaluation scale for mental illness in childhood and adolescence, and its usefulness has been validated.[18–20] As stated above, we conducted CGAS evaluations at 3 time points, *i.e.*, (a) when the first medically unexplained somatic symptom appeared ((3) above), (b) when the first psychiatric symptom appeared, ((8) above), and (c) at psychosis onset ((12) above). Because APS is a condition that does not reach the threshold for onset of psychosis, we evaluated APS patients at only two time points: (a) and (b). CGAS evaluations of medical records were done independently by two psychiatrists (H.H. and T.F.) with at least 5 years of experience in clinical child psychiatry, and the results were averaged. We performed a reliability analysis of the evaluations by the 2 psychiatrists and confirmed high interrater reliability of the scores at each time point (Cronbach α: (a) 0.904, (b) 0.813, (c) 0.731).

The Friedman test was used to compare means at the 3 time points, and adjustments for multiple comparisons were made by using the Steel-Dwass method. The Wilcoxon signed-rank test was used to compare means at 2 time points in the APS group.

This study was conducted with the approval of the Toho University School of Medicine Ethics Committee (approval No. 27059).

Results

Patients and clinical characteristics

A total of 18 patients (5 males and 13 females) met the selection criteria (Table 2). The definitive diagnosis was schizophrenia in 8 patients (44.4%), schizoaffective disorder in 2 patients (11.1%), bipolar disorder in 3 patients (16.7%), and APS in 5 patients (27.8%). The pathway to psychiatric care was referral by a pediatrician in 13 patients (72.2%), referral by an physician in 3 patients (16.7%), and another pathway in 2 patients (11.1%).

The most common medically unexplained somatic symptom was headache (6 patients, 33.3%; *e.g.*, "I have a throbbing ache in the back of my head"), followed by vertigo (5 patients, 27.8%; *e.g.*, "My head is spinning"), and nausea (4 patients, 22.2%; *e.g.*, "I feel sick, like I'm going to throw up"). More than 1 somatic symptom was present in 13 patients (72.2%).

The most common first psychiatric symptom was hypobulia (8 patients, 44.4%), followed by impaired concentration (7 patients, 38.9%), easy fatigability, and persecutory ideation (4 patients each, 22.2% each).

Intervals after appearance of somatic symptoms

The mean (SD) age when the first medically unexplained somatic symptom appeared was 13.4 (2.1) years in

the psychosis group and 12.0 (1.0) years in the APS group (Table 3). Age when the first psychiatric symptom appeared was 15.2 (2.0) years in the psychosis group and 12.8 (1.6) years in the APS group. Age at psychosis onset was 16.7 (2.5) years in the psychosis group.

The interval between appearance of the medically unexplained somatic symptom and appearance of the first psychiatric symptom was 22.7 (24.6) months (range 1–70 months) in the psychosis group and 9.6 (11.2) months (range 2–29 months) in the APS group. The interval between the appearance of the medically unexplained somatic symptom and psychosis onset was 38.8 (27.5) months (range 5–79 months) in the psychosis group.

Table 2 Patient characteristics (n = 18)

Gender, n (%)	
Male	5 (27.8)
Female	13 (72.2)
Diagnosis, n (%)	
Schizophrenia	8 (44.4)
Schizoaffective disorder	2 (11.1)
Bipolar disorder	3 (16.7)
Attenuated psychosis syndrome	5 (27.8)
Pathway to psychiatric care, n (%)	
Referred by pediatrician	13 (72.2)
Referred by physician	3 (16.7)
Others	2 (11.1)
Somatic symptoms, n (%)	
Headache	6 (33.3)
Vertigo	5 (27.8)
Nausea	4 (22.2)
Abdominal pain	3 (16.7)
Fatigue	3 (16.7)
Pain in arms and/or legs	2 (11.1)
Dyspnea	2 (11.1)
Palpitations	2 (11.1)
Orthostatic hypotension	2 (11.1)
Cold hands and feet	2 (11.1)
First psychiatric symptom, n (%)	
Hypobulia	8 (44.4)
Impaired concentration	7 (38.9)
Easy fatigability	4 (22.2)
Persecutory ideation	4 (22.2)
Depressed mood	3 (16.7)
Mood swings	3 (16.7)
Hypersensitivity	2 (11.1)

Differences in CGAS scores between time points

In the psychosis group, the mean (SD) CGAS score was (a) 79.1 (11.4) when the first medically unexplained somatic symptom appeared, (b) 51.5 (6.9) when the first psychiatric symptom appeared, and (c) 43.5 (5.5) at psychosis onset (Table 4). Mean CGAS score significantly differed in the psychosis group between times (a) and (b), (a) and (c), and (b) and (c).

