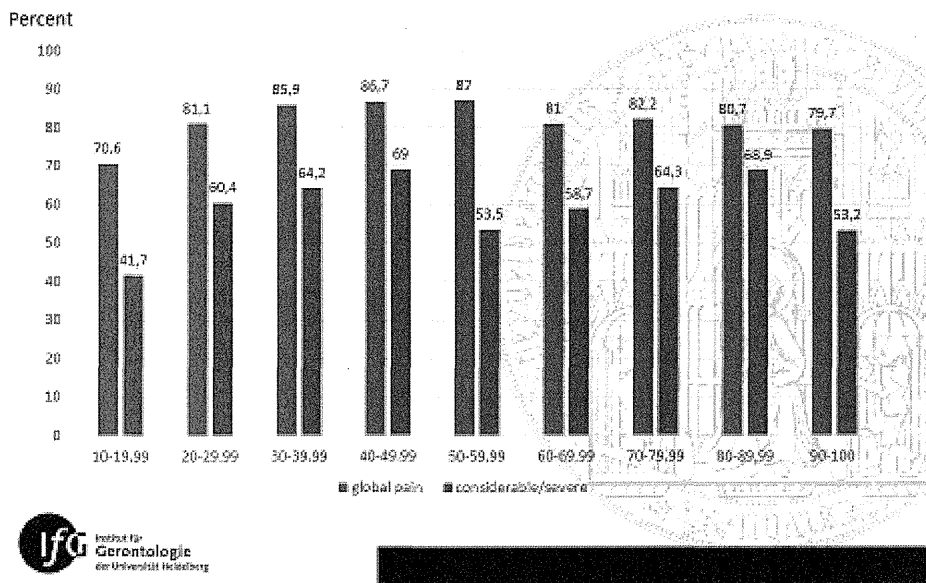


UNIVERSITÄT
HEIDELBERG
Zukunft. Seit 1386.

Global pain and severe pain in %.
Institute of Gerontology 2015 (n=820)



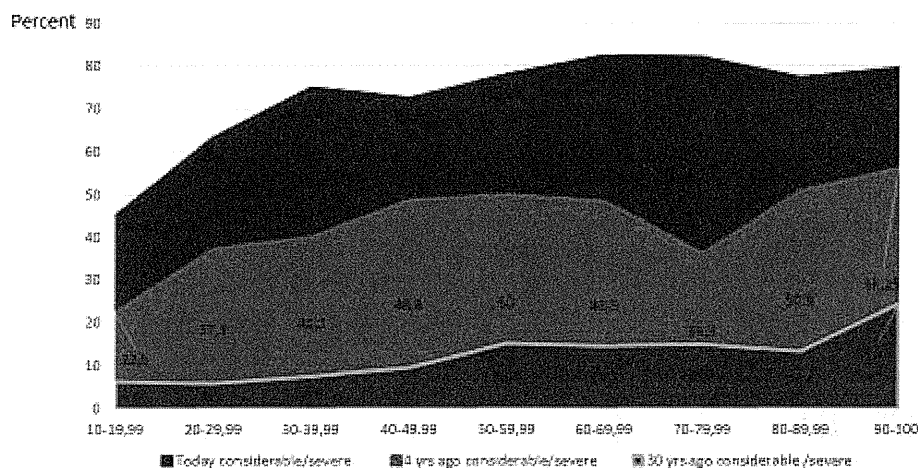
Participants with a low amount of 10 to 20 points reported to suffer from global pain in over 70 percent, they suffer from considerable or severe pain in 41 percent. Thalidomide affected people with 30 or more damage points show a mean percentage of participants suffering from global pain of 83 percent and participants suffering from considerable or severe pain show a mean proportion of 61,5 percent.

This highly heterogeneous sample shows increasingly a tendency towards homogenization concerning discomfort, loss of mobility and functionality, physical resilience and pain.

Similar findings were collected in impairment of physical resilience or fatigability. This severe symptom is due to pain, to arthrosis and to weakness of skeletal muscles. Muscular weakness causes pain as consequence of a higher tonus of muscles, a hardening of muscles and shaking. The results show that this process is increasing since 30 years and through the last 5 to 10 years this process accelerated rapidly. The data confirm that the more areas were damaged, the higher was the degree of weakness.

UNIVERSITÄT
HEIDELBERG
Zukunft. Seit 1386.

