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Research progress of treatment-resistant schizophrenia

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Abstract

In order to solve the problem of the developmental limitations of patients with refractory schizophrenia in the psychiatric field, this paper makes a qualitative systematic review of refractory schizophrenia to provide reference and guidance for future research and clinical treatment. The article will elaborate on neurobiology, neuroimaging, treatment and so on.

Keywords: treatment-resistant schizophrenia; clozapine; neurobiology; neuroimaging; therapy

Schizophrenia is a serious neuropsychiatric disorder that affects about 0.5-1% of the population. About 30% of patients are classified as refractory schizophrenia. Refractory schizophrenia is defined as the absence of response to at least two trials of antipsychotic drugs of sufficient dose and duration, and these patients are usually treated with clozapine, the only evidence-based drug therapy for refractory schizophrenia[1].However, clozapine has been linked to serious adverse events such as paralytic intestinal obstruction, myocarditis, agranulocytosis, etc., limiting clinical use[2].The cause of schizophrenia is currently unknown, and there are certain limitations to treatment. Therefore, by summarizing relevant data, this paper focuses on a comprehensive overview of neurobiology, neuroimaging, treatment, etc., aiming to enhance the more in-depth research and treatment of refractory schizophrenia.

I Information and Methodology

1.1 Sources and search strategies

1.1.1 Sources

CNKI, Wanfang Database and PubMed were searched to collect and summarize the research on patients with refractory schizophrenia at home and abroad from January 2007 to August 2022.

1.1.2 Search strategy

Chinese search uses the theme term "refractory schizophrenia" and the English search uses the theme term "refractory Schizophrenia" and "Treatment-resistent schizophrenia". Chinese search formula: refractory schizophrenia; The English search query is: ("refractory Schizophrenia"OR"refractory Schizophrenias"OR"Treatment-resistent schizophrenia"OR"Treatment-resistent schizophrenias".

1.2 Exclusion criteria for inclusion in the literature

Inclusion criteria: (1) The study subjects were patients who met the diagnostic criteria for refractory schizophrenia; (2) Chinese and English literature. Exclusion criteria: (1) duplicate publications or duplicate detected documents; (2) The full text of the document cannot be obtained.

1.3 Literature screening and quality assessment

Two researchers independently conducted a literature search, cross-reviewed, comprehensively checked out the literature, and if there is a dispute over whether it is included, the opinions of the instructor are sought. The two researchers will conduct screening and quality assessment respectively, conduct preliminary screening by reading the title and abstract, and then select the documents that meet the requirements in strict accordance with the inclusion exclusion criteria by reading the full text.

2 Results

2.1 Basic information of the included literature

A total of 3911 articles were obtained in the preliminary search, including 2600 English articles and 1311 Chinese documents. By excluding duplicate documents, reading titles and abstracts, 115 articles were screened; By reading the full text, 59 documents whose detailed content did not meet the requirements were excluded, and a total of 56 documents were finally included.See Figure 1.