In the APS group, the mean (SD) CGAS score was (a) 62.8 (9.4) when the first medically unexplained somatic symptom appeared and (b) 46.2 (1.6) when the first psychiatric symptom appeared; the difference was statistically significant.

Discussion

The mean (SD) CGAS score when the first medically unexplained somatic symptom appeared in the psychosis group was 79.1 (11.4). The descriptions of the CGAS (Table 1) indicate that psychosocial functioning in this group was lower than in healthy people when the first medically unexplained somatic symptom appeared. Mean CGAS score when the first psychiatric symptom appeared was 51.5 (6.9), which is significantly lower than when the somatic symptom appeared. The mean interval between appearance of the somatic symptom and appearance of the first psychiatric symptoms was 22.7 (24.6) months, and a marked drop (approximately 30 points) in psychosocial functioning score occurred during this relatively brief pe-

Table 3 Intervals after appearance of somatic symptoms

	Psychosis group (n = 13)	APS group (n = 5)
Age at appearance of first somatic symptom, years (mean ± SD)	13.4 ± 2.1	12.0 ± 1.0
Age at first visit to psychiatry department, years (mean ± SD)	14.9 ± 1.7	13.6 ± 1.9
Age at appearance of first psychiatric symptom, years (mean ± SD)	15.2 ± 2.0	12.8 ± 1.6
Age at onset of mental illness, years (mean ± SD)	16.7 ± 2.5	—
Interval between appearance of first somatic symptom and appearance of first psychiatric symptom, months (mean ± SD)	22.7 ± 24.6 (range 1–70)	9.6 ± 11.2 (range 2-29)
Interval between appearance of first somatic symptom and psychosis onset, months (mean ± SD)	38.8 ± 27.5 (range 5–79)	—

APS: attenuated psychosis syndrome

Table 4 Changes in CGAS scores between time points

	Mean ± SD			P-value		
	(a) Time of appearance of first somatic symptom	(b) Time of appearance of first psychiatric symptom	(c) Onset of mental illness	(a) vs. (b)	(b) vs. (c)	(a) vs. (c)
Psychosis group	79.1 ± 11.4	51.5 ± 6.9	43.5 ± 5.5	$p<0.01$	$p<0.05$	$p<0.01$
APS group	62.8 ± 9.4	46.2 ± 1.6	—	$p<0.05$		

CGAS: Children's Global Assessment Scale, APS: attenuated psychosis syndrome

riod. Mean (SD) CGAS score at psychosis onset was 43.5 (5.5), a significant decrease in comparison with the time when the first psychiatric symptom appeared. In other words, psychosocial functioning had also decreased during the interval between the appearance of the first psychiatric symptom and the onset of full-blown psychosis. Many of the present patients had been examined in a psychiatry department before the appearance of the first psychiatric symptom, or a relatively short time thereafter, and intervention had been performed relatively early. Nevertheless, a significant decrease in psychosocial functioning occurred and the patients' symptoms progressed to psychosis. These findings suggest that many patients develop psychosis because their condition is not diagnosed and that the risk of mental illness is not appreciated by pediatricians or general practitioners when patients are examined for a chief complaint of somatic symptoms. It is thus important to obtain a comprehensive medical history, with a focus on psychosocial functioning, after a medically unexplained somatic symptom appears in childhood or adolescence and to evaluate changes in psychosocial functioning, when needed, while carefully monitoring the patient's course.

The mean (SD) CGAS score when the first medically unexplained somatic symptom appeared in patients with APS (who are believed to have a higher risk for future psychosis) was 62.8 (9.4), and psychosocial functioning when the somatic symptom appeared was obviously lower than in healthy people. The CGAS score when the first psychiatric symptom appeared was 46.2 (1.6), which was significantly lower than the score at the time when the somatic symptom first appeared. The results in the APS group suggest that psychosocial functioning had decreased between the time when the somatic symptom first appeared and the time when the first psychiatric symptoms appeared, *i.e.*, 9.6 (11.2) months.