Impairment of physical resilience over 30 years in %.
Institute of Gerontology 2015 (n=832)



ifg
Institut für
Gerontologie
der Universität Heidelberg

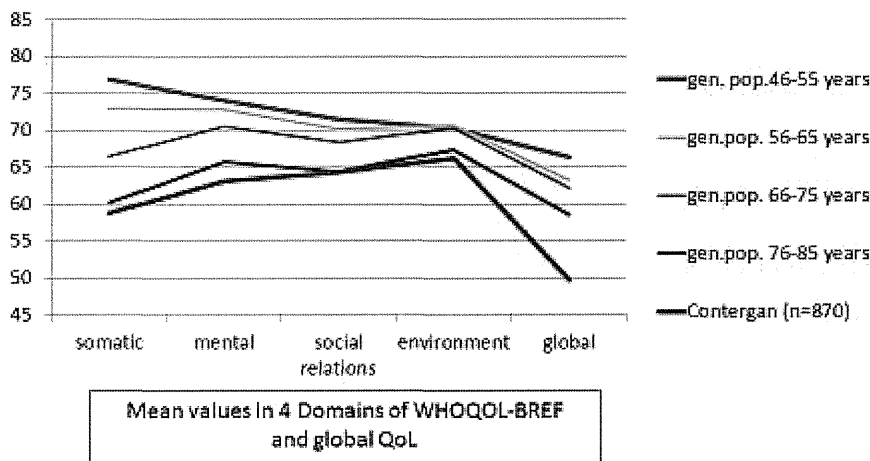
This progressive loss of physical resilience results in a decrease of daily activities, an increase of need of assistance and the participation in all kind of social activities is at risk. Participants need more rest and for a longer interval than years ago. They say that 20 years ago they were able to work e.g. in the garden for three, four, five hours and needed for recovering maybe one hour or less. At present they work one hour and need up to a 24 hour's rest to feel well again.

This process is developing through a period of 30 years. An accelerated increase is found through the last 4 years and in all damage groups. Participants with 60 to 70 damage points show an impairment of physical resilience of 14,7 percent 30 years ago, 4 years ago there were 48,5 percent and at present there are 82,5 percent.

It is impressing to witness how people affected by Thalidomide are rapidly aging and how they are losing their functionality, too. There is a decrease of autonomy in daily activities which requires an increasing need of assistance. The participation in all kind of social activities is actually at risk and on a long run maybe it will endanger affected people.

With so many different damages and disorders it is not easy to live, and even being a very brave population, quality of life is affected, too, as can be seen in the following figure.

Quality of Life in Thalidomide victims compared to the general population in Germany. German Contergan Study 2012



The mean values of four different domains of QoL as well as the global QoL are compared in thalidomiders and the general population in different age groups. The QoL of thalidomiders is worse than the QoL of the general population age 75 to 85 years. Both men and women in the sample have a distinctly higher percentage of depressive disorders compared with the general population in the correspondent age group. In the interviews about a third of the participants that showed depressive symptoms.

The need of treatment of depressive disorders, especially the treatment of trauma is very high in this population, as they find themselves in a state of crisis. They lived their life adapted successfully to their physical situation. Since about 5 to 10 years the development is reversed, they are losing skills and mobility, they never know when and in which amount they may lose physical faculties, whether they will be able to compensate the loss or not. They leave their jobs as they are not anymore able to attend their regular work. It is a very severe burden, they feel they cannot rely on themselves, they do not know what will happen next, where they will be next year. The more areas of the body are affected, the higher the risk of a depressive decompensation.

It is not only the physical situation that influences the mood, there are everyday problems that influence the mood, too, as e.g. the personal assistance. It is a very vital matter with a considerable impact on mental health. It is not easy to live with so many different damages and discomfort and even being very a brave population, as they are, quality of life is affected.

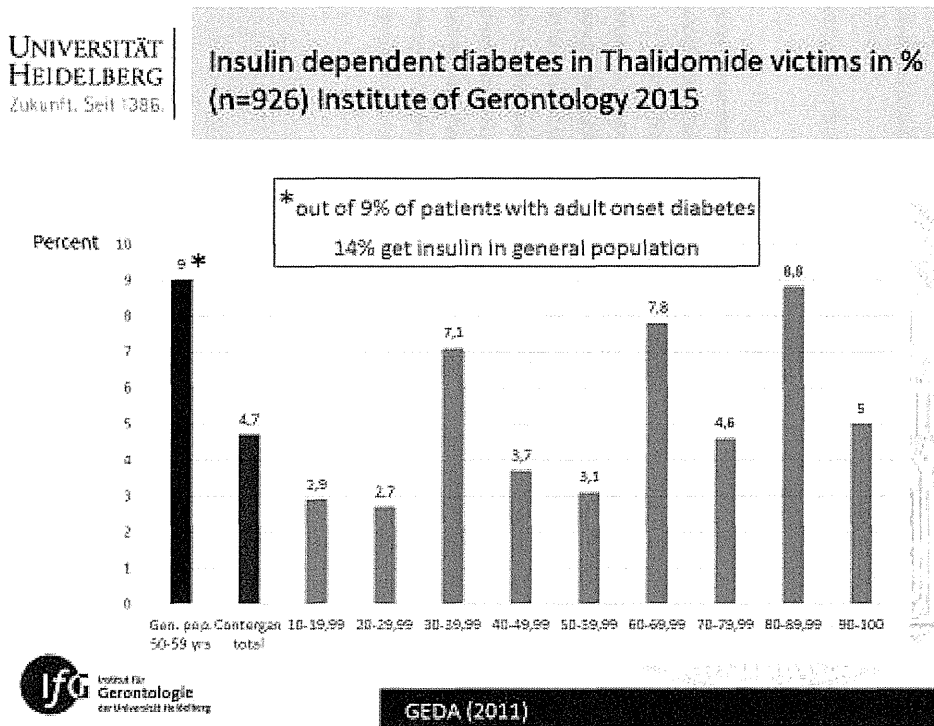
What kind of damage may be found in internal organs?

