

Tardive Dyskinesia and Adverse Perinatal Events

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The authors screened and examined sixty one children and adolescents who were receiving neuroleptic treatment from consecutive psychiatric admissions and psychiatric consultations to psychiatric center for the presence of Tardive Dyskinesia (TD) using standardized assessment tools (AIMS and ADS). Assessment was done on more than one occasion and the diagnosis of positive cases of TD was based on TD Research Criteria. Histories of perinatal adversity, developmental milestones and neuroleptic exposure were obtained for both TD and Non-TD subgroups.

Results showed that twenty percent (20%) of the sample received a diagnosis of TD. Patients were more likely to be younger males with previous hospitalization, with longer duration of neuroleptic exposure, have longer duration of maximal daily dose in mg chlorpromazine equivalents, and with history of exposure to adverse perinatal, neonatal events, developmental delays and neurological events, than non TD patients. In a series of multiple regression analyses, only neuroleptic exposure, adverse perinatal and developmental events were strongly associated with TD. The explanations and implications of our results are discussed.

(Egypt.J. Psychiat.,1994, 17:220-227).

Introduction

Tardive dyskinesia is one of the most identified consequences of prolonged neuroleptic drug treatment in children and adolescents (Paullison et al, 1975, Gualtieri et al, 1984, McAndrew et al, 1972, Gualtieri, et al, 1982, Richardson et al, 1991, Campbell et al, 1988).

These children may be future candidates for a lifetime of neuroleptic treatment which increases their risk of developing TD with its consequent ethical and legal complications (Wettestein and Appelbaum, 1984, Gadow, 1992, Whitaker and Rao, 1992). The long term neuroleptic - induced movement disorders in children and adolescents which have been reported as reversible withdrawal emergent symptoms (WES) and irreversible TD, may reach up to 50% (Winsberg et al, 1978, Polizos et al, 1973, Engelhardt et al, 1975).

Several clinical reports have suggested that brain damage (Angle and McIntire, 1968), minimal brain dysfunction (Kane et al, 1980), abnormal birth injuries and developmental delay (Browning and Ferry, 1976, Burk et al, 1982) may play a factor in the predisposition for severe and persistent forms of neuroleptic - induced movement disorders. Recent research data suggest that pregnancy complications, perinatal events, and neurological abnormalities could be related to psychiatric disorders and predispose to drug complications (Takei et al, 1994, Cantor et al, 1994 a, b). On the contrary, McAndrew et al (1972), in a retro-

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spective study, failed to show any relationship between tardive dyskinesia and brain damage as rated on a scale that included clinical, historical, laboratory, and psychological findings.

Furthermore, several investigators have reported that pre, peri- & neonatal complications appear with increase frequency in the histories of children with psychiatric disorders (Bryson et al, 1988 and Tasi, 1987).

We carried out this study to address the relationship between tardive dyskinesia and history of adverse perinatal and developmental events in children and adolescents treated with neuroleptic drugs.

Subjects and Method

Patients were sample from consecutive admissions and consultations to a psychiatric hospital in a pilot study of neuroleptic-induced extrapyramidal symptoms in children and adolescents under 18 years of age. All subjects were assessed during neuroleptic treatment by the use of AIMS and the Simpson Abbreviated Rating Scale (ADS) (Guy, 1976 and Simpson et al, 1979) Assessment was done on admission, or on consultation after two and four weeks of neuroleptic treatment. Sixty-one patients aged 8-18 years were surveyed over a seven month period. The diagnosis of positive cases of TD was based on Tardive Dyskinesia Research Criteria proposed by Schooler and Kane (1982). Briefly these criteria include a history of at least 3 months neuroleptic exposure, the presence of at least "moderate" dyskinetic movements in one or more body areas or at least "mild" dyskinesia in two or more body areas, and the absence of other conditions that might produce abnormal involuntary movements. In addition, patients were considered as having TD if they exhibited these dyskinetic movements on two examinations within at least a two-week interval and were on a fixed neuroleptic dosage. Each patient was examined by

one of the two investigators. The interrater and the test-retest reliability coefficients for the ADS (global all TD score) were. 0.71 and 0.80 respectively. Both ADS and AIMS global severity scores correlated with interrater and test-retest coefficients of 9.7 and 9.3 respectively. Diagnoses of psychiatric disorders were assigned according to DSM-III-R and most of these youngsters and adolescents have schizophrenia or severe conduct and behavioral problems.