In mental illness, especially in schizophrenia, there is a period of nonspecific prodromes — such as loss of sleep, anxiety, impatience, and somatic symptoms — before the illness manifests clinically. Changes in brain parenchyma are already present during the prodromal period, and earlier studies found reduced cognitive functioning due to organic changes in the brain.[21, 22] Diminished cognitive function may be associated with decreased psychosocial functioning preceding the onset of manifest psychosis observed in the present study.

A previous report found that the interval between the appearance of prodromal symptoms in schizophrenia and full-blown onset of psychosis and clinical evaluation was relatively long, 48 months or longer.[23] If attention is paid to the decrease in psychosocial functioning in the relatively brief interval between the appearance of a medically unexplained somatic symptom and the appearance of the first psychiatric symptom, as suggested in the present study, clinicians might be able to intervene early, before the onset of full-blown psychosis.

Earlier studies suggested that medically unexplained somatic symptoms in childhood and adolescence are predictors of mental illnesses such as depression and anxiety disorder in young adults and adults.[24–26] One report noted that children with medically unexplained somatic symptoms in childhood and adolescence tend to exhibit more anxiety and depressive symptoms than do children with a medical diagnosis or healthy children.[27] Other reports indicate that children who received diagnoses of depression and separation anxiety disorder tended to have somatic complaints.[28, 29] Consequently, medically unexplained somatic symptoms in childhood and adolescence are now considered to be closely associated with depression and anxiety disorder. Our findings indicate that attention needs to be paid to medically unexplained somatic symptoms as potential prodromes of SMIs, including schizophrenia, and other common mental disorders.

Headache was the most frequent (6 patients; 33.3%) medically unexplained somatic symptom in this study and is the most frequent somatic symptom in childhood and

adolescence.[30] It was reported to be the most frequent form of somatization in previous studies of somatization in adolescence.[31–34] The present results suggest that headache is a somatic symptom that should be evaluated as a potential prodrome of psychosis and that it needs to be viewed cautiously.

Earlier studies reported that psychiatric symptoms such as depressive mood and anxiety were frequently the first sign preceding a psychotic episode.[6, 23, 35] Hypobulia was the most common psychiatric symptom in the present study (8 of the present patients; 44.4%), followed by impaired concentration (7 patients; 38.9%), which differs from the findings of previous studies of Western populations.[6, 23] Hypobulia and impaired concentration are more common and nonspecific than depressive mood and anxiety. Thus, it is possible that methods such as those considered in the present study, which begin to follow a patient's course when medically unexplained somatic symptoms appear, might identify psychiatric symptoms at an earlier stage. In addition, few studies have evaluated prodromes of psychosis in Japanese adolescents, and cultural and regional differences may be important factors.

Limitations

The CGAS was developed for children aged 4 to 16 years and was based on the GAS,[17] a scale for adults.[16] However, some of the present patients were older than 16 years when the first psychiatric symptom appeared and at the time of psychosis onset. The CGAS is structurally very similar to the GAS, and no theoretical reason has been suggested for selecting age 16 years as the upper age limit for the CGAS.[36] Because several studies have used the CGAS for persons older than 16 years, without a decrease in interrater reliability,[37–40] we believe that its use as a scale to evaluate psychosocial functioning in the present study was appropriate. In addition, this was a retrospective study of medical records, and data on symptoms and psychosocial functioning may have been inadequate. Future, prospective studies should enroll a larger number of cases.

Conclusion

This medical chart review investigated 18 patients with medically unexplained somatic symptoms during childhood and adolescence who subsequently developed an SMI. Headache was the most common medically unexplained symptom preceding an SMI. CGAS score assessment when the first somatic symptom appeared, when the first psychiatric symptom appeared, and at psychosis onset revealed that psychosocial functioning was already lower than that of healthy persons when the first somatic symptom appeared, and that scores had significantly progressively decreased at the time when the first psychiatric symptom appeared and at the time of onset of full-blown psychosis. These findings highlight the need for careful assessment of psychosocial functioning at the earliest stage, a comprehensive history of patients who exhibit medically unexplained somatic symptoms in childhood or adolescence, and evaluation of changes in psychosocial functioning, as the need arises, while carefully monitoring patient course.