Thalidomide is a well-known inhibitor of angiogenesis and on this background most damages can be explained. The percentage of damages in internal organs increased up to today by almost 25 percent. The capability of compensation is decreasing, the damage turns up and people feel discomfort.

In the sixties everybody was impressed by the visible orthopedic malformations, therefore internal damages were often overseen and only very severe internal dysfunctions detected. At present there are

better diagnostic methods than 50 years ago, the representation of small vessels, bile ducts, or of the nerve system is feasible.

The next figure shows data from the survey of 2015 concerning the prevalence of insulin-dependent diabetes mellitus, 43 participants were identified. The following samples are described: the general German population of the thalidomide's age group, the whole sample of participants in the survey of 2015 and the 43 participants suffering from insulin-dependent diabetes mellitus in relation to the amount of damage points. Most of them were highly affected and had a high amount of damage points.

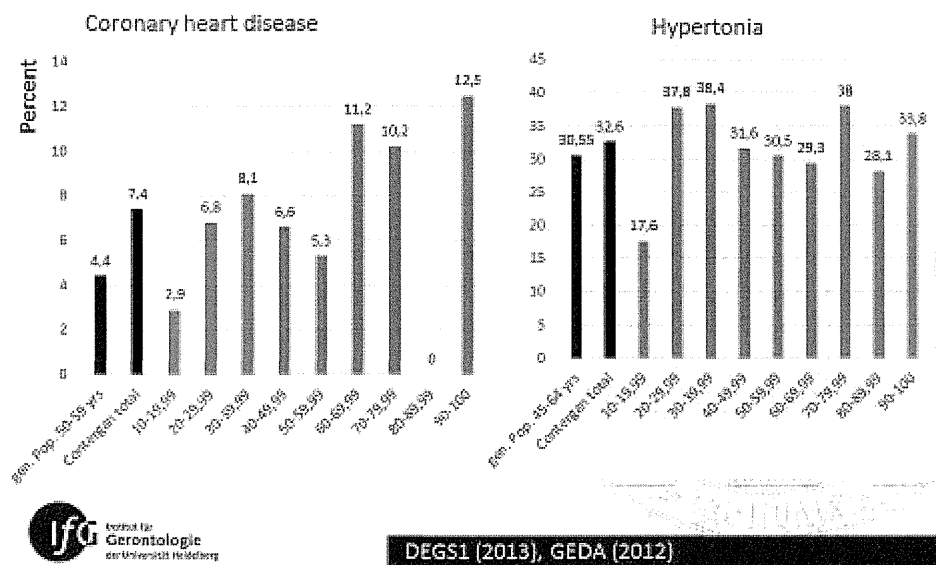


The statistics of the survey of the Robert Koch Institute GEDA (Gesundheit in Deutschland aktuell) record in the general population age 50 to 59 years 9 percent of individuals suffering from diabetes mellitus with adult onset. Out of these 9 percent a fraction of 14 percent are insulin-dependent patients, that corresponds to about 1 percent of the general population suffering from late onset and insulin dependent diabetes mellitus.

In the total sample of the thalidomiders there were 4,7 percent, the fourfold amount. The participants with 80 to 90 damage points show the highest amount of insulin-dependent participants with 8,8 percent. The cause is unknown, there might be damages in the pancreas caused by prenatal reduced blood flow on account of Thalidomide intoxication. The participants were able to compensate as long as they had resources, getting older the resources diminished and decompensation occurred.

Two participants stated to have diabetes mellitus type 1, one of them started taking insulin with 3 years, the other with 50 years. The rest of the participants suffer from a late onset diabetes mellitus, all of them starting insulin after the age of 36 years, most of them after 48 years.

Coronary heart disease and arterial hypertension are found to have a higher representation in the population of thalidomide affected people.

