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40 years later: the health related quality of life of women affected by thalidomide

This paper is dedicated to the memory of Widukind Lenz

Almost 40 years ago, in November 1961, thalidomide, West Germany's best-selling sedative was withdrawn from the markets.

Introduction, Historical background

Until then thalidomide had been marketed in 46 countries world-wide, including Europe, the British Isles, Australia, Asia, Africa, the Americas, Canada, and New Zealand. In some countries, it was available on prescription only, in other countries, including Germany, it was sold over the counter. Thalidomide was used and recommended for a variety of ailments, but predominantly as a safe tranquilizer and sleeping pill devoid of the known toxic side effects of barbiturates. Thalidomide was first released in Germany by the end of 1957 and sold under the name Contergan. Its 'safer than other sedatives' marketing strategy had been highly successful and sales had increased on a massive scale in Germany and internationally as well. About a year after the release of Contergan, first complaints of side-effects, mostly peripheral neuropathies, appeared and were brought to the attention of the manufacturer, Chemie Grünenthal, who dismissed the claims of an association between the intake of thalidomide and polyneuritis as unsubstantiated.

By the end of 1959 and in 1960 more and more pediatricians were starting to see newborns with limb and ear malformations that most of them had never seen before in their entire time of practice. These first cases were believed to be random cases of phocomelia, severe but rare limb defects of genetic origin. The medical community was unaware that they were seeing the first victims of an unfolding epidemic of congenital malformations caused by the teratogenic effects of thalidomide. The spectrum of malformations attributable to thalidomide includes severe deformations such as absence of ears and deafness, defects of ocular and facial muscles, absence or hypoplasia of the arms, defects of the femur and the tibia, malfor-

mations of the heart, bowels, uterus and gallbladder. Thalidomide causes different malformations during fetal development, the individual type of malformation depending on the time of intake by the mother. It only causes malformations if taken within a time period from day 35 to day 49 after the last menstruation, if taken before or after that period no malformations occur.

In Germany, pediatricians with training in clinical genetics, were mystified by the apparent outbreak of phocomelia. One of them, Widukind Lenz, started to investigate the prevalence at birth of phocomelias in Hamburg. In Germany, a country that even today does not keep population-based registers of infants born with congenital malformations, this was a daunting task. But the statistics assembled by Lenz were telling: from 1930 to 1955 the city's 212.000 birth records reported only 1 case of phocomelia; between September 1960 and October 1961 among 6.420 babies born, 8 cases had been reported. Led by this statistical evidence Lenz began to interview mothers of affected children and even placed ads in newspapers to search for more recent cases. When Lenz started to interview the mothers, he did not have a clue what may have caused the sudden rise of phocomelias. He did not ask methodically about drug intake, until a woman told him that she had taken Contergan during her pregnancy and because she had experienced peripheral neuritis she had been very worried about the health of her baby. With that information as a possible clue, Lenz began to reinterview the women inquiring specifically about Contergan intake. He found out that 14 mothers had taken the drug. By November 16, 1961, he felt certain enough to inform Grünenthal about his findings and expressed his concern that any delay in withdrawing the drug from the market could result in potentially harming hundreds of unborn

children. In Lenz's opinion, Contergan should be withdrawn immediately. In a letter he wrote on that day to Grünenthal he stated: "In view of the incalculable human, psychological, legal and financial consequences of this problem, it is, in my own opinion, indefensible to wait for a strict scientific proof of the harmfulness or harmlessness, as the case may be, of Contergan. I consider it necessary to withdraw the medicament from sale immediately, unless its harmlessness as a teratogenic agent in man is conclusively proved" [1, pp. 99-100]. In Lenz's own words, it took 10 more days of intensive discussions with representatives of Grünenthal, who were fiercely resisting the withdrawal of their highly profitable drug, and with German health authorities before the drug was withdrawn from the market, a decision largely due to reports of Lenz's findings in the popular press [1, p. 39; 2].

The evidence Lenz had put forward was supported by other independent observations. In December 1961, *The Lancet* published a letter to the editor by W. McBride, an Australian obstetrician, expressing his opinion that thalidomide was causing congenital malformations [3]. Also in December, *The Lancet* and the *British Medical Journal* [1, p. 105] announced the withdrawal of thalidomide from the British market.

The epidemic of limb malformations that had followed the increasing sales figures of thalidomide was now expected to end in late summer 1962 and so it happened. In August 1962, Helen Taussig wrote in the *Scientific American* 'For most people, the story of thalidomide has ended. The tragedy will go on, however, for the infant victims of the 'harmless' sedative and their families for the rest of their lives.' [4, p. 13].

More than 10.000 thalidomide-impaired babies were born worldwide and about 40% of them have died before their first birthday [5]. It is estimated that about 5.000 survived childhood.

In Germany a criminal trial of executives of Grünenthal was opened in 1968. The case was that "they had put on sale a drug which caused an unacceptable degree of bodily harm without having tested it properly, and that they had failed to react to information on side effects in due time, and instead had tried to suppress information" [5]. By the end of 1970, the proceedings of the trial were suspended for good. Neither a verdict of guilty nor an acquittal was rendered as Grünenthal and the attorneys representing the plaintiffs had settled for an out-of-court agreement. In 1971, the foundation "Hilfswerk für behinderte Kinder" (Founda-

tion for Handicapped Children) was established by the German government. The foundation was set up to design a compensation scheme funded by the money Grünenthal had agreed upon to contribute and by additional financial support provided by the Federal Government. A total of 2.866 thalidomide victims were finally covered by the scheme and by the early 1990s more than 500 million DM (about 255.646.000 EURO) had been paid [5].

