Aripiprazole once-monthly as treatment for psychosis in Turner syndrome: literature review and case report

Somministrazione mensile di aripirazolo long-acting come trattamento dei sintomi psicotici nella sindrome di Turner: revisione della letteratura e caso clinico

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SUMMARY. Turner syndrome (TS) is a neurogenetic disorder characterized by partial or complete monosomy-X, usually resulting of a sporadic chromosomal nondisjunction. It is one of the most common sex chromosome abnormalities, affecting approximately 1 in 2,000 live born females. There are sporadic few case reports of concomitant TS with schizophrenia worldwide. No defined psychiatric condition has been traditionally related to TS, and it is not mentioned in DSM-IV. Although it is not associated with any psychiatric syndrome, several case reports in the literature describe a similar constellation of symptoms in TS that may represent a biologically-based entity. Aripiprazole once-monthly is a second generation antipsychotic recently developed. Its efficacy and non-inferiority to oral aripiprazole have been demonstrated in preventing relapse in patients with schizophrenia. Experience with oral aripiprazole and the current availability of the long-acting formulation suggest a potential benefit in a variety of clinical scenarios and therefore consideration as a treatment option in the treatment of schizophrenia and psychotic symptoms in several disease like TS.

KEY WORDS: aripiprazole, Turner syndrome, psychosis, schizophrenia, long acting, second generation antipsychotic.

RIASSUNTO. La sindrome di Turner (ST) è una malattia neurogenetica caratterizzata da parziale o completa monosomia-X, di solito risultante da una non disgiunzione cromosomica sporadica. Si tratta di una delle più comuni anomalie dei cromosomi sessuali, colpendo circa 1 su 2.000 femmine nate vive. Nessuna condizione psichiatrica è stata tradizionalmente legata alla ST, ed essa non è menzionata nel DSM-IV. Nel mondo, tuttavia, sono riportati casi di ST concomitanti con patologia schizofrenica e/o con sintomatologia psicotica. Benché la ST non sia associata ad alcuna sindrome psichiatrica specifica, i casi riportati in letteratura che descrivono una simile costellazione di sintomi arrivano quasi a rappresentare un'entità biologica a sé stante. Di recente è stata sviluppata la formulazione mensile intramuscolare dell'antipsicotico di seconda generazione aripiprazolo. La sua efficacia e non inferiorità rispetto alla formulazione orale è stata dimostrata nel trattamento della sintomatologia psicotica e nella prevenzione delle recidive nei pazienti con schizofrenia. L'attuale disponibilità della formulazione aripiprazolo long-acting rappresenta un potenziale beneficio in una varietà di casi clinici, e può essere presa in considerazione come opzione terapeutica anche nella schizofrenia e nei sintomi psicotici associati alla ST.

PAROLE CHIAVE: aripiprazolo, sindrome di Turner, psicosi, schizofrenia, long acting, antipsicotici atipici.

INTRODUCTION

Turner syndrome (TS) is a neurogenetic disorder characterized by partial or complete monosomy-X, usually resulting of a sporadic chromosomal nondisjunction. TS is one of the most common sex chromosome abnormalities, affecting approximately 1 in 2,000 live born females[1,2]. In this common genetic syndrome a woman has a 45XO or 45XO/46XXmosaic karyotype.

TS is associated with certain physical and medical features including estrogen deficiency, short stature and increased risk for several diseases with cardiac conditions being among the most serious.

Girls with TS are typically treated with growth hormone and estrogen replacement therapies to address short stature and estrogen deficiency. The cognitive-behavioral phenotype associated with TS includes strengths in verbal domains with impairments in visual-spatial, executive function and emotion processing[3].

Furthermore neuroanatomical imaging provided evidence of abnormalities in several brain structures, including the parietal lobe, amygdala, hippocampus, and orbito-frontal cortex[4].