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References

1) McGorry P, Bates T, Birchwood M. Designing youth mental health services for the 21st century: examples from Australia, Ireland and the UK. Br J Psychiatry Suppl. 2013; 54: s30-5.
2) Mizuno M, Nemoto T, Tsujino N, Funatogawa T, Takeshi K. Early psychosis in Asia: insights from Japan. Asian J Psychiatr. 2012; 5: 93-7.
3) Morita K, Kobayashi H, Takeshi K, Tsujino N, Nemoto T, Mizuno M. Poor outcome associated with symptomatic deterioration among help-seeking individuals at risk for psychosis: a naturalistic follow-up study. Early Interv Psychiatry. 2014; 8: 24-31.
4) Nishii H, Yamazawa R, Shimodera S, Suzuki M, Hasegawa T, Mizuno M. Clinical and social determinants of a longer duration of untreated psychosis of schizophrenia in a Japanese population. Early Interv Psychiatry. 2010; 4: 182-8.
5) Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr Bull. 1996; 22: 353-70.
6) Iyer SN, Boekestyn L, Cassidy CM, King S, Joober R, Malla AK. Signs and symptoms in the pre-psychotic phase: description and implications for diagnostic trajectories. Psychol Med. 2008; 38: 1147-56.
7) Norman RM, Scholten DJ, Malla AK, Ballageer T. Early signs in schizophrenia spectrum disorders. J Nerv Ment Dis. 2005; 193: 17-23.
8) Yung AR, McGorry PD. The initial prodrome in psychosis: descriptive and qualitative aspects. Aust N Z J Psychiatry. 1996; 30: 587-99.
9) Gourzis P, Katrivanou A, Beratis S. Symptomatology of the initial prodromal phase in schizophrenia. Schizophr Bull. 2002; 28: 415-29.