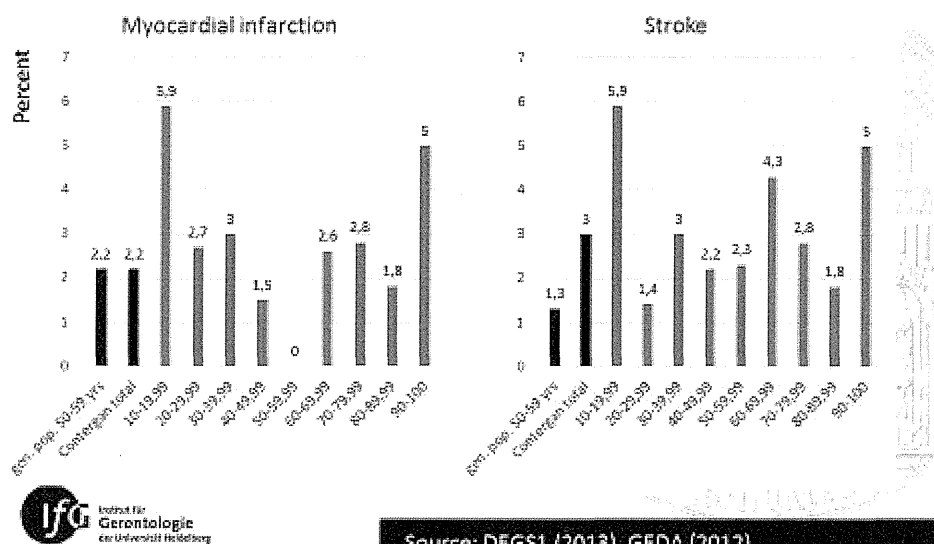
Coronary heart disease and hypertonia in Thalidomide victims in % (n=926) Institute of Gerontology 2015


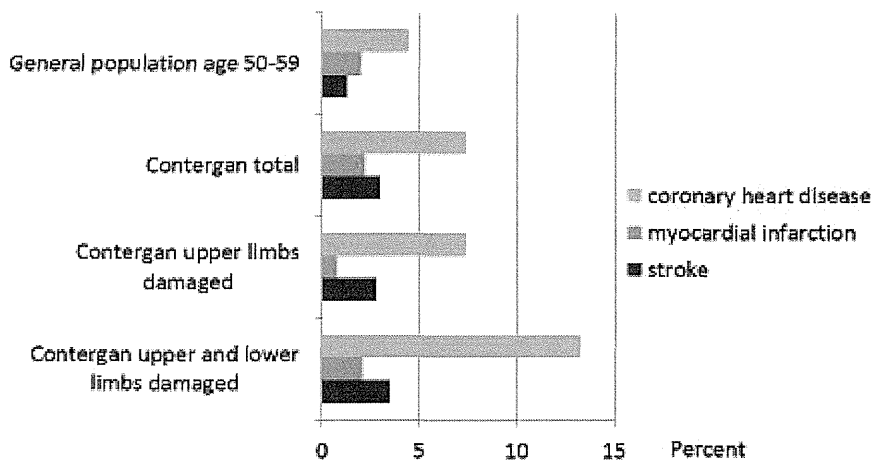
In the general population age 50 to 59 years we find coronary heart disease in 4,4 percent. In the survey of 2015 the sample shows in 7,4 percent coronary heart disease. In participants with a high amount of damage points there are documented up to 12,5 percent, which represents a three- to fourfold ratio of coronary heart disease in this population compared with the general population.

In the general population age 45 to 64 years the prevalence of hypertonia is about 30 percent. In the sample or 2015 we found a mean value of 32,5 percent. The pattern of distribution of participants with high blood pressure concerning their damage points is different from coronary heart disease. This may be due to difficulties in measuring blood pressure in this population. The usual measuring methods often are not applicable in patients with severe malformations. To prevent coronary heart disease, strokes and myocardial infarctions it is an urgent need to develop measuring methods for this endangered patients.

Myocardial infarction and stroke endanger thalidomiders severely. The general population age 50 to 59 years and the total Thalidomide sample seem to have identical numbers concerning the prevalence of myocardial infarction, but show an almost threefold prevalence of stroke. In both diagnosis the risk seems to be high for all participants independently of the amount of physical damage.

Myocardial infarction and stroke in Thalidomide victims in % (n=926) Institute of Gerontology 2015



Cardiovascular diseases in %. (N=921)
Institute of Gerontology 2015

The amount of participants suffering from coronary heart disease is considerably higher in the participants (Thalidomiders total 7,4 percent) than in the general population age 50 to 59 years (4,4 percent). Participants with damage in upper and lower limbs show the highest risk with 13,3 percent. The frequency of myocardial infarction is almost the same in both populations, as we saw already, participants with upper limb damage show myocardial infarction in 0,8 percent, with upper and lower limb damage in 2,1 percent. Stroke is found to occur in Thalidomide affected people almost three times more often than in the general population. Participants with damage in both upper and lower limbs are affected in up to 3,5 percent, participants with only upper limb damage in 2,8 percent.

The Thalidomide affected population, especially the persons with damage in both upper and lower limbs, are severely endangered by coronary heart disease and by stroke, coronary heart disease being a high risk for myocardial infarction.

