Refractive evaluation in thalidomide embryopathy*

Kerstin Strömland1 and Marilyn T. Miller2

1 Department of Pediatric Ophthalmology, University of Göteborg, East Hospital, S-41685 Göteborg, Sweden
2 Department of Ophthalmology, University of Illinois at Chicago, Chicago, Ill., USA

Received July 8, 1991 / Accepted July 18, 1991

Abstract. To evaluate the ocular findings associated with thalidomide embryopathy, we examined 86 of 100 Swedes who had a proven correlation between birth defects and the mother's intake of thalidomide during pregnancy. Cycloplegic refraction, keratometry, and axial length measurements were performed. The subjects were divided into four groups according to their physical malformations, giving a time frame for when in gestation the insult occurred (the sensitive phase for thalidomide is 20–36 days after conception). The results indicate a trend toward shorter and longer axial lengths, high refractive errors, and corneal astigmatism in thalidomide embryopathy compared to controls, and in addition there was a tendency for those anomalies to occur in the group with the earliest thalidomide-induced defects. It is suggested that thalidomide disturbs the growth and shape of the eye and that this effect is exerted early in its teratogenic period.

Introduction

Thalidomide (α-phthalimidoglutarimide) was synthesized in the Federal Republic of Germany in 1954 and marketed in Europe and a number of countries (not including the United States) in 1956 and 1957. It was considered an effective sedative and hypnotic drug which, even at extremely high doses, failed to evoke significant toxic effects in animal experiments [13, 26]. In 1961, Wiedemann [29] and Kosenow and Pfeiffer [12] drew attention to an alarming increase in the incidence within Germany of hypoplastic and aplastic malformations of the extremities, and Lenz [14] speculated that ingestion of thalidomide by the mothers during pregnancy was the cause. At the same time, the teratogenic potential of thalidomide had been recognized in Australia by McBride [17, 18]. The drug was withdrawn from the market in late 1961.

Together with limb defects a number of other anomalies were reported [15]. Lenz and Knapp [16] and Nowack [21] defined the critical period as being 35 to 50 days from the first day of last menstruation (20 to 36 days after conception) and suggested that the distribution of the organ systems involved, and the severity of the defects, depended on the specific period in the susceptible range that the drug was ingested (Table 1). There are few reports on the ocular abnormalities that affected the victims of thalidomide embryopathy [2, 9, 11, 22-24, 31].

The purpose of the present study was to study the influence that thalidomide had on the development and function of the eyes. We wanted to evaluate all ocular findings associated with thalidomide embryopathy, and therefore we examined the Swedes who had a proven correlation between birth defects and the mother's intake of thalidomide during pregnancy. Their refractive findings and their combination with other systemic and ocular recognition of abnormalities are presented. Other ocular anomalies, mainly the findings of abnormal ocular motility, have been published elsewhere [19].

Patients and methods

A refractive examination on 86 of 100 Swedes ranging in age from 26 to 29 years who had thalidomide embryopathy was performed at several hospitals and clinics throughout Sweden. Fourteen patients were excluded from the study: 7 could not be reached by mail, 6 declined to take part, and 1 woman was severely ill due to cancer of the colon. The examination included visual acuity measurements, cycloplegic refraction using 1% cyclopentolate hy-
Table 1. Timetable for the teratogenic action of thalidomide

<table>
<thead>
<tr>
<th>Age after conception</th>
<th>- days</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>27</th>
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<th>29</th>
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<th>32</th>
<th>33</th>
<th>34</th>
<th>35</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>- weeks</td>
<td></td>
<td>3</td>
<td>4</td>
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</table>

<table>
<thead>
<tr>
<th>Anotia</th>
<th>Ear anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thumb hypoplasia</td>
<td>Triphalangism</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>Lower limbs</td>
</tr>
</tbody>
</table>

Group 1.

Group 2.

Group 3.

Group 4.

drochloride, apical keratometry measurements with an ophthalmometer (Javal-Schiötz), and axial length determination by A-scan ultrasonography. All of the measurements were done on both eyes of 70 subjects. In the other 16 subjects, it was possible to obtain only some of the measurements, and three patients could not be accurately examined.

The subjects were divided into four groups, depending on how they were affected by thalidomide. Group 1 included those who had anotia and severe hearing loss but no limb anomalies (thumb excluded). Group 2 consisted of subjects who had upper and/or lower limb anomalies (upper limb included at least radius dysplasia, thumbs were not considered) and no ear malformations or hearing loss. Group 3 included those who had an ear anomaly or severe hearing loss combined with an anomaly of the limbs, either upper, lower or both. Group 4 consisted of subjects who did not fit into the above categories, but had malformations such as isolated thumb anomalies. The groupings relied on the teratogenic phase of thalidomide (Table 1) [16, 21], separating the subjects into those who were affected early and not late (group 1), only late (group 2), both early and late (group 3), and those with miscellaneous findings (group 4).

The data were statistically described by mean standard deviation (SD) and standard error of the mean (SEM). The variability of the characteristics studied was shown by confidence intervals with Student's t-test. Differences were considered as significant if the probability for the hypothesis of no-difference between groups was less than 5%.

Results

Axial length

Axial length was measured in a total of 73 subjects, 42 males and 31 females (144 eyes). The results are given in Table 2A. Figure 1 shows the 90% confidence limits for axial length measurements. The interval for group 1 was lower than in the other groups, but the mean difference was not significant, as shown in Figure 1. Group 1 had the greatest range of axial lengths (19.95–26.62 mm). There were some individuals with very short or long axial lengths. Table 3 shows the patients with values ± 1 and 2 SD and their refraction. Two subjects in group 3 each had one eye with an axial length that was longer than those in any other group (28 mm), and both were highly myopic.

There were two subjects (three eyes) with microphthalmia whose axial length could not be measured. One was a male in group 2 with severe bilateral microphthalmia. The other was a female in group 3. She had microphthalmia in her right eye and, in the functioning left eye, the longest measured axial length (28.34 mm). Furthermore, she was highly myopic; she had Duane's syn-