10) Kessler RC, Berglund PA, Bruce ML, Koch JR, Laska EM, Leaf PJ, et al. The prevalence and correlates of untreated serious mental illness. Health Serv Res. 2001; 36 (6 Pt 1): 987-1007.
11) Planner C, Gask L, Reilly S. Serious mental illness and the role of primary care. Curr Psychiatry Rep. 2014; 16: 458.
12) Yung AR. Risk, disorder and diagnosis. Aust N Z J Psychiatry. 2011; 45: 915-9.
13) American Psychiatric Association. Diagnostic and statistical manual of mental disorders 5th ed, American Psychiatric Association Publishing, Arlington (VA), 2013.
14) Yung AR, Woods SW, Ruhrmann S, Addington J, Schutze-Lutter F, Cornblatt BA, et al. Whither the attenuated psychosis syndrome? Schizophr Bull. 2012; 38: 1130-4.
15) American Psychiatric Association. Diagnostic and statistical manual of mental disorders 5th ed, American Psychiatric Association Publishing, Arlington (VA), 2013. p. 783-6.
16) Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, et al. A children's global assessment scale (CGAS). Arch Gen Psychiatry. 1983; 40: 1228-31.
17) Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry. 1976; 33: 766-71.
18) Bird HR, Canino G, Rubio-Stipec M, Ribera JC. Further measures of the psychometric properties of the Children's Global Assessment Scale. Arch Gen Psychiatry. 1987; 44: 821-4.
19) Green B, Shirk S, Hanze D, Wanstrath J. The Children's Global Assessment Scale in clinical practice: an empirical evaluation. J Am Acad Child Adolesc Psychiatry. 1994; 33: 1158-64.
20) Dyrborg J, Larsen FW, Nielsen S, Byman J, Nielsen BB, Gautè-Delay F. The Children's Global Assessment Scale (CGAS) and Global Assessment of Psychosocial Disability (GAPD) in clinical practice — substance and reliability as judged by intraclass correlations. Eur Child Adolesc Psychiatry. 2000; 9: 195-201.
21) Katagiri N, Pantelis C, Nemoto T, Zalesky A, Hori M, Shimoji K, et al. A longitudinal study investigating sub-threshould symptoms and white matter changes in individuals with an 'at risk mental state' (ARMS). Schizophr Res. 2015; 162: 7-13.
22) Pantelis C, Bartholomeusz CF. Social neuroscience in psychiatry: pathways to discovering neurobiological risk and resilience. World Psychiatry. 2014; 13: 146-7.
23) Häfner H, Maurer K, Trendler G, an der Heiden W, Schmidt M. The early course of schizophrenia and depression. Eur Arch Psychiatry Clin Neurosci. 2005; 255: 167-73.
24) Campo JV. Annual research review: functional somatic symptoms and associated anxiety and depression — developmental psychopathology in pediatric practice. J Child Psychol Psychiatry. 2012; 53: 575-92.
25) Bohman H, Jonsson U, Päären A, von Knorring L, Olsson G, von Knorring AL. Prognostic significance of functional somatic symptoms in adolescence: a 15-year community-based follow-up study of adolescents with depression compared with healthy peers. BMC Psychiatry. 2012; 12: 90.
26) Shelby GD, Shirkey KC, Sherman AL, Beck JE, Haman K, Shears AR, et al. Functional abdominal pain in childhood and long-term vulnerability to anxiety disorders. Pediatrics. 2013; 132: 475-82.
27) Imran N, Ani C, Mahmood Z, Hassan KA, Bhatti MR. Anxiety and depression predicted by medically unexplained symptoms in Pakistani children: a case-control study. J Psychosom Res. 2014; 76: 105-12.
28) McCauley E, Carlson GA, Calderon R. The role of somatic complaints in the diagnosis of depression in children and adolescents. J Am Acad Child Adolesc Psychiatry. 1991; 30: 631-5.
29) Livingston R, Taylor JL, Crawford SL. A study of somatic complaints and psychiatric diagnosis in children. J Am Acad Child Adolesc Psychiatry. 1988; 27: 185-7.
30) Casucci G, Terlizzi R, Cevoli S. Headache in school age. Neurol Sci. 2014; 35 (Suppl 1): 31-5.
31) Vila M, Kramer T, Hickey N, Dattani M, Jefferis H, Singh M, et al. Assessment of somatic symptoms in British secondary school children using the Children's Somatization Inventory (CSI). J Pediatr Psychol. 2009; 34: 989-98.
32) Romero-Acosta K, Canals J, Hernández-Martínez C, Penelo E, Zolog TC, Domèneck-Llaberia E. Age and gender differences of somatic symptoms in children and adolescents. J Ment Health. 2013; 22: 33-41.
33) Garber J, Walker LS, Zeman J. Somatization symptoms in a community sample of children and adolescents: further validation of the children's somatization inventory. Psychol Assess. 1991; 3: 588-95.
34) Kelly C, Molcho M, Doyle P, Gabhainn SN. Psychosomatic symptoms among schoolchildren. Int J Adolesc Med Health. 2010; 22: 229-35.
35) Kobayashi H, Yamazawa R, Nemoto T, Murakami M, Kashima H, Mizuno M. Correlation between attenuated psychotic experiences and depressive symptoms among Japanese students. Early Interv Psychiatry. 2010; 4: 200-5.
36) Schorre BE, Vandvik IH. Global assessment of psychosocial functioning in child and adolescent psychiatry. a review of three unidimensional scales (CGAS, GAF, GAPD). Eur Child Adolesc Psychiatry. 2004; 13: 273-86.
37) Rey JM, Starling J, Wever C, Dossetor DR, Plapp JM. Inter-rater reliability of global assessment of functioning in a clinical setting. J Child Psychol Psychiatry. 1995; 36: 787-92.
38) Rangel L, Garralda ME, Hall A, Woodham S. Psychiatric adjustment in chronic fatigue syndrome of childhood and in juvenile idiopathic arthritis. Psychol Med. 2003; 33: 289-97.
39) Thomsen PH. Child and adolescent obsessive-compulsive disorder treated with citalopram: findings from an open trial of 23 cases. J Child Adolesc Psychopharmacol. 1997; 7: 157-66.
40) Weissman MM, Warner V, Fendrich M. Applying impairment criteria to children's psychiatric diagnosis. J Am Acad Child Adolesc Psychiatry. 1990; 29: 789-95.