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A Preliminary Trial of Dietary Manipulation in Schizophrenia

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ABSTRACT

Most of the reseorehes mode on the etiology of schizzophremo suggested the presence of a biochemicol disorder in the from neurotransmitter imbalance Dopomine (DA), and Norepinephine (NE) are the most neuretonsmitters appeor to be invowed in schizophrenio.

This study is mode on 10 schizophrenic potimts (5males, 5 females), with an average age of 50. 9years and on overage duration of illness of 26. 8 years All of them was preuiously exposed to nigh a diet defficient in phenylalanin (PHE), and Tyrosine (TYR), the precursors of DA, NE, and serotonin The preliminary results showed marked, although temporny, impreuement in theer octive symptoms, that suggesst the usefuellness of usuing this diet poor in PE and Type as osupplemeut to the phooma colcgical regimen of those potients who foiled to respond to psychophormological treatment alone.

INTRODUCTION

There is a general consensus that schizophrenia is a serious disorder, in which the sufferer shows evidence of a severe disruption in cognitive and affective interactions with the environment, and usually manifests signs of a characteristic thought disorder. Furthermore, it is quite often associated with delusions and auditory hallucinations. what clinicians are unable to agree upon, however, is whether schizophrenia is a unitary disorder or whether it is the final manifestation and outcome of a variety of independent diseases with a final common pathway.

Over the years many theories and hypotheses have been proposed regarding the etiology of schizophrenia. All of them, however, have been tentative and none of them has been sufficiently comprehensive so as to explain satisfactorily the various aspects and features of the disease.

Kety, *et al* (1975) in their study of schizophrenia in biological and adoptive families, have proven, beyond any doubt, the hereditary nature of the disease. Genetic factors, accordingly, play a major role in the development of schizophrenia. These factors are either responsible for the disease itself or are simply able to pass on the propensity to develop the disease. Since genes are known to operate through biochemical means then it must follow, in all probability, that schizophrenia reflects some biochemical injury or fault.

Again in the field of biochemistry many theories have been suggested, but it is, however, in the area of neurotransmitters that most of the positive findings have been made.

Neurotransmitters are the dynamic components of neuron tissue (crow

1981) Furthermore, a neurotransmitter is one functionally significant component that identifies a particular set of neurons (crow 1981) Since the disorder in schizophrenia is presumed to affect a circumscribed set of neuron systems, and since the disturbance is most probably biochemical, then it is quite plausible that it involves a specific neurotransmitter mechanism.

Over the past few years, recognition of the importance of "transmitter balance (Domino, 1975) in regulating normal behaviour has naturally led to the concept of transmitter imbalance as the ultimate basis of abnormal behaviour. Such transmitters may act either by conveying messages directly or by modulating other means of transmission.

At the level of the synapse itself, transmission occurs by the outpouring of a quantum of the chemical. A decrease in the optimum quantity of the chemical may fail to effect a transmission, while a pathological increase may also, paradoxically, fail to effect a transmission through the occurrence of a depolarizing block. A delicate balance, therefore, has to be maintained.

Imbalance in neurotransmission may arise from diverse Primary causes such as inherited metabolic abnormalities, degenerative processes, viral infections auto-immune mechanisms, drugs, nutritional factors, and others. Thus, in case of schizophrenia, the concept encompasses the possibility of multiple etiologies all leading to a final common pathway.

The number of putative Central Nervous System (CNS) transmitter candidates now exceeds 40 (Iverson, 1982). The ones, however, that appear to be somehow implicated with schizophrenia are dopamine and norepinephrine.

Dopamine(DA)

The suggestion that some disturbance of dopaminergic function exists in schizophrenia stems largely from the following observations:

1) High doses of dopamine-releasing agents (such as amphetamines and methyl phenidate) can precipitate, in normal subjects, a psychosis closely resembling paranoid schizophrenia (Connel, 1958; Griffith, 1972; Crow, 1976).

2) More impressive, however, is the ability of low doses of amphetamines to exacerbate schizophrenic symptoms (Janowsky, 1976; Angrist, 1980)

3) Levodopa, which acts almost wholly through DA, can also worsen schizophrenic symptoms(Angrist, 1973).

4) The neuroleptic drugs possess the property of blocking DA receptors with a potency that parallels their therapeutic efficiency (Van Praag, 1976).

5) Neuroleptic drugs which are known to block DA receptors not only ameliorate the symptoms of schizophrenia but can also reverse the action of amphetamines (Crow, 1987)

6) The most frequently reproducible finding in post-mortem schizophrenic brains is an increase in the total number of DA receptor binding sites observed in the caudate, nucleus accumbens, and olfactory tubercle (Owen, 1978; Synder, 1982).

