12. Side Effects/Tardive Dyskinesia

TARDIVE DYSKINESIA (TD) AND COGNITIVE EVOKED POTENTIALS

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Chronic schizophrenic patients (n=26) with moderate TD were selected according to AIMS scale. 13 patients with severe formal thought disorders (+FTD) were matched for age, sex, education, chronicity, dosage, hospital care, with 13 FTD schizophrenics selected for minimal formal thought disorders. Psychometric tests of 'frontal' organic signs were also administered (D2, verbal fluency, tremometer, dynamometer, finger-tapping). The neuroleptic drugs used in standard combinations were Haldoperidol, Levomepromazine and Cyamemazine, Fluphenazine Decaonate, Pipotiazine, ranging from 25 mg to 400 mg/day, with a mean/mode of 250 mg/day. Benzodiazepines varied around the "Diazepam equivalent" of 15 mg/day.

Cognitive event-related potentials (ERPs), N1, P2, N2, P3a, P3b, N4, N7 were recorded at Fz, Cz and Pz (10–20 system) during binaural oddball detection of targets (P.20, 1500Hz) at 2 speed of stimulation (2/sec, 1/sec). None of the frontal organic psychometric measures were significant. Neuroleptic dosage was not correlated to any measure. Controlling for dosage covariate, +FTD schizophrenics presented dyskinesia in the oro-facial area. Group differences on ERPs replicated earlier results with flatter and smaller positive waves in patients with the most severe negative FTDs, and larger frontal late negative waves (N4–N7) in patients with positive content thought disorders. Severe dyskinesia on AIMS scale inversely correlated with smaller N1 amplitudes in all patients, reflecting lower arousal and sensory processing. ERPs showed more sensitivity to TD and to cognitive symptoms than traditional organic 'frontal' tests.

RELATIONSHIP BETWEEN TARDIVE DYSKINESIA, INTELLECTUAL IMPAIRMENT AND BRADYPHRENIA

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There are a number of possible explanations for the robust association between cognitive dysfunction and orofacial tardive dyskinesia (OFTD). First, a low level of intellectual functioning may be a risk factor for OFTD. Second, both may be occurring as independent manifestations of neuroleptic toxicity. Lastly, there may be shared elements of pathophysiology, possibly within the basal ganglia. More specifically, the two conditions may be occurring together as manifestations of a subcortical syndrome. To test this last hypothesis, the relationships between orofacial dyskinesia and cognitive functioning were examined in 63 chronic inpatients with schizophrenia. Current IQ levels were significantly lower in those patients with both OFTD and trunk and limb dyskinesia (TLTD), compared with their non-dyskinetic fellows. The relationships were examined between orofacial dyskinesia, premorbid IQ (assessed with National Adult Reading Test) and current intellectual level (WAIS-R), cognitive speed and motor speed (Information Processing Battery of AMIPB). The findings were in accord with the possibility that there are shared elements of pathophysiology between OFTD and cognitive slowing (bradyphrenia). Possible mechanisms will be discussed, particularly involving frontal-subcortical pathways.

SEROTONERGIC ASPECTS OF ACUTE EXTRAPYRAMIDAL SYNDROMES IN NONHUMAN PRIMATES

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Serotonin has been proposed to play a critical role in dopamine antagonist-induced acute extrapyramidal syndromes (EPS). To evaluate this issue, a series of double-blind, placebo-controlled studies was conducted in nonhuman primates.

Six Cebus albifrons monkeys were pretreated with haloperidol .05 mg/kg i. m. One hour later 5HT2 antagonists ritanserine .5–5.0 mg/kg i.m. or ICI 170,809 .5–5.0 mg/kg i.m. or the 5HT1A agonist 8-OH DPAT .05–.5 mg/kg i.m. or the anticholinergic benztropine .03–.3 mg/kg i.m. or a saline placebo control i.m. was administered. Behaviors of dystonia and bradykinesia were evaluated for 5 hours after the second drug was administered.

The 5HT2 antagonists and saline had no effect on haloperidol-induced dystonia and bradykinesia. However, the 5HT1A agonist 8-OH DPAT and the anticholinergic benztropine dose-relatedly decreased these symptoms.

These results do not indicate a primary role for 5HT2 antagonism in modulating acute EPS, whereas 5HT1A agonists as well as the classic anticholinergic drugs have substantial effects in mitigating dopamine agonist-induced EPS. Neuroleptics with 5HT1A agonist properties may be free of EPS and 5HT1A agonists may be good candidates for anti-EPS drugs.