Platelet Monoamine Oxidase Activity in Children and Adolescents with Psychiatric Disorders

by J. Gerald Young, Donald J. Cohen, Merilyne C. Waldo, Reza Feiz, and Jerome A. Roth

Abstract

Platelet monoamine oxidase (MAO) activity was studied in 108 children and adolescents with psychiatric illness and 67 control subjects. Platelet MAO activity was higher in male children with a psychiatric disturbance than in male control subjects. There was a gradual decline in platelet MAO activity during childhood and adolescence. Associations were demonstrated between MAO activity and hemoglobin, hematocrit, and platelet count, and should be considered in biological studies of vulnerability to psychiatric illness.

Many biochemical and clinical properties of platelet monoamine oxidase (MAO) activity have been determined since the first reports of its reduction in chronic adult schizophrenia (Domino and Khanna 1976; Meltzer and Stahl 1974; Murphy and Wyatt 1972; Nies et al. 1974; Sullivan, Stanfield, and Dackis 1977; Zeller et al. 1975). Most subsequent studies support the original findings, although several investigators do not concur (Belmaker et al. 1976; Friedman et al. 1974; Owen et al. 1976; Shaskan and Becker 1975; White, McLeod, and Davidson 1976). The prevailing view is that reduced platelet MAO activity is a biological marker for major psychiatric disorders in adulthood, and it has also been related to a specific paranoid symptom cluster in schizophrenic patients (Potkin et al. 1978; Schildkraut et al. 1976). Inadequately controlled variables, differences in diagnostic criteria, and small subject samples may underlie differences among research findings. Biological factors, such as enzyme characteristics and hormones, are considered possible sources of variance (Murphy et al. 1977).

Stable biological markers would be a great advantage in research investigating childhood risk factors for adult psychiatric disorders, as well as in studies of the relationship of the psychoses of childhood and adulthood. Previous publications from our laboratory have reported on platelet MAO activity in normal children and adolescents and in children with early childhood autism (Cohen, Young, and Roth 1977; Roth, Young, and Cohen 1976). This article describes an analysis of the influence of age, platelet count, and hematocrit on platelet MAO activity, and the impact of psychiatric disturbance on platelet MAO activity in children and adolescents.

Subjects

The subjects of this study were 108 children and adolescents (80 males, 28 females) with moderate-to-severe psychiatric disturbances; they ranged in age from 4 through 21 years. Each child was given a detailed evaluation and classified diagnostically, according to DSM-III (Task Force on Nomenclature and Statistics of the American Psychiatric Association 1978) and the system proposed by the Committee on Child Psychiatry of the Group for the Advancement of Psychiatry (1966), after two child psychiatrists agreed that the criteria were fulfilled (Cohen 1976; Cohen et al. 1978). The childhood autism population was sizable enough to permit detailed analyses within the group. The other childhood psychiatric patients were from di-
verse diagnostic subgroups, including reactive disorders, personality disorders, attention deficit syndromes, central language disorders, childhood schizophrenia, and organic brain syndromes. This diagnostically heterogeneous population provided a broad-based psychiatric contrast group suitable for analysis comparing the autistic children with other youngsters suffering from behavioral syndromes. Future studies will investigate the other diagnostic subgroups in greater detail. On no relevant demographic variable was there a significant difference among the subgroups in the heterogeneous psychiatric population, or between this population and the autistic children.

In addition, there were two separate types of control subjects: "family controls" and "normal controls." These groups were combined, for some analyses, as "all controls." The family control group consisted of 15 males and 14 females with no known medical or psychiatric disorders, who were parents or siblings of a child with a developmental disturbance; they were separated from other controls because of a possible (genetic) difference in enzyme activity. No more than one (randomly selected) member of an individual family was included in the family controls. The normal control group included 22 males and 16 females with no known personal, medical, or psychiatric disorder or immediate family history of psychotic disorder. Combined, the control groups contained 37 males and 30 females.