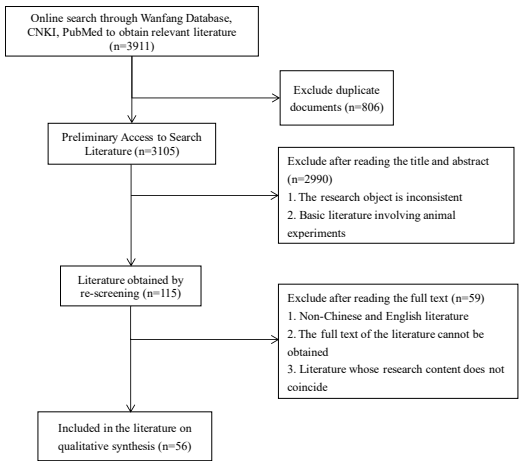

Figure 1 Literature search flowchart

2.2 Neurobiology

Due to the high complexity of human brain structure and functional activities, the exact causes and influencing factors of refractory schizophrenia are not very clear, and its pathogenesis is still unclear. A relatively large number of these studies suggest that refractory schizophrenia and non-refractory schizophrenia may be associated with different dopaminergic and glutamergic regulation[3-5]. First- and second-generation antipsychotics are largely based on the dopaminergic hypothesis, and some studies have shown that dopamine activity in the striatum and imbalances in glutamatergic neurometabolites in all cortical regions of the brain may lead to psychotic symptoms and functional decline[6, 7].Some scholars[8]have proposed it, Patients with refractory schizophrenia may be associated with the interaction of glycine signaling with glutamagnogeneous postsynaptic density.Studies by Huang et al.[9]have shown that glutamatergic concentrations in the anterior cingulate cortex play an important role in the classification of refractory schizophrenia and cognition.Huang et al.[10]proposed that the upregulated serotonin(5-HT) biosynthetic pathway may be associated with refractory schizophrenia, suggesting that the targeted mechanism of 5-HT conversion from tryptophan may contribute to the development of new pharmacological approaches to refractory schizophrenia. Studies have compared the anisotropic fraction (FA) of white matter in patients with refractory schizophrenia and non-treatment-resistant schizophrenia. The FA of the corpus callosum (CC) was significantly reduced in the refractory schizophrenia group compared to the non-refractory schizophrenia group, and it is hypothesized that focal abnormalities in CC may be a potential biomarker for refractory schizophrenia[11].In view of the imbalance of the transvulcanization pathway and the imbalance of other pathways caused by the transvulcanization pathway, some scholars[12]have proposed a treatment plan for refractory schizophrenia. Recent studies[13]have speculated that refractory schizophrenia may be related to the gut microbiota. Scholars[14]have also discussed the efficacy of D-amino acids in patients with refractory schizophrenia, including D-serine, D-aspartic acid, and D-alanine.Labonté et al.[15]support the view that persistent inflammation is a marker of the biological signature of treatment resistance to schizophrenia. Huang et al.[16]proposed that in patients with refractory schizophrenia, elevated levels of kynusine creatine in saliva are associated with enlarged choroidal plexus and clinical phenotypic severity. Future research should focus on in-depth study of these mechanisms in order to improve the capacity of personalized drug use.

2.3 Neuroimaging

With the development of CT, MRI, fMRI, MRS, PET, SPECT and other technologies, the study of brain structure and brain function in vivo makes it possible to further determine the pathophysiological mechanism of refractory schizophrenia. Since the first MRI study of schizophrenia, this technique has been used to quantify gray matter (GM) and white

matter (WM) and to measure discrete, cortical and subcortical brain structure. Studies on WM bundles have shown that in patients with schizophrenia, white fiber bundles in the frontal lobe and temporomopa-brain regions appear disordered and unevenly aligned, and WM diffusion anisotropy is reduced. Recently, diffusion tensor imaging (DTI) studies identified several areas of fractional anisotropy reduction, reflecting alterations in WM connectivity and supporting a "disconnected model of schizophrenia."[1].Zhang [17]conducted brain CT scans of 80 patients with refractory schizophrenia and compared them with the brain CT results of 80 normal physical examiners, and found that more than half of patients with refractory schizophrenia had different types of brain atrophy.The findings of Kim et al.[18]suggest that disrupting the functional connections of the thalamic cortical pathway has potentially refractory markers of refractory schizophrenia in the thalamic subregion and cortical functional networks and thalamic cortical pathways. The relationship between brain structural changes and cognitive dysfunction in patients with schizophrenia is strong, and the findings of Liu et al.[19]suggest that patients with refractory schizophrenia have significantly impaired cognitive function compared with patients with early schizophrenia and healthy controls, with reduced cortical thickness and subcortical volume. These abnormalities can serve as biomarkers for the early identification of refractory schizophrenia. Woodward et al.[20]studies have shown that assisted exercise accelerates symptom improvement in patients with refractory psychosis. Although the mechanism is unclear, these results suggest that people with chronic schizophrenia experience hippocampal plasticity after exercise. Identifying the underlying mechanisms of refractory schizophrenia is a major challenge in developing personalized medicine for the treatment of schizophrenia in the field of psychiatry, and the use of brain imaging information can improve safety and efficacy in order to better achieve precision medicine.

2.4 Treatment

2.4.1 Medication

Lozapine is the only drug approved for the treatment of refractory schizophrenia, and clozapine treatment improves the core symptoms of schizophrenia and can also significantly improve quality of life, function, and disability[21]. However, clozapine is still underutilized because it causes sedation, oversecretion, orthostatic hypotension, dysphagia, weight gain, diabetes, and dyslipidemia, and even agranulocytosis, cardiomyopathy, myocarditis, pneumonia, paralytic bowel obstruction, and epilepsy[22, 23].Studies by Krivoy et al.[24]found that clozapine treatment was associated with optimal clinical improvement at peaks in two different serum concentrations of around 350 and 650 ng/ml. Because of the side effects of clozapine, clinicians are also trying to switch to or combine other antipsychotics, or combine several other antipsychotics, and some in combination with traditional Chinese medicine to reduce or avoid the use of clozapine.

