NMS and genetic drug oxidation

Sir: Our recent paper (Otani et al., Journal, June 1991, 15B, 850–853) of the familial occurrence of NMS suggests that the predisposition to this syndrome may be related to a genetic factor. Meanwhile, the genetically determined oxidation polymorphism is involved in the metabolism of haloperidol (Gram et al., 1989) and perphenazine (Dahl-Puustinen et al., 1989) is related to the debrisoquine/sparteine/mephenytoin-type polymorphism, whereas that of diazepam is dependent on the mephenytoin polymorphism (Bertilsson et al., 1989). Therefore, we studied whether patients developing NMS would show an impaired drug oxidation capacity (i.e. poor metaboliser status).

The subjects were five patients with NMS. Patient 1 was the mother, and patient 2 was the elder daughter described in our recent report. Patient 3 (68-year-old female), patient 4 (20-year-old female), and patient 5 (63-year-old male) were unrelated by lineage and birth. Patients 1, 3 and 4 developed two episodes. At the onset of the first episode of patient 3, serum haloperidol level was 16 ng/ml (daily dose 10 mg), and at the second episode of patient 4, serum zotepine level was 9 ng/ml (daily dose 40 mg). The assessment of oxidation capacity (i.e. phenotyping test) by metoprolol tartrate (100 mg) and racemic mephenytoin (100 mg), which are metabolised by two independently different P-450 isozymes (Horai et al., 1989), was conducted after recovery from NMS, with their consent. At the time of the phenotyping test, all but patient 2 were taking one or two benzodiazepines such as alprazolam, diazepam, flunitrazepam, and nitrazepam, and patient 1 was also taking zotepine. The phenotyping procedure was similar to that in our previous study (Horai et al., 1989), except that the two test drugs were administered simultaneously. Oxidation capacities of metoprolol and mephenytoin were expressed by the log_{10} urinary metoprolol/a-hydroxymetoprolol ratio (log_{10} MR) and the log_{10} percentage of urinary excretion of 4-hydroxymephenytoin per the dose administered as racemate mephenytoin (log_{10} 4-HM% of dose), respectively. Their phenotyping test values (log_{10} MR and log_{10} 4-HM% of dose) were as follows: —□0.240 and 1.26 in patient 1, —□0.323 and 1.21 in patient 2, —□0.210 and 1.04 in patient 3, —□0.991 and 1.20 in patient 4, and 0.238 and 1.41 in patient 5.

Contrary to our hypothetical expectation, all the cases showed a normal oxidation capacity (extensive metaboliser status) of both the test drugs according to the phenotyping criteria used in our previous Japanese population study (Horai et al., 1989). One may wonder if the phenotypic expression in four of the five cases might have been modified by the possible drug interactions, because they were taking a neuroleptic and/or benzodiazepines when phenotyped. However, if this were the case, the oxidation status should have changed from an extensive to poor metaboliser phenotype. Serum levels of neuroleptics measured at the onset of NMS were not toxic in the two patients; the haloperidol level in patient 3 was within the therapeutic window proposed by Santos et al. (1989). The zotepine level in patient 4 was within the range similar to the previously reported 21 patients (i.e. 5–317 ng/ml) without developing any significant side effects including NMS. Therefore, this report suggests that the development of NMS appears to be ascribable neither to a genetically determined impaired drug oxidation nor to a toxic neuroleptic level.


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CORRIGENDUM

Journal, May 1991, 158, 603 (column 1, under The ESF Programme on the Molecular Neurobiology of Mental Illness). The sentence beginning “...” should read: “Last year it agreed to contribute £40K p.a. to the total of £1m for the five years of the programme. This supports co-ordination ...”.

A HUNDRED YEARS AGO

Influence of Surroundings in Producing Insanity

In the last number of the Journal of Mental Science Dr Savage discusses this question, and begins by protesting against the acceptance of what is a too widely spread notion — viz., that nearly all insanity is the outcome of direct neurotic inheritance. The influence of heredity is not denied or minimised, but the great importance of environment is insisted upon. To quote the words of the author: “We are what we are in mind and body to a great extent as organic results of our forefathers, but that we are no longer naked savages is some evidence that progress and development in the individual and the race may take place as the result of changing surroundings”. There can be no two opinions as to the encouragement to be got from such a view. A too great insistence upon heredity as the determining cause of insanity must land us in a hopeless pessimism as regards treatment, whereas a recognition of the influence of surroundings is the first step towards the construction of a reasonable and efficacious system of therapeutics. The author also cites many examples of hallucinations and delusions which are suggested by surroundings; and whilst all will not be inclined to accept his dictum that disorder of function may lead to disease of tissue, there will be few who will not share his opinion as to the efficacy of restful, pleasant surroundings in the treatment of mental disorder as compared with the virtues of “medicine out of a bottle”.

Reference
Lancet, 31 October 1891, 998.

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