Sample number for various analyses varied because all laboratory values were not available for each subject. Statistical correlations were calculated using values obtained on a single venipuncture.

Some patients (10 percent) were in residential treatment at the time the sample was obtained, but most were living at home with their families and attending special day school programs. All children were in good general health at the time the blood samples were taken. Forty-nine children were receiving medications which have previously been shown not to alter MAO activity (Murphy 1976); the mean platelet MAO activity of children receiving medication did not differ from the mean of the drug-free children in either males or females.

Methods

Consent was obtained from each adult and competent child, and from parents of children and those unable to assent. Blood, obtained by standard venipuncture, was immediately placed on ice; platelets were separated by centrifugation within 3 hours of collection and were stored frozen for a maximum of 14 days before assay. Platelets disrupted by sonic oscillation were incubated in the presence of 1.67 × 10⁻⁵ M ¹⁴C-tyramine. The platelet protein was assayed using the method of Lowry et al. (1951), and platelet MAO activity was expressed as nmoles deaminated product formed per mg protein per 60 minutes incubation. Details of the method are reported elsewhere (Roth, Young, and Cohen 1976).

Platelet counts were performed on a continuous flow automated platelet counter; red blood cell (RBC), hemoglobin (expressed as grams/100 ml blood), and hematocrit (packed volume of RBC/unit volume of blood, expressed as percent) were determined by standard methods.

Results

We will review MAO activity in relation to sex, age, platelet count, hemoglobin concentration, packed red cell volume, and psychiatric disturbance.

Sex Differences in Platelet MAO Activity. Platelet MAO activity is greater in females than males (table 1) in each of the groups comprising our total population (t = 3.2, p < .01, for the total population; t = 3.4, df = 130, p < .001, for the total population under 21.1 years of age).

Age and Platelet MAO Activity. There is a negative relation between age and platelet MAO activity in the total population of patients and control subjects (n = 176, r = -.24, p < .001): this relation remains statistically significant when the total population is divided according to sex, but not when broken down into smaller subject groups. Figure 1 (a, all males; b, all females) demonstrates that patients and controls are generally distributed into two groups, although with overlap, on the age-MAO scatterplots.

Platelet Count and Platelet MAO Activity. Mean platelet counts in all groups are within the normal range (table 1).

There is a significant positive correlation between platelet count and platelet MAO activity in male patients (r = .28, p = .04) and the total male population (r = .20, p = .005) (figure 2). A partial correlation, controlling for age, indicates that the correlation is not due solely to the influence of age (r = .24, p = .02 for the total male population). In contrast are negative correlations between platelet count and platelet MAO activity in all female groups, reaching significance in all female controls (r = -.51, p = .02) and the total female population (r = -.38, p = .01) (figure 2). The corresponding partial correlation (controlling for
Table 1. Platelet monoamine oxidase activity in children with psychiatric disorders and controls