Norepinephrine (NE)

The role of NE in the etiology of schizophrenia is not as clear as that of DA. NE is known to play a major role in behaviours such as feeding, aggression, locomotion, memory, reward and others. At a more intrinsic level it may be a neuromodulator rather that being a neurotransmitter.

In schizophrenia it is possible that anhedonia, withdrawal, and flatness of affect represent an insufficiency of NE at its synapses (Kety, 1978). An abnormal increase may also result in the same outcome through the occurrence of a depolarizing block.

It may be surmised from the above

considerations that both DA and NE appear to play a decisive role in the development of schizophrenia.

Phenylalanine (PHE) which is the precursor of both DA and NE, is an essential amino acid and so cannot be manufactured in the body. like other amino acids, it can not, also, be stored in the body. It also, therefore, got to be supplied continuously and adequately in the diet furthermore, the concentration of PHE in the blood relative to other large neutral amino acids (LNAA) appears to reflect its availability to the CNS. This has been adequately shown by Wurtman, *et al* (Wurtman , 1981) who based their conclusions on the following criteria:

1) the lack of significant feedback control of plasma levels of the precursor.

2) the lack of a real blood-brain barrier for the precursor to control its influx into, or efflux from, the CNS.

3) the existence of a low affinity (and thus unsaturated) transport system mediating the flux of the precursor between blood and brain.

4) low affinity kinetics for the enzyme that initiates the conversion of the precursor to the transmitter.

5) the lack of end-product inhibition of the enzyme, in vivo, by its ultimate product, the neurotransmitter.

PHE is in many ways similar to tryptophan (TRP). TRP is a LNAA; it is an essential amino acid; and it is also a precursor of the neurotransmitter serotonin. Variations in its availability in the diet results in modification of behaviour. A deficiency in TRP is now believed to be the cause of pellagra rather than it being due to deficiency of niacin per se (Bender, 1984). It has also been shown that excessive TRP will also influence behaviour. Oral administration of TRP has been important to reduce sleep latency and to increase subjective sleepiness in subjects with long sleep latencies (Fernshrom, 1983). A single, one gram dose was sufficient to diminish the times required for a subject to obtain stage one or stage two sleep; however, people took this dose with a carbohydrate tended to have the shortest sleep latency (Wertman *et al* 1981). Carbohydrates stimulate the production of insulin and insulin in its turn encourages the uptake of LNAA, other than TRP, into muscles and so allows TRP to pass freely through the blood-brain barrier without competition of other LNAA.

METHOD

Initially a pilot study was done on five schizophrenics who were manifesting an active symtomatology. A diet poor in PHE and Tyrosine (TYR) was given for two weeks and whatever medications these patients were on was tapered off and discontinued within one week. Tow showed a marked improvement, one of whom remained symptom free for over six months . The other person relapsed two weeks after the termination of the trial and the resumption of an ordinary diet. The remaining three had been previously diagnosed as suffering from a schizo-affective disorder and although the florid signs and symptoms such as hallucinations and delusions, subsided, they became very much more depressed.

Taking these findings into consideration, and bearing in mind that certain susceptible individuals are liable to pass into a severe depression it was decided, in this present trial to provide such individuals with an antidepressant at the outset as a precautionary means. Either Desipramine or Maprotilene was given. Both of them are known to act through NE reuptake.

A signed consent was obtained from all prospective participants. The trial was restricted to those patients who had been refractory to treatment and who had failed to respond to the various psychopharmaceuticals satisfactorily. They had been receiving quite high doses of neuro-

leptics both orally and in injectable form with very little success. They were all showing active signs and symptoms in the form of hallucinations and delusions. The diet which provided around 2000 kcal., contained from 450 to 500 mgs. of PHE and 200 to 300 of TYR. The main protein was provided by the powder 3200 AB* which has been developed for use in cases of phenylketonuria. The PHE requirements of human adults has been estimated to be around 16 mgs. per kg per day (Rozen, 1957). The participants were maintained on this diet for a period of two weeks.

RESULTS

Only 10 out of 13 completed the two weeks trial of the diet. Of the 10 who completed the trial, 5 were males and 5 were females with an average age of 50. 9 years and an average duration of illness of 26. 8. years. All of them had been receiving high doses of neuroleptics and inspite of this their psychotic signs and symptoms could not be controlled. Suppression or modification of these psychotic signs and symptoms was taken as a measure of the response to the diet.