Abnormalities of sex chromosomes are associated with various forms of neuropsychiatric disorders, such as schizophrenia. Both TS and schizophrenia are relatively infrequent conditions. Consequently, individuals having both illnesses

are rare. Genetic factors play an important role in the developing schizophrenia. The risk of schizophrenia is 3 times higher in people with mild learning disability than in the general population and chromosomal abnormalities are increased. In general, TS is found about three times more often in female schizophrenics than in the general female population[5].

Recently the hypothesis of a locus within the pseudoautosomal region of the X chromosome conferring susceptibility to schizophrenia has been studied. De Lisi et al.[6] reported that neuropsychiatric findings of XXY karyotype individuals with schizophrenia result from genes within the pseudoautosomal region in the X chromosome and tend to avoid normal extra-X chromosome inactivation. These regions may produce their gene products in excess, influencing normal brain growth and differentiation. On the other hand non-pseudoautosomal regions of the X chromosome, mapping to a locus on Xp21, have been associated with the development of schizophrenia[7].

There are sporadic few case reports of concomitant TS with schizophrenia worldwide. TS may lead to an increased risk for schizophrenia. Interestingly, most TS females had a 45,X nonmosaic karyotype, whereas the majority of comorbidity between TS and schizophrenia had a mosaic karyotype (45,X/46,XX). Thus, it has been suggested that the potential of gene dose-effect might be associated with abnormal expression of an X chromosome gene product, which have susceptibility for schizophrenia in TS[8].

Genetic analyses have identified the short stature homeobox (SHOX) gene as being a candidate gene for short stature and other skeletal abnormalities associated with TS, but currently the gene or genes associated with cognitive impairments remain unknown.

A polymorphism of the HOPA gene within Xq13 termed HOPA(12bp) is associated with schizophrenia, mental retardation, and hypothyroidism. Interestingly, Xq13 is the X-chromosome region that contains the X-inactivation center and a gene escaping X-inactivation whose gene product may be involved in the X-inactivation process as well as in the pathogenesis of sex chromosome anomalies such as TS. These genes that escape X-inactivation may produce their gene products in excess, influencing normal brain growth and differentiation[9].

However, significant progress has been made in describing neurodevelopmental and neurobiologic factors underlying these impairments and potential interventions are on the horizon[10].

Given the potential role of genes on the X-chromosome in the pathogenesis of schizophrenia, the study of unique populations with abnormalities in this chromosome, such as women with TS, may offer clues into this illness.

TURNER SYNDROME AND PSYCHIATRIC DISEASES

No defined psychiatric condition has been traditionally related to TS, and TS is not mentioned in DSM-IV. Although it is not associated with any psychiatric syndrome, several case reports in the literature describe a similar constellation of symptoms in TS that may represent a biologically-based entity[11-23].

Much writing about the psychological aspects of TS has focused on the influence of the physical stigma of TS on psychological development in young womanhood, highlighting short stature, failure to sexually mature at the same age as their peers, the issue of infertility, and how these issues relate to self-image and femininity. A "TS personality" characterized by excessive dependence, immaturity, depressiveness, passivity, distractibility, and docility is suggested by Nielsen and Thomsen[24], although no rigorous scientific study has examined these claims.

Other psychological aspects considered are parental difficulties in accepting the disorder and discussing it openly, and the difficulties in building a self-image as a sexually developed adult[25].

Less is known regarding psychosocial and psychiatric functioning in TS. Studies attempting to correlate TS with psychiatric illness statistically have had mixed results.

Shyness, anxiety, low self-esteem and depression, frequently linked to self-consciousness over physical appearance and/or infertility, have been described in studies of TS. However, psychiatric functioning remains an area of limited and conflicting information in TS, requiring further study.

In a study of 100 individuals with TS, age 16-61, Schmidt et al.[26] used 4 rating scales and noted significantly higher anxiety, shyness and depression as well as lower self-esteem compared to controls. These findings were irrespective of factors such as age, education and marital status.