<table>
<thead>
<tr>
<th></th>
<th>Normal controls</th>
<th>Family controls</th>
<th>All controls</th>
<th>Patients</th>
<th>Total population</th>
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<tr>
<td></td>
<td>(n = 22)</td>
<td>(n = 15)</td>
<td>(n = 37)</td>
<td>(n = 81)</td>
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<td><strong>Means ± SD</strong></td>
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<tr>
<td>Age</td>
<td>21.6 ± 11.3</td>
<td>37.0 ± 15.1</td>
<td>27.9 ± 14.9</td>
<td>12.0 ± 4.1</td>
<td>16.9 ± 11.6</td>
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<tr>
<td>Platelet MAO activity</td>
<td>21.2 ± 8.1</td>
<td>20.1 ± 7.0</td>
<td>20.8 ± 7.6</td>
<td>26.4 ± 7.2</td>
<td>24.6 ± 7.8</td>
</tr>
<tr>
<td>Platelet count</td>
<td>283.0 ± 79.0</td>
<td>268.0 ± 63.0</td>
<td>277.0 ± 72.0</td>
<td>311.0 ± 84.0</td>
<td>298.0 ± 81.0</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>39.9 ± 4.7</td>
<td>42.5 ± 2.7</td>
<td>41.1 ± 4.1</td>
<td>38.0 ± 3.1</td>
<td>39.1 ± 3.7</td>
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<tr>
<td></td>
<td>(n = 19)</td>
<td>(n = 13)</td>
<td>(n = 32)</td>
<td>(n = 58)</td>
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<td>(n = 16)</td>
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<td><strong>Means ± SD</strong></td>
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<tr>
<td>Age</td>
<td>21.1 ± 10.2</td>
<td>29.7 ± 15.3</td>
<td>25.1 ± 13.3</td>
<td>11.9 ± 2.8</td>
<td>18.7 ± 11.8</td>
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<tr>
<td>Platelet MAO activity</td>
<td>27.5 ± 8.4</td>
<td>25.5 ± 8.1</td>
<td>26.6 ± 8.2</td>
<td>31.1 ± 9.1</td>
<td>28.7 ± 8.8</td>
</tr>
<tr>
<td>Platelet count</td>
<td>283.0 ± 56.0</td>
<td>307.0 ± 67.0</td>
<td>295.0 ± 61.0</td>
<td>322.0 ± 88.0</td>
<td>308.0 ± 75.0</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>38.6 ± 3.2</td>
<td>37.2 ± 2.7</td>
<td>37.9 ± 3.0</td>
<td>35.6 ± 8.6</td>
<td>36.8 ± 6.3</td>
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<td></td>
<td>(n = 11)</td>
<td>(n = 11)</td>
<td>(n = 22)</td>
<td>(n = 19)</td>
<td>(n = 41)</td>
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**Note.** Age: years; platelet MAO activity: nmoles/mg protein/hr; platelet count: X 10^9/mm^3; hematocrit: %.

For the total female population is age) for the total female population is significant ($r = -0.36, p = 0.02$).

A strong positive correlation between platelet count and platelet MAO activity in males with early childhood autism ($n = 19$) contributes to these relations. These relations were thus assessed without autistic children. The correlation between platelet count and platelet MAO activity in females is slightly enhanced. The correlations between platelet count and platelet MAO activity in males with early childhood autism ($n = 19$) contribute to these relations. These relations were thus assessed without autistic children. The correlation between platelet count and platelet MAO activity is no longer significant in male groups when autistic patients are eliminated. When two autistic girls are not included, the moderately strong negative correlation between platelet count and platelet MAO activity in females is slightly enhanced.

The correlations between platelet count and platelet MAO activity for male and female total populations were compared after they were age-controlled and the autistic patients deleted. The difference between the correlations for males and females is significant, as calculated using indicator (dummy) variables (Draper and Smith 1966) and comparing the slopes of the regression lines ($t = 2.08, df = 69, p < .05$ (figure 2)).

**Hemoglobin, Hematocrit, and Platelet MAO Activity.**

Correlations of hemoglobin and hematocrit with age, platelet count, and platelet MAO activity were nearly identical. The correlation between hemoglobin and hematocrit was $+.96 (p < .001)$ for all patients and control subjects (combined sexes) and varied little in subgroups. We describe only hematocrit in further statistical analyses.

The mean hematocrit of each group in table 1 is within the normal range.

A significant negative correlation between hematocrit and platelet MAO activity is evident in male patients ($r = -0.48, p = .001$) and the total male population ($r = -0.32, p = .004$). A strong negative correlation between hematocrit and platelet MAO activity in males with early childhood autism ($r = -0.99, n = 18, p < .001$) inflates the correlations, so they were recalculated without autistic children. The correlation is partially due to the impact of age on hematocrit and platelet MAO activity. However, the negative correlation between hematocrit and platelet MAO activity in the male patient group maintains significance when autistic males are not included ($r = -0.33, p = .05$) (figure 3).
Figure 1. Platelet MAO activity and age