Of the 10 who completed the two-week trial only one (N. G) did not show any measurable response in behaviour. She is a 64 years old woman who has been suffering from paranoid schizophrenic illness, for over 33 years, and who believes that her husband has been persistently trying to poison her the last 33 years. Her delusion did not change. On the other hand, (V. P), who is 30 years old and who had been under psychiatric care for over 12 years, reacted completely differently. She was convinced that she was of royal descent and that she was engaged to be married to prince Charles. This delusion disappeared during the trial, only return three weeks after going back to a normal diet. All other participants showed various degrees of response. Some showed a complete suppression of their psychotic symptoms while the response in other was only partial. This partial response consisted in a diminution of the frequency of the hallucinatory episodes.

An interesting observation was made on (B. B), who was 43 years old at the time of the trial. He first came under psychiatric care when he was 13. He was investigated extensively and hospitalized and treated at various centres unsuccessfully. Over the years every possible diagnosis was, at one time or another, applied to him. He was admitted to the trial and the Millon Multiazial Inventory (MCMI) was administered at the beginning and at the completion of the trial.

The reported final conclusion after scoring the tests, was: "It is evident that pharmacological treatment regimen has masked or suppressed the dysthymic symptoms evident and diagnosed as such at the time of the first administration of the MCMI ".

DISCUSSION

This preliminary clinical trial is far from being adequate. Only a double-blind prospective study could unequivocally rule out the possibility of a placebo effect. Furthermore, the study period of two weeks is much too short and limited. The diet itself is quite safe and a comparable one is given to phenylketonuric pregnant women and phenylketonuric children with no ill effects.

In spite of these shortcomings it was quite evident that the majority of participants did show substantial improvement, if only temporarily. Further exploration of this line of investigation is, therefore, warranted and recommended.

In the meantime, a diet poor in PHE

*This powder is produced by mead Johnson Nutritional Group

and TYR could be tried as a supplement to the treatment of those patients who fail to respond to psychopharmacologicaltreatment alone.

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ABSTRAIT

Un Essai Primaire de la Manipulation Dietitic chez les Schizophrènes

La plupart des recherches sur l'aetiologie de la schizophrénie suggèrent la présence de désordre biochimique dans la balance entre les neurotransmetteurs Dopamine (DA) et Norepinephrine (N.E.) sont les uns les plus impliqués dans la schizophrénie.

Cette étude est faite à partir de 10 patients schizophrènes (5 Hommes et 5 femmes) dont la moyenne d'âge est 50,9 ans, et la durée moyenne de maladie est de 26.8 années. Chacun entre eux a été d'abord soumit à de fortes doses de neuroleptiques et ceci sans succès.

Ils ont reçu un régime faible en phenylalanine (P.H.E.) , et tyrosine (TYR.), les précurseures de DA, NE, et sérotonine .

Les premiers résultats ont montré une amélioration de leurs symptomes actifs, évidente bien que temporaire, ce qui suggère l'utilité de ce régime pauvre en PHE et TYR comme supplément du traitement pharmacologique de ces patients qui n'avaient pas réagi au seul traitement psychopharmacologique.

الموجز

تجربة مبدئية لمعالجة النظام الغذائى فى الفصام

لقد أظهرت معظم الأبحاث وجود خلل كيميائى قد يعزى إليه مرض الفصام ، واجمعت معظمها على أن هذا الخلل غالبا ما يتمثل فى عدم أتزان الموصلات العصبية وبخاصة الدوبامين والنور إيبنفرين، وتهدف هذه الدراسة إلى تحرى إمكانية ضبط أصول الموصلات العصبية فى غذاء المرضى الفصاميين وأثر ذلك فى العلاج .

ولقد أجريت هذه الدراسة على ١٠ مرضى فصاميين ، خمسة من الرجال وخمسة من النساء ، متوسط أعمارهم ٥٠,٩ عاما ، ومتوسط التاريخ المرضى لهم ٢٦,٨ عاما ، وخضعوا كلهم من قبل للعلاج الكيميائى بمضادات الذهان بجرعات عالية ، ولم تكن نتائجها مرضية . وقد أخضع المرضى لنظام غذائى متضمنا كميات قليلة من التيروسين والفينيل ألانين (أصول الموصلات العصبية المفترض اشتراكها فى إحداث الفصام أو تأثيرها على تطوره) لمدة إسبوعين .

ولقد جاءت النتائج الأولية لتشير إلى حدوث تحسن ملحوظ (وإن كان مؤقتا) على الأعراض النشطة لأغلب المرضى . وأشارت هذه الدراسة إلى إمكانيا استخدام مثل هذا النظام الغذائى مكملا للنظام الدوائى فى الفصاميين الذين لم يستجيبوا جيدا للعلاج الكيميائى الدوائى وحده .