Girls with TS age 9-17 demonstrated lower self-esteem and higher levels of state anxiety than controls using different self-report measures. They were at risk of psychological problems. Therefore, in addition to medical treatment and monitoring, girls with TS should also be supported psychologically by social, educational and psychotherapeutic interventions which aim to address their self-esteem and emotional difficulties[27].

In a 2006 study of Carel et al.[28] indicated that low self-esteem and poor social adjustment are associated with delayed or absent sexual relationship experiences. Moreover, whereas many reports have suggested height, physical appearance and/or infertility as underlying factors in low self-esteem, they demonstrated that hearing loss, socioeconomic status and cardiac problems also may contribute to impaired social adjustment.

Another group noted lower self-perception and bodily attitude but no evidence of depression in 50 females with TS (mean age 18 + 0.3) who completed self-report scales[29].

One study that included self-report and parental ratings indicated that girls with TS age 6-22 were not significantly more anxious than controls[30].

A large study involving 100 women with TS age 16-61 utilizing a structured diagnostic interview indicated that lifetime incidence of mood disorders, but not anxiety, was twice as high as community based samples. However, current and lifetime prevalence of psychiatric syndromes including mood and anxiety disorders was not substantially higher in TS than that of individuals in medical outpatient or gynaecological clinics. This suggests that mood disturbance in TS is not likely specific to TS but rather increased due to medical problems in general[31].

McCauley et al.[32] surveyed 10 cytogenetic studies of chronically psychotic patients, and in a total of 6,483 patients found 11 cases of TS, or three times the expected number if the diseases were to occur simultaneously only randomly.

Bamrah and MacKay[33], however, found no correlation between TS and psychotic illness.

In an early review of studies, including over 5,000 patients (some overlapping with Bamrah and MacKay), Moor found only two cases of TS. In evaluating case studies, he suggests a psychological "fragilité" in TS that confers a vulnerability to psychiatric syndromes[34].

Despite the unclear statistical data, a surprising cluster of authors have noted unusual cases of TS and psychiatric illness, and several case-reports have appeared in psychiatric literature.

Mellbin briefly describes four TS women; two suffered from psychoses: one had "attacks of laughing or weeping" and the other, who also suffered from epilepsy, slowly became withdrawn and psychotic at age 23, "began feeling that her end was near, refused to eat," yet recovered within a few weeks of her hospitalization and never had another episode[35].

In another report, Nielsen[36] describes 13 case histories of women with TS. Two of them featured women who had psychotic reactions to life stressors, and another one had a psychiatric syndrome that was questionably organic. One of the women with psychosis was first hospitalized at age 53, following her mother's definitive diagnosis with dementia. She was "anxious and agitated… occasionally very disturbed and screaming". She responded well to "psychotropic drugs" later in her hospitalization. The other psychosis patient presented with psychiatric symptoms at the age of 42 after hospitalization related to diabetes. She was "slightly paranoid". One year later, "she was very unstable and occasionally on the borderline of a paranoid state".

Prior et al.[37] also describes two cases. His first patient presented with a psychotic episode at age 28. She, however, did fit the clinical diagnosis for schizophrenia and was treated successfully with zuclopenthixol. The second patient presented with mood and psychotic symptoms and responded to risperidone. Both cases were noted for diagnostic and treatment difficulties. The second patient was, in other institutions, diagnosed with bipolar disorder, and over many years was treated variously with thioridazine, pipothiazine, amitriptyline, paroxetine, lithium and zopiclone. On another occasion, she returned with auditory hallucinations and received risperidone.

Trapet et al.[38] described a case that illustrated the influence that the patient's psychological issues had on the content of her psychotic features. The patient had a monozygotic twin brother, apparently healthy. In her 20s, she was hospitalized with depression, euphoria, erotomania, and sometimes a mute dissociative state. Later, she claimed that someone had "switched her head," and had speech disturbances that suggested schizophrenia. She had a prolonged remission, but relapsed under life stresses. Her syndrome included agitated depression, bizarre behaviors, and a psychosis with genetic themes. The psychosis passed with antipsychotic treatment, to be replaced by apathy. The authors, like others, hypothesized an "inherent genetic vulnerability" to psychotic syndromes in TS, triggered by stressful circumstances.