**MALES**
- Mean MAO Activity: 24.6 ± 7.6
- Mean Age: 16.9 ± 11.6
- r = -0.26, p = .005, N = 118
- Y = 27.57 - .17X
- • = Patients, ○ = Controls

**FEMALES**
- Mean MAO Activity: 28.7 ± 8.8
- Mean Age: 18.7 ± 11.8
- r = -0.28, p = .04, N = 58
- Y = 32.0 - .19X
- ▲ = Patients, △ = Controls

**Developmental Changes Summarized.** Table 2 presents the variable means for males and females in three age groups: prepubertal (0–10.9 years), pubertal (11.0–14.9 years), and postpubertal (15.0–20.0 years). The general trends with increasing age are clear: decreasing platelet MAO activity, decreasing platelet count, and increasing hematocrit.

**Platelet MAO Activity in Psychiatric Patients and Control Subjects.** Mean MAO activity of pediatric psychiatric patients (combined sexes) is significantly greater than that of either primary control group or both control groups together (t = 3.35, p < .001 for the latter). When grouped by sex, the mean MAO activity of male and female patients is significantly greater than that of respective control groups (t = 3.86, p = .001 for males; t = 1.97, p = .05 for females) (table 1).

Frequency histograms in figure 4 depict this shift toward greater platelet MAO activity in both male and female patient groups when compared to control groups. Note that it is not the height of the bars that is to be compared in the figure, but the relative distributions of patients and controls.

The mean age of patients is less than that of the controls, so that their higher mean platelet MAO activity could result from the negative relationship between age and MAO activity. Mean MAO activities were corrected for age effect by selecting only patients and control subjects younger than 21.1 years old (107 patients with a mean age of 11.6 years, 26 controls with a mean age of 11.7 years).

Male patients under 21.1 years old had a mean platelet MAO activity of 26.4 ± 7.3 (n = 78), while male controls under 21.1 years had a mean platelet MAO activity of 21.3 ± 7.8 (n = 13). These mean activities are significantly different (t = 2.28, p = .03).

Female patients under 21.1 years of age had a mean platelet MAO activity of 31.1 ± 9.1 (n = 28), while female controls under 21.1 years had a mean platelet MAO activity of 30.0
Figure 2. Platelet MAO activity and platelet count

**MALES**
Mean MAO activity = 24.9 ± 8.1
Mean platelet count = 299 ± 81
r = .29 p = .005 N = 90
Y = 16.08 + .03X

**FEMALES**
Mean MAO activity = 28.1 ± 9.2
Mean platelet count = 307 ± 75
r = -.38 p = .01 N = 41
Y = 42.68 -.05X

± 6.3 (n = 13), not significantly different.

Discussion

Sex. Since platelet MAO activity is higher in females than in males before puberty, the differences may depend on genetic control. A superimposed estrogen-progesterone effect in the range of 20 percent occurs during the menstrual cycle, varying according to species and tissue (Belmaker et al. 1974; Redmond et al. 1975). The effect of androgens on platelet MAO activity is less clearly defined (Redmond et al. 1976).

Whether the differences between the sexes or the fluctuations with hormonal levels are translated into functional (behavioral or metabolic) effects is not yet clear. For example, MAO could play a role in the expression of sex differences in temperament. From another perspective, MAO may be involved in the initiation or mediation of fluctuating sex hormone levels during periods of developmental transition, especially if there are parallel changes in the hypothalamus, the site of highest brain MAO activity (Robinson et al. 1977). Platelet MAO activity increases after menopause and may predispose to depression during this period, particularly in women because of their higher MAO activity (Robinson 1975; Robinson et al. 1971). We have shown that platelet MAO activity declines during puberty, and parallel developmental changes seem to occur in brain (Robinson et al. 1977). The contribution of this trend to the expectable emotional upsets of adolescence or the onset of severe disorders, such as schizophrenia, remains to be explored.