Unfortunately the causes of death of this relatively young population are not known, therefore the share of diseases of the cardiovascular system as cause of death is unknown, but due to statements of participants there is good reason to believe that they are an important cause of death. This situation makes it urgent to explore the background of these findings, to learn the possible causes of this risky situation, to study the vessels, their course, their buildup and structure all over the body to find out where the risks are and to manage either prevention or therapy.

The following figure identifies prenatal damage in the cardiovascular system and possible health effects.

Internal organs: prenatal damage of cardiovascular system and health effects

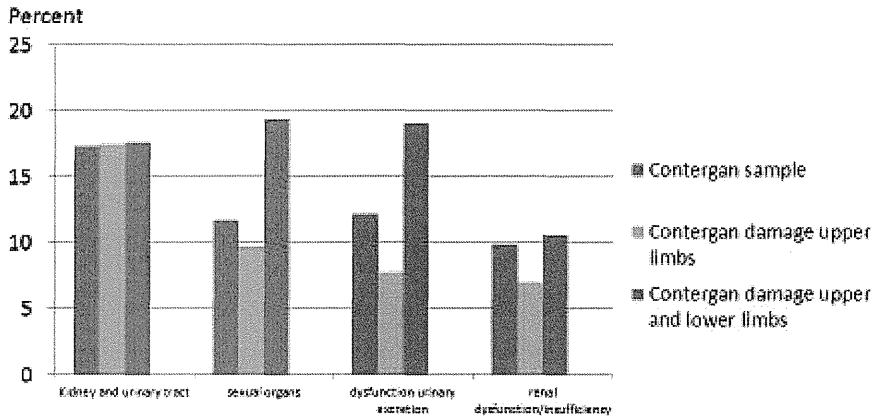
Organs	Prenatal damage	Possible health effects
Heart	Dysplasia/malformation	<ul style="list-style-type: none"> • Cardial Insufficiency • Cardiopathy
Blood vessels	<ul style="list-style-type: none"> • Weakness of vascular wall (Hypoplasia of muscularis) • Reduced vascularisation, reduced diameter of vessels • Atypical course of vessels • Truncation of vessels • Missing vessels 	<ul style="list-style-type: none"> • Myocardial infarction • Stroke • Reduced blood supply e.g. cold hands and feet, pain • Dysfunction of lymphatic and venous system • Dysplasia of intrahepatic ducts?

Thalidomide is well known as a substance with the property to impair the growth of blood vessels. The period of life with the fastest growth is the prenatal period. There is a solid scientific basis to verify it. There is strong evidence that Thalidomide causes the pathological changes in vessels that can be seen nowadays due to improved diagnostic methods. Impaired vessels impair the development and function of internal organs and the musculoskeletal system.

Concerning malformations and damages of the urinary tract, the participants with damage in both upper and lower limbs are the more affected group as seen before, too.

UNIVERSITÄT
HEIDELBERG
Zukunft. Seit 1386.

**Internal organs:
prenatal damage of the urogenital system in %.**
(n=870) German Contergan Study 2012



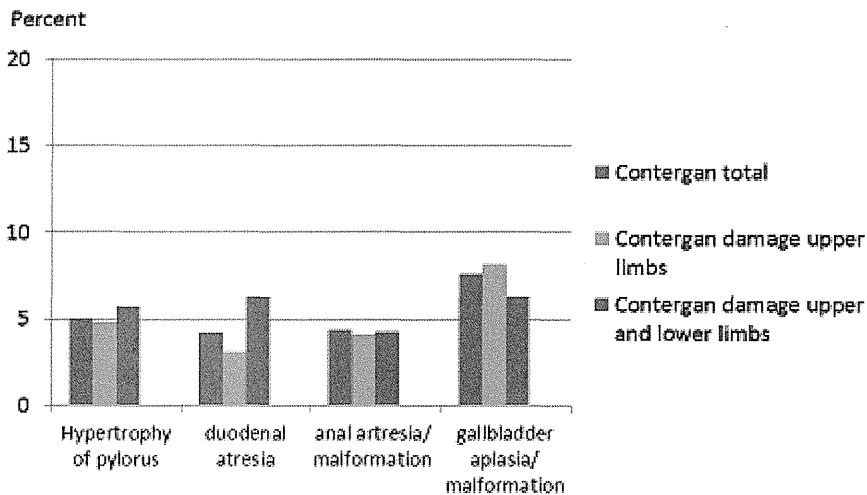
ifg Institut für Gerontologie der Universität Heidelberg

About 17 percent of the sample of 2012 show a prenatal malformation of the kidneys and/or urinary tract. About 10 percent suffer from renal dysfunction or insufficiency. Participants with damage in both upper and lower limbs develop as twice as often malformations of sexual organs and a dysfunction of the urinary excretion in 19 percent. The malformation, dysplasia or aplasia of sexual organs, the missing descensus testis cause childlessness. In about 12 % of the total sample the participants stated to be childless, childlessness being one of the most serious and straining outcomes of the thalidomide damage.