Molina et al.[25]studies have shown that after taking amisulpride and quetiapine there was an improvement in cognitive and clinical symptoms in patients with refractory schizophrenia. Barnes et al.[26]suggest that intensive treatment with amisulpride in combination with clozapine requires treatment for more than 6 weeks, but vigilance for cardiac abnormalities and other side effects is still required. Studies have shown that the beneficial effects of adjunctive memantine on memory are persistent, with negative, positive, and overall symptoms of patients treated with refractory schizophrenia treated with clozapine further improving[27]. The results of the study by Kulkarni et al.[28]suggest that raloxifene hydrochloride (120 mg/day) reduces disease severity and increases the likelihood of clinical response in women with refractory schizophrenia. Caliskan et al.[29]proposed that the addition of long-acting antipsychotics to clozapine is clearly well tolerated in patients with refractory schizophrenia and may have a positive effect on the course of the disease. Evidence is currently limited and larger sample sizes need to be studied in depth.

Men et al.[30]proposed that the effect of epileptic dream awakening soup combined with clozapine in the treatment of refractory schizophrenia was ideal, which could improve patients' cognitive function, reduce adverse reactions, and have a high safety. The results of the study by Hu et al.[31]show that warm bile decoction combined with amisulpride

has a good effect and is safe in the treatment of refractory schizophrenia. Liu et al.[32]proposed the use of self-immersive blood awakening soup combined with aripiprazole for the treatment of refractory schizophrenia, which is conducive to improving the clinical symptoms of patients, improving the quality of life, and the efficacy is good. Studies have shown that the use of a cure for patients with refractory schizophrenia with warm bile decoction is more conducive to improving patients' symptoms, promoting the recovery of cognitive function, increasing serum cerebrogenic nerve growth factor (BDNF) levels, and improving therapeutic efficacy[33]. Jiang et al.[34]proposed that the combination of traditional Chinese medicine and Ginkgo biloba capsules for the treatment of refractory schizophrenia can effectively reduce psychiatric symptoms, improve cognitive function, increase BDNF levels, and help reduce the risk of adverse reactions. Integrative medicine therapy is effective in the treatment of refractory schizophrenia with mild adverse reactions. TCM has potential utility as an alternative adjunct therapy to the treatment of refractory schizophrenia, but further high-quality research is needed.

2.4.2 Physical therapy

2.4.2.1 Electroconvulsive therapy (ECT)

Electroconvulsive therapy is the stimulation of electrodes that induce seizures, usually located on either side of the scalp, and were introduced into the treatment of schizophrenia in 1938. However, ECT is a controversial treatment for long-term side effects such as memory loss. Therefore, it is important to determine the clinical efficacy and safety of patients with schizophrenia who do not respond to treatment[35]. The results of studies such as Purohith[36] suggest that maintaining ECT is a safe and effective treatment for symptom control in the long-term treatment of refractory schizophrenia. There is medium-quality evidence that ECT has a positive effect on the medium-term clinical response in patients with refractory schizophrenia relative to standard care. However, the inclusion of ECT in standard therapy for other outcomes has no obvious and convincing advantages or disadvantages. The available evidence is also too weak to explain whether the inclusion of ECT in standard care is superior to the inclusion of other antipsychotics in standard treatment[37]. There is not enough evidence to support or refute the use of ECT alone, and more high-quality evidence is needed before definitive conclusions can be drawn.

2.4.2.2 Repeated transcranial magnetic stimulation (rTMS)

Evidence for the pharmacological effects of clozapine is limited, in contrast to non-pharmacological strategies, such as repeated transcranial magnetic stimulation, defined as the repeated application of magnetic pulses through the scalp to target the anterior frontal or temporal cortex, may be promising. Studies have shown that rTMS can reduce auditory hallucinations and negative symptoms in schizophrenia patients taking any antipsychotic drug[38-40]. Wang et al.[41] studies suggest that a 2-week intermittent theta burst stimulation (iTBS) intervention may be a new and effective treatment of visuospatial working memory (vsWM) deficits in patients with refractory schizophrenia, which can regulate activity in local brain regions.