Age. Our data show a decrease in platelet MAO activity through childhood and adolescence in both sexes. The MAO activities in human platelet, plasma, and brain (autopsy) tissue were reported to be higher in a "juvenile" group than in a young adult group (Robinson et al. 1977), which suggests that the relation of platelet MAO activity and age may reflect a parallel association in brain tissue.

We have previously described a negative relation in childhood be-
Figure 3. Platelet MAO activity and hematocrit: Male nonautistic psychiatric patients under 21.1 years old

Male children and adolescents
Nonautistic psychiatric patients
Mean MAO activity = 27.2 ± 7.0
Mean hematocrit = 37.5 ± 2.9
r = -.33 p = .05 N = 34
Y = 56.8 - .79X

Between age and cerebrospinal fluid (CSF) concentration of the principal metabolite of dopamine (homovanillic acid, HVA) following probenecid (Cohen et al. 1977). This association has been extended for a larger population of 160 psychiatric patients between 4 and 60 years of age, with the major alteration occurring between 8 and 20 years (Leckman et al., in press). The decrease in CSF HVA, a metabolite reflecting brain turnover of the parent amine, dopamine, may be related to decreased activity of the catabolic enzyme, MAO.

Because of the proximity of deep brain structures to the ventricles, it may be hypothesized that alteration in hypothalamic dopaminergic turnover may particularly contribute to the developmental changes in CSF HVA. The dopaminergic pathway in the hypothalamus modulates hypothalamic factors for the gonadotropins and prolactin, centrally involved in pubertal changes.

The relation between enzyme activity and an organism's age is complex. Developmental effects on MAO activity are species- and tissue-specific. For example, MAO activity in rat heart increases over the life span, while MAO activity in rat brain remains stable (Novick 1961; Prange et al. 1967). MAO activity in rat liver increases during a middle epoch and declines in old age (Prange et al. 1967), resembling the inconstant effects of development on human platelet MAO activity. Also, iso-

Table 2. Means of prepubertal, pubertal, and postpubertal age groups

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td></td>
<td>Platelet MAO activity</td>
<td>Platelet count</td>
</tr>
<tr>
<td>0 to 10.9 years</td>
<td>26.7(^1)</td>
<td>351,700(^2)</td>
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<tr>
<td></td>
<td>(40)</td>
<td>(30)</td>
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<tr>
<td>11.0 to 14.9 years</td>
<td>25.6</td>
<td>271,700(^2)</td>
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<td>(36)</td>
<td>(29)</td>
</tr>
<tr>
<td>15.0 to 20.0 years</td>
<td>22.4(^1)</td>
<td>260,000(^2)</td>
</tr>
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<td></td>
<td>(14)</td>
<td>(10)</td>
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</tbody>
</table>

Note.—The number of subjects in each group is given in parentheses. See note to table 1 for units of measurement.

\(^1\) p < .10, t test.
\(^2\) p < .001, F test.
\(^3\) p < .05, F test.
enzymes in the same tissue may follow different developmental patterns, but human platelet MAO appears to be homogeneous and has been identified as the B type (Collins and Sandler 1971; Edwards and Chang 1975; Robinson et al. 1968). Developmental patterns of MAO activity in specific tissues may be altered by environmental factors. For example, in visual pathways of rat brain, MAO activity is influenced by the amount of light, while in rat testes, MAO activity is responsive to androgen concentration (Grégois 1975).

Platelet Count. Comparison of platelet counts between diagnostic groups must be cautious, in view of the decline from the first year of life to puberty (Ritvo et al. 1971). The platelet count in autistic children has been reported to be increased when compared to a control group, and we have previously reported a nonsignificant trend in that direction (Cohen, Young, and Roth 1977; Ritvo et al. 1970). The data reported here also suggested an elevated platelet count among autistic males until the effect of age was considered.

Young human platelets are relatively large and heavy; platelets decrease in size with aging. Functionally, large platelets are more stable and are more active metabolically. There is an inverse relation between platelet count and platelet size, so that total platelet volume is a more stable index for an individual than platelet count (Karpatkin, Khan, and Freedman 1978). The makeup of the platelet population may change in response to stress, disease, or drugs.