Further studies, including comorbid case reports are needed in order to discern the pathogenesis of schizophrenia in TS. It is important for practitioners to understand the clinical spectrum and the natural courses, including the development of schizophrenia, in mosaic TS.

The vast majority of TS patients are of normal intelligence, social functioning and employment, yet the case reports of psychiatric disorders in this syndrome are strikingly similar and were considered unique enough to warrant description. Despite the descriptive and observational information, the literature lacks rigorous, statistical examination directed toward identifying the described syndrome in TS. The fact that the syndrome is not widely present in TS women hints at a shared organically-based vulnerability to this particular psychopathology inherent in a subset of TS patients. At a glance, the available case reports share several unique features, such as diagnostic difficulty and/or patients who receive many heterogeneous diagnoses. There may in fact be a previously unreported, unique psychiatric-genetic vulnerability found in women with TS, as yet unidentified, that would appear to be characterized by mild psychotic features that remit, or respond well to antipsychotic medication, stress-precipitated onset and prominent anxiety symptoms, relatively late-in-life onset, labile mood (e.g., depressive or hypomanic features), confusional features that can resemble organic disease, and a relatively benign course[39].

LONG ACTING INJECTABLE ANTIPSYCHOTIC IN SCHIZOPHRENIA

Schizophrenia is a severe and debilitating psychiatric disorder. Pharmacological interventions aim to ameliorate symptoms and reduce the risk of relapse and costly hospitalisation. Despite the established efficacy of antipsychotic medication, compliance to treatment is poor, particularly with oral formulation. Relapse in schizophrenia has been associated with poor adherence to oral medication. A possible method to optimize medication adherence could be to switch patients from oral to depot medication. The emergence of long acting injectable (LAI) antipsychotic formulations in recent years has aimed to counteract the poor compliance rates observed and optimise long term patient outcomes with a better pharmacokinetic coverage[40,41].

Aripiprazole is an atypical antipsychotic drug that is proposed to act via partial agonism of dopamine D2 receptors. Trials with oral aripiprazole have shown that, compared with some other atypical antipsychotics, aripiprazole is associated with fewer metabolic disturbances and has a favourable cardiovascular tolerability profile[42].

Aripiprazole once-monthly (AOM) is a second generation antipsychotic (SGA) recently developed as a LAI in the form of a suspension of lyophilized aripiprazole reconstituted with an aqueous diluent, for intramuscular deltoid or gluteal administration.

The most common adverse events were injection site pain and headache of mild intensity occurring at a similar rate with deltoid and gluteal administration. Exposure ranges with deltoid and gluteal administration overlapped, suggesting that these sites may be used interchangeably. Despite a higher incidence of adverse events, deltoid muscle provides a more accessible injection site and could facilitate patient acceptance[43].

Its efficacy and non-inferiority to oral aripiprazole have been demonstrated in preventing relapse in patients with

schizophrenia. Aripiprazole LAI appears cost-effective versus other SGA-LAIs, with a reduction in hospitalization and associated costs compared with previous antipsychotic treatment. Safety and tolerability are comparable to oral aripiprazole, particularly in terms of metabolic and neurological side-effects, with no new safety signals[44-48].

Pharmacokinetic data support 400 mg as the starting and maintenance dose of AOM; the plasma concentration profile of aripiprazole after initiating AOM 400 was consistent with therapeutic concentrations observed with oral aripiprazole 10 to 30 mg/d. Median aripiprazole plasma concentrations reach therapeutic levels within 7 days of initiating AOM 400. Because of interpatient variability, a 14-day overlap with oral aripiprazole or another antipsychotic medication is considered sufficient to ensure therapeutic concentrations. The efficacy and safety of AOM 400 were comparable between subpopulations of patients previously stabilized on 10- or 30-mg doses of oral aripiprazole[49-51].