Concerning the gastrointestinal tract there are affected about 5 to 6 percent of the participants.

UNIVERSITÄT
HEIDELBERG
Zukunft. Seit 1386.

**Internal organs:
prenatal damage of the gastrointestinal tract in %.**
(n=870) German Contergan Study 2012



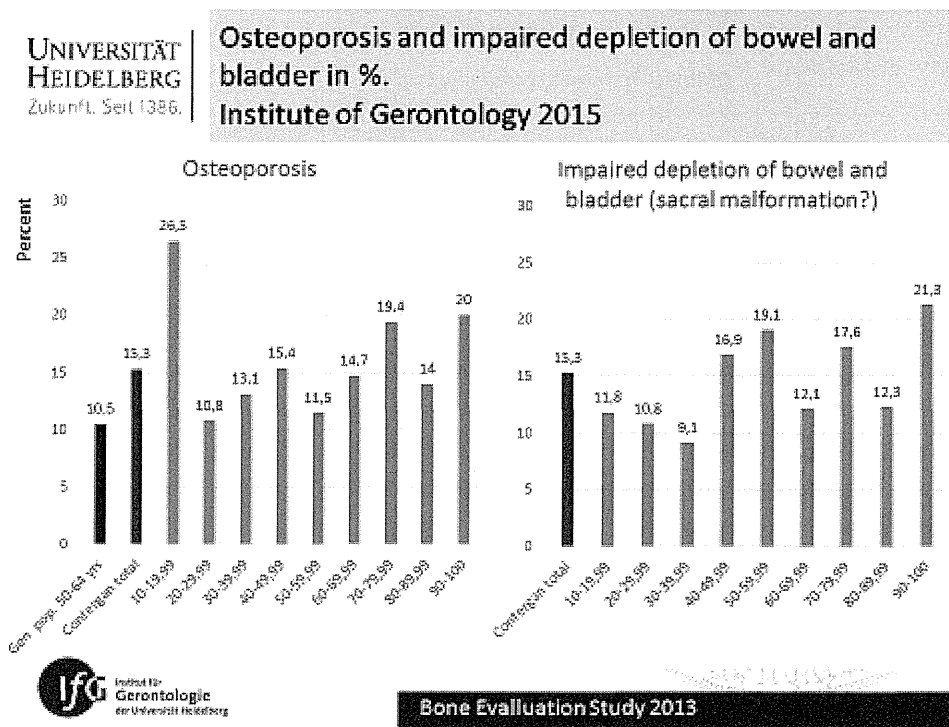
ifg Institut für Gerontologie der Universität Heidelberg

The most frequent prenatal damage is the gall bladder aplasia or malformation. There are hypertrophy of the pylorus, duodenal or anal atresia or malformation, too. Some participants report problems during colonoscopy that may give a hint to atresia in the colon.

In the following picture there are two important issues, the osteoporosis and the impaired function of the bladder and bowel.

There are more participants suffering from osteoporosis than in the general population, as is to be expected. Thalidomide affected people show functional impairment and reduced mobility, too. The most important stimulus for the buildup of the bones is missing.

In the course of the interviews questions about different body functions were asked and participants described an impaired depletion of bowel and/or bladder, problems existing since early childhood. The participants referred quite often to additional malformation of the pelvis and sacral bone. There may be a damage of the vegetative nerve system that supplies the bladder and the rectum caused by dysplasia of the pelvis.



Following the data of the survey of 2015 there are 15 percent participants suffering from osteoporosis, in the general population age 50 to 64 years there are 10,5 percent. The high amount of 26,5 percent of participants with 10 to 20 damage points is a striking result and gives a hint that there are other additional causes of osteoporosis in thalidomidiers than poor mobility and poor physical strain.


The impaired depletion of bowel and/or bladder shows up in 15 percent of participants. The data from the Foundation record prenatal dysplasia or malformation of pelvis in 10 to 12 percent. A possible connection between the malfunction since childhood and the prenatal malformation should be investigated.

The last figure describes the prenatal damages of internal organs and potential health effects in Thalidomide affected people.