In this study, platelet MAO activity was expressed relative to platelet protein per sample, and values should be unaffected by total platelet count. Relative recoveries of platelet protein and MAO activity should remain constant through the platelet isolation procedure, and possible differences in MAO activity secondary to platelet size (age) should be balanced by reciprocal platelet count changes. An alternative method expresses platelet MAO activity in terms of platelet count. The platelet count method (using benzylamine as substrate) has resulted in activities highly correlated with the platelet protein method (using tryptamine as substrate) \( r = .85, p < .001, n = 48 \). This compared well to other determinations of MAO activity with two different substrates (tryptamine and benzylamine) using only the platelet protein method \( r = .89, p < .001, n = 75 \) (Murphy et al. 1976). Thus, the associations between platelet count and MAO activity do not appear to be the result of obvious artifacts (such as leukocyte contamination), the platelet isolation method, or platelet heterogeneity.

The origin of the negative association between platelet count and MAO activity in females, and the divergent relation in males, is not yet evident.

Hematocrit. The negative correlation between platelet MAO activity and hematocrit in the male patient and total population groups is intriguing. This association persists in the pa-
tient group after correction for age differences and deletion of the biasing autistic group. The relation does not occur in the control groups, is weak (but significant) in nonautistic psychiatric patients, and reaches an extreme in autistic patients. This order of correlations parallels group ranking according to severity of clinical impairment and may be compatible with a genetic mechanism.

The basis of this unexpected association between hematocrit and platelet MAO activity in male children with psychiatric illness is not clear, but may relate to the fact that iron is an essential component of hemoglobin and is required for retaining optimal MAO activity. We have discussed this in detail elsewhere (Young, Cohen, and Roth 1978).

**Psychiatric Patients vs. Controls in Childhood.** Deviations in platelet MAO activity in adult psychiatric patients are uniformly in the direction of reduction. An increase in MAO in children with psychiatric disturbances is surprising. The spectrum of childhood disorders included in our study ranges from neurotic problems to the psychoses, but in no diagnostic group is there a mean reduction in platelet MAO activity. A conservative assessment of our data would be that the overall group of male children with psychiatric disorders has a higher platelet MAO activity than male controls.

An initial stimulus for the investigation of platelet MAO activity in a pediatric population was its possible utility as a biological marker. Despite years of research, there is not yet satisfactory evidence to clarify whether there is continuity between the psychoses of childhood and adulthood. Similarly, it has been shown that children with psychiatric disorders represent a major population at risk for severe psychiatric disturbance during adulthood, but there is no biological evidence of the persistent trait.

When the data reported here are considered in terms of vulnerability to adult psychoses, several possibilities emerge: (1) The increased MAO activity in juvenile psychiatric patients could indicate that they are not the population which will later manifest severe psychopathology as adults; (2) the children might represent a vulnerable group whose MAO activity will be at the upper end of the bimodal MAO activity distribution suggested in the adult schizophrenic population; or (3) the negative correlations between platelet MAO activity and both age and hematocrit contribute to the disparity in findings between child and adult patient groups.

Platelet abnormalities are not unusual in severely disturbed children. Impaired adenosine triphosphatase function and decreased platelet serotonin occur in Down's syndrome (McCoy et al. 1974; Tu and Zellwenger 1965), and a more retarded subgroup of autistic children have increased blood serotonin (carried in platelets) (Ritvo et al. 1970; Schain and Freedman 1961). This hyperserotonemia may be due to a decrease in serotonin binding by the platelet or to abnormal platelet MAO function (Boullin, Coleman, and O'Brien 1970; Yuwiler et al. 1975). Normal MAO activity in autism suggested that impaired catabolism was not a factor (Cohen, Young, and Roth 1977), although the human platelet enzyme is type B and less active toward serotonin than type A MAO.

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