CLOZAPINE AND PHARMACOGENETIC TESTING : A NEW DAWN

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Introduction:

It is not often that there is such an excitement in psychiatry research as seen following breakthrough advances as the announcement of "Pharmacogenetic test (PGT)" for Schizophrenia by Prof David Taylor, Myogenes on 31 March 2021. Is this the "Eureka" moment in modern psychiatry?

Background:

Schizophrenia is one of the severe enduring mental illness with peak age of onset in early adulthood in both, men and women with a course of relapse and remission. The term "Schizophrenia" was originally termed by Eugene Bleuler (1911/1950)[1]. Bleuler's primary symptom was "cognitive", a form of thought disorder, loosening of associations. Globally, the prevalence (number of cases present in a population at a given time or over a defined period) of Schizophrenia is around 1.4 to 4.6 per 1000 population at risk. The incidence of Schizophrenia is around 1.5 per 10,000 in general population each year[(5)]. Antipsychotic medications remain the cornerstone of treatment.

Schizophrenia is characterised by delusions, hallucinations (Positive symptoms), affective flattening, poverty of speech, lack of volition, anhedonia (negative symptoms)[3] and disorganised thought process (reality distortion syndrome). Schizophrenia is associated with psychiatric co-morbidities and increased risk of suicide. The aetiology of Schizophrenia is multi-factorial with a combination of genetic, biological, psychological and social factors being implicated. However, no single causative factor is yet identified and there is no cure for this severe mental disorder. However, advances in pharmacotherapy with development of Chlorpromazine in 1950s, subsequent introduction of Haloperidol in mid 70s and series of second generation antipsychotic medications in the 1990s and the millennium have greatly improved control of symptoms, course and prognosis.

The course of Schizophrenia shows a high degree of inter-individual variability, with about 20% of individuals with first psychotic episode remaining symptom free for 10 years. WHO[6] studies have shown a slightly better prognosis in less developed countries compared to the developed ones. In nearly 50% of cases the illness takes are course of relapse and remission. It is estimated that around 25% of cases with Schizophrenia are resistant to currently available treatment, often termed as Treatment Resistant Schizophrenia (TRS). In these cases the disorder usually has an entrenched, long-term, chronic course with persistent psychotic symptoms, gradual cognitive decline, psychosocial impairment affecting the individual sufferer's quality of life.

Clozapine: benefits and side-effects

Clozapine, a dibenzodiazepine, a novel antipsychotic drug was synthesized in 1956 and commercially sold in 1972. Although it is not known to cause any extra-pyramidal side-effects and tardive dyskinesia it was (and remains) associated with increased incidence of agranulocytosis in 1970s resulting in restrictions in use. Interest in Clozapine was re-ignited after the landmark study by Kane et al (1988)[4] found that Clozapine was superior to Chlorpromazine in over 30% of patients with TRS who had not responded to two or more antipsychotic medications in the past. Clozapine is undisputedly, the "gold standard" for Treatment Resistant Schizophrenia (TRS). There is clinical evidence that Clozapine reduces suicide risk in sufferers and improves quality of life.

As Clozapine is associated with various haematological side-effects including neutropenia (3%) and agranulocytosis (0.8%) of cases treated with Clozapine. Hence, regular monitoring of full blood count is mandatory for patients who are prescribed Clozapine. Up until now it was not possible to predict who is likely to benefit from Clozapine and who is likely to develop serious side-effects. If a patient develops haematological side-effects they can lead to a medical emergency and temporarily or permanent withdrawal of Clozapine therapy. Agranulocytosis if not adequately treated can lead to fatality. This has severe ramifications not only for clinical management but also patient's psychosocial life. Rebound psychosis following Clozapine withdrawal is well recognised and can be severe requiring psychiatric re-hospitalisation.

Will pharmacogenetic test add value?

So before commencing a patient on Clozapine it will be valuable to know if the patient is likely to respond to its what dose is likely to benefit, risks for developing haematological side-effects such as neutropenia or agranulocytosis.

We are sharing with you the ground-breaking innovation in pharmacogenetics. The "Clozapine test" which is likely to have a huge impact and help clinician's decision making whether Clozapine is the appropriate next step for Treatment Resistant Schizophrenia (TRS) patients who have shown limited improvement with two or more other antipsychotic medications. Prof David Taylor, Professor of Pharmacy, South London & Maudsley Mental Health NHS Trust gives us insight into the advantages of this pharmacogenetic test. The Clozapine test is now available in U.K. and is marketed by Myogenes ltd.

References:

1. Bleuler, E. (1911/1950) Dementia praecox or the group of schizophrenias. New York: International Universities Press. Translated by J. Zinkin from Dementia Praecoxoder der Gruppe der Schizophrenien. In: Handbuch der Geisteskrankheiten (ed. G. Aschaffenburg). Deuticke, Leipzig.
2. Claghorn, J et al (1987), Journal of Clinical Psychopharmacology, Dec 7(6): 377-384.
3. Crow, T.J (1985) The two syndrome concept: origins and current status. Schizophrenia Bulletin11, 471-486.
4. Kane J, Honigfeld G, Singer J, Meltzer H et al (1988), Clozapine for treatment resistant schizophrenia. A double-bind comparison with chlorpromazine, archives of General Psychiatry, Sep; 45(9): 789-796.
5. Jablensky, A, Sartorius, N, Ernberg G et al (1992) Schizophrenia: manifestations, incidence, and course in different cultures. A World Health Organisation (WHO) ten-country study, Psychology Monograph Suppl , 20: 1-97
6. Sartorius N, Gulbinat W, Harrison G, Laska E et al (1996) Long term follow up of Schizophrenia in 16 countries. A description of International study of Schizophrenia conducted by World Health Organisation (WHO); Social Psychiatry and Psychiatric Epidemiology. 31 (5): 249-258.

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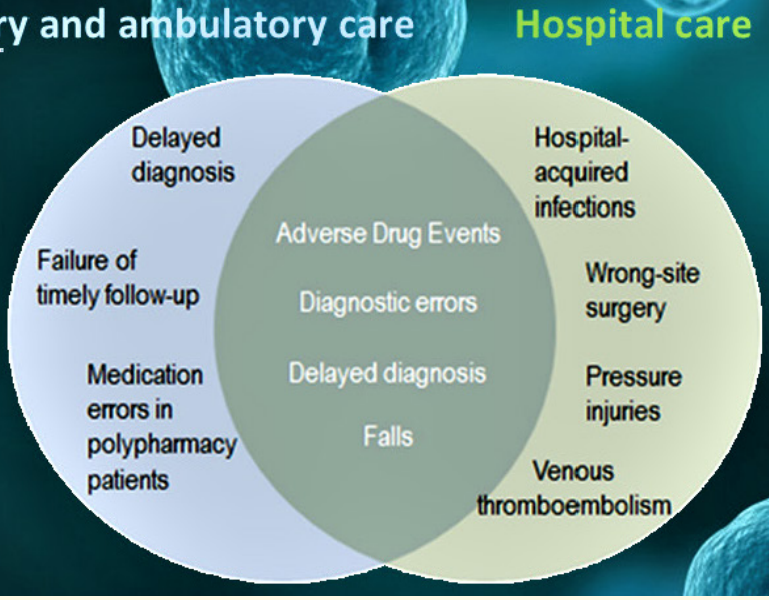

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