UNIVERSITÄT HEIDELBERG

Internal organs: health effects of prenatal damage

Organs	Prenatal damage	Possible health effects
Kidney	Malformation and/or dysfunction. E.g. Aplasia, Dysplasia, polycystic kidney, pelvic kidney	Kidney stones, renal insufficiency as a result of <ul style="list-style-type: none"> ▪ Malformation ▪ Too little fluid intake
Gastrointestinal tract	<ul style="list-style-type: none"> ▪ Hypertrophy pylorus ▪ Aplasia of gallbladder ▪ Duodenal, anal atresia ▪ Malformation of pelvis and lower spine 	<ul style="list-style-type: none"> ▪ Indigestion ▪ Risk of incontinence after operative treatment ▪ Partial paralysis of bladder and/or intestine ▪ Dysfunctional sexual life
Sexual organs	Aplasia or malformation of sexual organs	<ul style="list-style-type: none"> ▪ Operative removal ▪ Sexual dysfunction ▪ Childlessness ▪ Serious psychological burden
Endocrine glands	Malformation or dysfunction of glands	Reduced hormonal production


 Institut für Gerontologie der Universität Heidelberg

What do we learn out of those results?

1st: Thalidomide victims are an endangered population.

2nd: Health care professionals should know more about possible pathologies due to Thalidomide to be able to provide a better health care and to minimize risks of all kinds. In addition Thalidomide affected people need a low-threshold and easily accessible psychological and psychotherapeutic support.

3rd: Society – all of us - we should appreciate their lifelong achievements, their creativity in developing strategies to adjust to all requirements, their humor.

All activities they are performing need more energy, more strength, more time and more fantasy e.g. to develop devices and strategies to maintain autonomy. More and more they need a higher amount of assistance.

We are bound to improve their situation by all means.

Thank you for your attention.

Hinoshita : Thank you very much, Dr. Ding-Greiner. One more additional comment to tell you. Last year, we visited her office at the Institute of Gerontology, University of Heidelberg when she warmly accepted us, Professor Kayamori and Dr. Shiga and me. Thank you very much for it. Someone has a question. Dr. Schulte-Hillen, please.

Schulte-Hillen : Thank you very much. Thank you very much for this fantastic presentation. I would like to know I found very frightening aspect that apparently diabetes and cardiovascular diseases seems to have higher prevalence in a premed group than in others. And can you say something, can you

comment on the fact that on the idea proves this is secondary to low activity life style, like I mean somebody without legs how should he make sports?

Ding-Greiner : If you get late onset diabetes you may say it's caused by life style. But I think it's different in the case of an insulin-dependent diabetes. There may be a prenatal damage in the pancreas caused by Thalidomide. We got a lot of statements from thalidomiders suffering from damage in different organs. Diagnostic by MRTs show often unusual findings. Maybe they have a damage in the pancreas, difficult to explain in the general population but comprehensible knowing that Thalidomide intoxication is the cause. We asked for insulin-dependent diabetes because it is different from the normal late onset diabetes. Clinicians should work on it, should find the underlying cause. I only have the numbers, out of the results of what people told me. But I'm sure this data are reliable, Thalidomide affected people are not lying, they do not say they have diabetes when they don't. In clinical observation and studies there will be found out more.

The other problem you mentioned is coronary heart disease. It was interesting, when participants told me they had myocardial infarction or a stroke, I asked whether doctors looked at their vessels and what they did find. Did they find advanced arteriosclerosis? Mostly they said, no, the doctor said they have very fine arteries. This is strange to me, therefore I suppose that there are other prenatal damages in the arteries. The vessels may be thinner in diameter, the walls thinner as in general population and thus they may break easier. A participant told me that she suffered from a couple of strokes. The vessels in the neck were found to be altered and very thin in diameter, so she got a stent and since then she feels better. Thus I think it is very important to look at the vessels and maybe we will find the cause of all kinds of disorders. If physicians know about that and start looking about it, it will be possible to prevent stroke. Thalidomiders are very, very at risk concerning stroke and it is a terrible thing to have a stroke in addition to thalidomide damages.

Schulte-Hillen : Thank you very much.

Ding-Greiner : You are welcome.

Hinoshita : Dr. Ding-Greiner, as for diabetes mellitus do you think diabetes was caused by the original congenital defect of the pancreas in thalidomiders?

Ding-Greiner : Thalidomiders run in principle the same risk to get diabetes as the general population, but not everybody is insulin-dependent. It takes a couple of years until people get insulin-dependent. Thalidomiders are quite young to suffer from insulin-dependent diabetes. Maybe there are prenatal damages in the pancreas, a destruction of tissue that causes the deficiency.

Hinoshita : So we need some body image like CT?

Ding-Greiner : Yes.

Hinoshita : And also it's necessary to measure insulin...

Ding-Greiner : Yes, exactly.

Hinoshita : Taking blood, you know.

Ding-Greiner : Yes. And I hope these data will inspire you to look for this kind of problems.

Hinoshita : Any other question? Nobody? Thank you very much, Dr. Ding-Greiner.

⑤**Dr. Shadi-Afarin Ghassemi**

“Long-term follow-up of thalidomide embryopathy in Sweden. Osteoarthritis in lower extremities, function in upper extremities, function in upper extremities and the new data on cervical spine.”