In the second phase of the study, charts and records were reviewed to obtain the clinical data on past and current treatment with neuroleptic and antiparkinson agents (AP), history of EPS, number and length of previous hospitalizations, family history of psychiatric disorders, and adverse perinatal and developmental events. Adverse events were modified from elsewhere (Szatmari and Taylor, 1984, Konstantareas 1986, Tasi, 1987, Bryson et al, 1988, Mason-Brothers et al, 1987) and included perinatal, neonatal, developmental delay, and neurological adversities.

Results

Twenty percent of our sample received a diagnosis of tardive dyskinesia (Probable TD, concurrent neuroleptics). Statistical analysis of the demographic and clinical variables of TD-patients (N=12, 20%) and non-TD patients (N=49, 80%) showed no significant association between TD and I.Q., family history of psychiatric disorders, history of EPS, current daily doses in mg chlorpromazine equivalents and duration of exposure to antiparkinson agents. Neuroleptic doses in the TD-Patients ranged from 100mg chlorpromazine equivalent to 1000 mg.

TD- patients were more likely to be younger males, mean $\pm$ SD age = 14.0 $\pm$ 2.5 years vs. 15.4 $\pm$ 2.3 years in non-TD patients ($p < 0.05$). Only two females

Table (1)
Adverse Perinatal and Developmental Events in TD Vs. Non-TD Patients

Event (s)	TD		Non-TD		χ^2	P value ^b
	N	%	N	%		
• Perinatal						
1 Event	6	55	8	19		
2 Events	1	9	3	7		
3 Events	1	9	3	7		
Total (one or more)	8	73	14	33	5.85	0.02
• Neonatal						
1 Event	1	10	2	5		
2 Events	2	20	0	0		
3 Events	1	10	1	3		
Total (one or more)	4	40	3	8	6.78	0.01
*Developmental Delay						
1 Event	1	10	2	5	0.33	NS
• Neurological						
1 Event	3	30	3	8	0.06	NS
• Total Number of children with one or more events	9	75	17	35	4.86	0.03

^a Percentages are based on the number of children for whom data were available in each category

^b NS= not significant

were in the TD group (17%) vs. 16 (33%) in the non-TD group. Previous hospitalization ($p<0.02$), duration of neuroleptic exposure ($p<0.001$), history of maximal daily dose (for one month) in mg chlorpromazine equivalents ($p<0.001$), and adverse perinatal and developmental events ($p<0.03$) were significantly associated with the diagnosis of TD. Table (1) compares the distribution of adverse perinatal, neonatal, developmental delay and neurological events.

In a series of multiple regression analysis including the independent varia-

bles: total duration of AP exposure, full scale I.Q., history of EPS, maximal daily dose in mg chlorpromazine equivalents and adverse perinatal and developmental events, in relation to the diagnosis of TD, only total duration of neuroleptic exposure and adverse perinatal and developmental events were strongly associated with TD. ($F= 20.39$, $F=8$.)

Discussion

While twenty percent of the sample exhibited movements suggestive of TD, it is difficult to infer a prevalence rate of

tardive dyskinesia in our sample. The TD syndrome in children and adolescents is predominantly a withdrawal phenomena and usually masked by neuroleptic treatment. Earlier studies showed higher rates when neuroleptics were discontinued in selected samples (Gualtieri et al, 1984, Gualtieri et al, 1982, Polizos et al, 1973). However the twelve patients with TD-like movements in our sample may represent a subgroup of the heterogeneous TD syndrome in which neuroleptic treatment do not mask the symptoms either because the neuroleptic doses are insufficient or the dyskinetic movements represent a severe or persistent form of TD. Dyskinetic movements that "break through", i.e., that are manifest on maintenance neuroleptic doses, may predict a particularly severe and persistent course (Gualtieri et al, 1982). However, other studies have suggested similar rates of TD in children during neuroleptic treatments (Paullson et al, 1975 and Campbell et al, 1983). These patients may represent a group of chronic disadvantaged youngsters at high risk of developing TD. This may be explained by the repeated hospitalization, the high doses and long duration of treatment. In addition, these patients showed more severe psychopathology (there were no significant differences when the total BPRS-C score was considered, but the differences were significant when the last three severity levels of the BPRS-C were calculated; 9.8 ± 3.7 vs. 4.5 ± 4.3 in TD and non-TD patients respectively). This severe psychopathology may be an expression of an underlying brain damage. (Breslau, et al, 1988). The higher incidence of adverse perinatal and neonatal events in TD patients than in non-TD patients could be explained by the multi-handicapped nature of the TD group.