2.4.2.3 Transcranial direct current stimulation (tDCS)

Transcranial direct current stimulation is a non-invasive, safe neuromodulatory technique. Transcranial direct current stimulation has been shown to be effective in refractory auditory hallucinations in patients with schizophrenia[42, 43], and that Frontotemporal tDCS may repair the functional network associated with abnormal hallucinations in patients with schizophrenia [44]. To improve refractory auditory hallucinations in schizophrenia, stimulation may be required twice a day and ≥ 10 times a day[45]. Lindenmayer JP et al. [46] proposed that tDCS therapy appears to be effective not only in patients with ambulatory and higher function, but also in patients with ultra-refractory schizophrenia.

2.4.2.4 Deep brain stimulation (DBS)

Deep brain stimulation has been used to treat drug-resistant patients with other psychiatric disorders, but trials for schizophrenia are lacking, in part because of uncertain electrode locations[47]. Some scholars[48]have proposed that DBS can effectively treat refractory schizophrenia by regulating the brain activity of the cortico-basal-thalamus-cortical circuit. Based on current evidence, the nucleus accumbens may be the strongest candidate

for DBS electrode placement in patients with schizophrenia, and the substantia nigra reticulum also shows promise in a case report. There is also potential interest in the ventral covered, although it has still not been attempted. The use of deep brain stimulation in the treatment of patients with refractory schizophrenia is currently quite meaningful, but the position of the electrodes is challenging.

2.4.3 Psychotherapy

2.4.3.1 Cognitive behavioural therapy (CBT)

Studies have shown that cognitive behavioral therapy is a safe and effective adjunct to the treatment of refractory schizophrenia and may play a role in the treatment of refractory schizophrenia treated by clozapine[50, 51]. This approach should be considered in this population, given the low risk associated with CBT therapy, and the limited number of alternative options for clozapine refractory schizophrenia.

2.4.3.2 Virtual Reality Assisted Therapy (VRT)

With the advancement of technology, virtual reality-assisted therapies began to be used to treat patients with refractory schizophrenia. VRT allows voice listeners to enter a direct conversation with an avatar, fully activated by a therapist who represents their most persecuted voice. The aim is to give them more control over their voices and improve their self-esteem. In addition to symptomatics, the results of a pilot project of this innovative therapy show a significant impact on quality of life[52]. The results of the du et al.[53] study suggest that VRT may be effective in reducing auditory hallucinations in refractory schizophrenia. VRT is particularly effective in treating pains associated with sound. VRT is a very novel and promising intervention for the treatment of refractory auditory hallucinations in schizophrenia.

2.4.3.3 Auditory Processing Cognitive Training (TCT)

Thomas et al.[54-56]studies have shown that computer-directed cognitive training in auditory processing improves auditory and language outcomes in patients with refractory schizophrenia.

3 Summary and outlook

Research on neurobiology and neuroimaging hypotheses has been limited to some extent by the different criteria used to define refractory schizophrenia and clinical heterogeneity. The clinical trial design of new therapies should take this heterogeneity into account, and further clinical research is needed to more clearly understand the potential neurobiology and neuroimaging of refractory schizophrenia, so as to achieve precision medicine for patients with refractory schizophrenia. None of the studies conducted to date have provided findings with strong requirements such as reproducibility, specificity, robustness, and clinical feasibility and cost-effectiveness, and therefore fail to provide a clear target for treatment. Future research should expand the sample size and carry out more in-depth research on the basis of previous generations. Clinicians should be "tailored" to the situation of patients with refractory schizophrenia, rather than blindly avoiding the use of clozapine, as long as the benefits outweigh the disadvantages, routine blood monitoring and other related tests can be used to use clozapine, and problems can be found and dealt with in time. Traditional Chinese medicine treatment, partial physical therapy, and psychotherapy have small adverse reactions, and can be included in adjuvant therapy according to the patient's situation. For some emerging treatments, as long as they are relatively safe, they should also be actively tried, thus opening the way for effective treatment of patients with refractory schizophrenia. At the same time, patients with refractory schizophrenia should also strengthen rehabilitation nursing care during the period, which can significantly improve the patient's compliance with medical treatment, improve the effect of drug treatment, and help patients to improve their symptoms and quality of life to a greater extent.

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