In July 1998, the US Food and Drug Administration (FDA) approved thalidomide for the treatment of patients with leprosy. In order to prevent the recurrence of birth defects, the manufacturer, Calgene, has developed a unique distribution protocol named the System for Thalidomide Education and Prescribing Safety (STEPS) [4, p. 156 ff.]. STEPS was developed in collaboration with the FDA and thalidomide patient organizations and includes a short videotape in which a woman impaired by thalidomide demands extreme caution against pregnancy while taking thalidomide. Today thalidomide is prescribed for more than 130 different conditions including a variety of autoimmune diseases and is standard protocol in myeloma treatment in cancer clinics [4, p. 194]. A large number of new clinical trials have been initiated since FDA approval 3 years ago. In 2001, the potential clinical applications of thalidomide are steadily rising.

Meanwhile, the thalidomide victims who survived are reaching middle age. So far, no study has been published that has investigated how they have fared in major areas of life such as education, employment, marital relationships and reproduction and above all, their health-related quality of life. Especially women impaired by thalidomide may be at a special disadvantage because of a combined discrimination based on gender and disability. Because of increasing reports from various thalidomide support groups about deteriorating health, especially about degenerative diseases that start to afflict distorted skeletons and strained cartilages, including reports about increasing problems to find health professionals who are familiar with thalidomide-related impairments, a survey to document the health-related quality of life of women affected by thalidomide was undertaken in 1998-2000.

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Methods

Data-collecting instruments:

One of the main objectives of the study was to evaluate the health-related quality of life among women impaired by thalidomide and to compare it with non-affected women born at the same time using the WHO QOL-BREF instrument. The WHO QOL-BREF is designed to assess quality of life in health and health care in different cultures, environments and populations including groups with different diseases and disabilities [6]. It is an abbreviated version of the WHO-QOL-100 quality of life instrument developed by the World Health Organizations Quality of Life Group [7]. It is currently available in over 30 different languages, allowing results from different populations and countries to be compared.

The WHO QOL-BREF contains 26 items and is scored over four major domains: physical health, psychological well-being, social relationships and environment, and produces a global quality of life score, as well. Domain scores are scaled in a positive direction, higher scores signify a higher quality of life with the highest possible score being 100. The WHO QOL emphasizes the importance of the individuals' perception of health and well-being. Quality of life is defined by this approach as the individuals' perception of their position in life in the context of the socio-cultural value systems they live in and in relation to their own goals, standards, expectations and concerns. Permission to use the WHO QOL-BREF was obtained by the German national center of WHO-QOL-groups at the Universitätsklinikum, Klinik und Poliklinik für Psychiatrie, Leipzig.

The WHO QOL-BREF was incorporated into a larger questionnaire that included:

- 13 items to document the socio-economic status of both samples including education, current type of employment, sources of income, housing, family and household size;

- 12 questions that were exclusively addressed to the sample of women affected by thalidomide. These questions were designed in order to yield specific data with regard to thalidomide-related impairments. Because of this specificity, they were not included in the control group questionnaire. The questions allow the description of intra-group and differences in characteristics only. Items included were: current medical conditions, access to health professionals familiar with thalidomide-related impairments, past and present experiences with health care professionals, un-

met health needs, availability and dependence on personal assistance, anticipated future health problems due to current thalidomide-related impairments.

Discussion

The findings of this study clearly show that the quality of life in health and in health care was judged significantly poorer by women impaired by thalidomide than by women of the same age from the general population residing in the same area. Women affected by thalidomide-related impairments had significantly lower global WHO QOL and physical health scores as compared to their statistical twins.

They are significantly less frequently married, have fewer children, live in smaller households on smaller net incomes, are less mobile and are more likely to report difficulties in obtaining the relevant information they need in everyday life. However, women impaired by thalidomide are more likely to be satisfied with their safety in daily life, with their physical environment, with their living conditions and the support they get from their friends. They seem to have succeeded in establishing a network to obtain social support and help through private relationships. Whether or not these relationships are at risk of becoming strained in the future due to deteriorating physical conditions remains to be seen. Women affected by thalidomide clearly dread to become increasingly dependent on help by their personal assistants. Although the majority expresses fear of being less able in the future to work, to pursue leisure activities and to meet daily tasks, their overall psychological well-being does not seem to be negatively influenced by this anticipation. At least it is not different from that of their controls. This finding can be interpreted as an indicator for successfully acquired coping mechanisms. Whether this will change within an aging thalidomide population remains to be seen.

Women impaired by thalidomide suffer from chronic pain because of a steady deterioration of bones and muscles and are more likely to be in need of health care and medical treatment than their peers. But they have difficulties in finding health professionals who are familiar with conditions related to thalidomide impairments. A substantial number reported deteriorating conditions over the last 12 months. Because of gradual deterioration, those who are employed are facing an uncertain future in regard to their ability to remain in the workforce. As thalidomide-impaired women are very likely to require more health and support

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services in the future, the problem of finding appropriate medical care will become more urgent. At a time when thalidomide is enjoying a renaissance, is tested in numerous clinical trials and used as an experimental drug of last resort for an increasing number of conditions, ironically the specific health needs of women impaired by thalidomide are in danger of being neglected. The time for action to improve the medical community's knowledge on the health problems of women impaired by thalidomide and for clinical investigations on how to prevent premature musculoskeletal deterioration is now.

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¹ Bei diesem Aufsatz handelt es sich um eine gekürzte Version. Die vollständige Fassung wird in der Zeitschrift *Community Genetics*, Vol. 5, No. 4, 2002 erscheinen.

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