The last finding was particularly interesting in relation to the risk factors predisposing for TD. Angle and McIntire

(1968) have suggested that in brain-damaged children with abnormal birth history or other antecedent CNS insult, there is an increased sensitivity to the neurological complications of phenothiazines. Kane et al (1980), addressing a strategy for the study of patients at high risk for TD, pointed out that some degree of pre-existing CNS dysfunction may be the most important single factor in producing high risk. TD patients in our sample were younger than non-TD patients, and developed TD after a relatively shorter duration, about 4 years, than that of adults, which is usually 6 to 8 years (Crane, 1974). Also, these patients continued to show the dyskinesia without reduction or discontinuation of their neuroleptics, and diagnosis of TD was confirmed on at least two examinations.

It is believed that neonatal CNS damage often results in less functional impairment than similar damage to an adult, and neonatally damaged CNS shows greater behavioral and neurological plasticity. Immature organs are usually more susceptible to injury than mature ones (Breslau, et al, 1988) and it is possible that organs tend to be most susceptible at the time of their most rapid growth, which in the case of the brain consists of the prenatal period (Takei et al, 1994) and the first two years or so after birth (Rutter, 1981). There is also evidence that neonatal ischemia may be the most important single factor contributing to the development of neurological handicap (Skov et al, 1984, Cantor et al, 1994 a, b).

Three of the TD patients have a history of maternal toxemia of pregnancy. One patient's mother was a heroin addict who had the complication of a late pregnancy and when the patient was a child he had been admitted to the hospital for nine months for vomiting, "colicky and shook all over". One child was hospital-

ized with the diagnosis of "failure to thrive" while pregnant. In one case the mother was a mentally retarded schizophrenic who received neuroleptics during pregnancy. Also, one child had a 4-6 week premature birth with forceps delivery, were born by forceps delivery. These findings cannot be explained on the basis of neurologically handicapped population, since neither developmental delay and neurological events variables were not significantly associated with TD nor intellectual impairment. Earlier studies, however, have suggested a continuum of reproductive causality (Pasamanick, 1960 and 1966). Thus, it is difficult to draw conclusions from these findings, except to suggest that the presence of an abnormal birth history among a subgroup of children may indicate a patient at high risk for developing late complications following long term neuroleptic treatment. (Campbell and Spencer, 1988, Faber, 1987).

The present findings, however, expands the current literature of the associated risk factors for TD, and suggest the need for a more systematic prospective study of the risk factors associated with the development of TD in children and adolescents. Such a study should assess TD on a longitudinal basis, if possible with discontinuation of neuroleptic treatment and followup for longer periods of time. In addition, more systematic assessment of perinatal, developmental and neurological adverse events is indicated. Furthermore, the search for more effective and safe drugs for psychiatric children and adolescents should continue (Campbell et al, 1992, Kaplan et al, 1994). Perhaps psychopharmacological guidelines should be established in the treatment of children and adolescents to demand trials of other non-neuroleptic drugs before shifting to neuroleptic medication (Biederman, 1991, 1992).

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Dyscinetique Tardif et les Évènements Défavorables Périnataux

Les auteurs ont examiné 61 enfants et adolescents qui ont pris des neuroleptiques pour la présence de (TD) en utilisant des moyens d'assessment standardisés. Les résultats ont démontré que (20%) ont été diagnostiqués comme (TD). Il existe encore une association claire entre les neuroleptiques événements défavorables périnataux et développementaux.

الحركات اللاإرادية المتأخرة (فى الأطفال والمراهقين) وأحداث ما حول الولادة

تعتبر الحركات اللاإرادية المتأخرة من المضاعفات العصبية التى تصاحب تناول المهدئات العظمى ولفترات طويلة، وقد تم فى هذا البحث تقييم واحد وستين طفلاً ومراهقاً من الذين كانوا تحت العلاج بالمهدئات العظمى ولفترة لا تقل عن ثلاثة شهور وإشتمل التقييم فى المرحلة الأولى على التقييم العصبى باستخدام مقياس مقننة للتعرف على وجود ودرجة وشدة الحركات اللاإرادية المتأخرة، وفى المرحلة الثانية تم تتبع واستخلاص العوامل الإكلينيكية والمضاعفات العصبية والمشاكل النمائية التى ظهرت لدى الأطفال والمراهقين وفى تاريخهم المرضى وخصوصاً بشأن مضاعفات الحمل والولادة وفترة ما بعد الولادة، وقد أظهرت النتائج وجود تاريخ مرضى بمضاعفات أثناء الحمل والولادة وبين ظهور الحركات اللاإرادية المتأخرة كمسألة ومضاعفات لتناول المهدئات العظمى، ويناقش البحث الدلالات والأبعاد.