CASE REPORT

R.T. is a 52 years old woman with Turner Syndrome, known to our psychiatric outpatient service for over twenty years. Medical history shows cardiac hypertrophy, hypoacusis, need for supplementary estrogenic therapy, thyroid disease with detection of TSH low levels and elevated thyroglobulin antibodies.

Psychopathological onset can be traced back to the adolescence, with symptoms worsened over the years and characterized by: irritability, agitation, rage crisis and dysphoria, behavior disorder with episodes of verbal and physical aggression; feelings of inadequacy, failure, worthlessness; decreased capacity for judgment, problems in conceptualizing, planning difficulties; mood characterized by mild hyperthymia; widespread and poorly structured paranoid delusions. The clinical situation is compatible with a diagnosis of undifferentiated schizophrenia.

Suggested therapies (carbamazepine, valproic acid, haloperidol, risperidone, paliperidone) were often independently suspended, complaining vague and unspecified side effects[52-54]. Over the years the patient has always shown little participation in treatment programs and rehabilitation proposal, with poor therapeutic compliance and long periods of absence for outpatient medical checkups.

Hospital treatment has been necessary for serious psychological impairment. Kennedy Axis V scale was administered, showing impairment in social and occupational skills and in attending to activities of daily living (no friends, frequent conflicts with peers because of inappropriate and frequently intrusive behavior, great difficulty in communicating thoughts and feelings), moreover were underlined problems with anger and irritability with occasional thoughts of violent behaviour[55].

It was then set the following therapy: valproic acid 500 mg/die (54.1 microg/mL concentration in blood), aripiprazole 20 mg/die per os and 400 mg once-monthly for intramuscular administration.

Brief Psychiatry Rating Scale score is reduced from 61 to 35, with great improvement in psychotic paranoid symptoms and behavior disorders.

Today, months after discharge, outpatient follow-up at our psychiatric service is still regular with good control of symptoms.

CONCLUSIONS

TS is fairly common, and, therefore, the existence of such psychiatric syndrome has practical implications for many patients and medical and psychological practitioners. Given the frequency of TS and the existing literature, this subject warrants more thorough, planned scientific investigation to confirm or deny the existence of the syndrome. If it is a unique syndrome, it is important to identify it in order to avoid labeling patients with a more severe diagnosis, to determine its frequency and epidemiology, to understand its biological basis, and, most importantly, to identify optimal treatment strategies.

Significant progress has been made in describing the cognitive-behavioral, neurobiologic, endocrinologic, physical and genetic factors associated with TC. However, many questions remain. Studies involving genetic analyses such as microarray technology will be necessary to examine gene expression profiles in girls with TS and identify potential candidate genes underlying the cognitive-behavioral impairments associated with TS. Continued studies of Xlinked genes that escape inactivation and have Y chromosome homologues also will be essential in identifying candidate genes involved in the cognitive-behavioral and physical phenotypes of TS. These studies would offer a unique opportunity to investigate the relationship between X chromosome gene function and cognitive-behavioral phenotype. Future studies could begin including individuals with mosaic TS genotypes and compare their outcome to those with a non-mosaic genotype.

Multimodal, interdisciplinary studies will be essential for identifying optimal, syndrome-specific interventions for improving the lives of individuals with TS.

Experience with oral aripiprazole and the current availability of the long-acting formulation suggest a potential benefit in a variety of clinical scenarios and therefore consideration as a treatment option in the treatment of schizophrenia and psychotic symptoms in several disease like TS[56-58].

Future research should assess the use of LAI antipsychotics earlier in the disease course of schizophrenia to see whether improved compliance and outcomes shortly following the onset of psychosis has the potential to alter the disease trajectory. Moreover it should be assessed whether changes in the disease trajectory can alleviate cost and resource pressures placed on national health services.

Conflict of interest: the authors declare that they have no conflict of interest.

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