Hinoshita : Then go ahead to the next presentation. The title is “Long-term follow-up of thalidomide embryopathy in Sweden: Osteoarthritis in the lower extremities, function on the upper extremities and new data on cervical spine” presented by Dr. Shadi-Afarin Ghassemi. She is a member of medical faculty, Gothenburg University from 1992 to 1998. She is now Ph.D. student in orthopaedics research at the Sahlgrenska Academy at the University of Gothenburg since 2006. And she has been a professional orthopedist in Kungälv Hospital in 2006, and ongoing. Then Dr. Ghassemi, please.

Ghassemi : Thank you very much. Thank you very much for having me today. Let me congratulate you all in Japan for Dr. Omura’s Nobel Prize this year in medicine. It’s actually very wonderful. Let me talk to you long-term follow-up of thalidomide embryopathy in Sweden, osteoarthritis in the lower extremities, functioning on the upper extremities and new data on cervical spine.

THE SAHLGRENKA ACADEMY
INSTITUTE FOR CLINICAL SCIENCES
DEPARTMENT OF ORTHOPAEDIC

Long-term follow-up of thalidomide embryopathy in Sweden. Osteoarthritis in lower extremities, function in upper extremities and new data on cervical spine.

Shadi Afarin Ghassemi Jahani MD
Tokyo, Japan
Nov 21, 2015

2016-06-17 1

THE SAHLGRENKA ACADEMY
INSTITUTE FOR CLINICAL SCIENCES
DEPARTMENT OF ORTHOPAEDIC

Co-authors

- Aina Danielsson, MD, PhD, Assoc. Prof.
- Jon Karlsson, MD, PhD, Prof.
- Helena Brisby, MD, PhD, Prof.

2016-06-17 3

My co-authors are associated Professor Aina Danielsson, Professor Jon Karlsson, and Professor Helena Brisby. Thalidomide was used as a sedative drug for pregnant ladies in delayed 1950s and early 1960s in Sweden. It was soon proved to be a very high potent teratogenic substance and led to thalidomide embryopathy. It happened in Sweden as in the rest of the world except USA because Mrs. Kelsey did a wonderful job against thalidomide in US. Hundreds of children with thalidomide embryopathy were born. Many of them died at the birth. And the survivors are of thalidomide embryopathy over 50 years old. At the time of our study, they were 108 individuals registered at the thalidomide association of Sweden with thalidomide embryopathy. It’s called Föreningen för de Neurosedynskadade. We did the

Introduction:

Thalidomide was used as a sedative drug for pregnant women in the late 1950s and early 1960s in Sweden.

It proved to be a high potent teratogenic substances in medical history, leading to Thalidomide Embryopathy (TE).

In Sweden as in the rest of the world, except USA, hundreds of children with TE were born. Many of them died at birth. The survivors of TE are now over 50 years old.

At the time of our study there were 108 individuals registered in The Swedish Association of Individuals with Thalidomide Embryopathy. "Föreningen för de neurosedynskadade, FFdN."

2016-06-17 5

Study I

Long-term follow-up of TE; malformations and development of osteoarthritis in lower extremities and evaluation of upper extremities function.

Ghassemi Jahani SA *et al.*, J Child Orthop. 2014; 8(5):423-33

2016-06-17 7

first study which was published last year on long-term follow-up of thalidomide embryopathy malformations and development of osteoarthritis in the lower extremities and evaluation of lower extremities function. The aim of the study was to study malformation and the lower extremities, to study osteoarthritis in the hips and the knees and clinical impact of them. And to see if the malformation of the upper all our extremities affected function as we could measure by evaluated disease-specific outcome questionnaires. 108 members of the thalidomide association in Sweden. They have very strict rules in this association. So all contacts goes actually through the association. And 24 had rejected all contact to any study whatsoever. So 84 will invite of those 33 did not answer at all, and 18 did not accept it, and 33 subjects accepted to participate in the study. Also because of the same strict rules we were not allowed to send any reminder to this group that didn't answer. We had exclude one because of the stroke, also another one severe mental problem. So we examined 31 participants, the mean age were 46 years old, 13 female and 18 male. Participants came from all part of Sweden except three. Two were living in Norway at the

Aims

- To study malformations of the lower extremities.
- To study osteoarthritis (OA) in the hips and knees and the clinical impact.
- Did malformation of the upper or lower extremities affect the function as measured by validated disease-specific outcome questionnaires?

2016-06-17 6


Material and Methods

```

graph TD
    A[All members 108] --> B[Invited 84]
    A --> C[Rejected 24]
    B --> D[Not accepted 18]
    B --> E[33 subjects accepted]
    B --> F[Did not answer 33]
    E --> G[31 participants]
    E --> H[Excluded Severe mental problem]
    E --> I[Excluded Stroke]
  
```

2016-06-17 11

time, and one is living in USA but he was visiting his home country. The study was multidisciplinary and in addition to the orthopedic part, we had ophthalmology, neuropsychology and radiology and then otolaryngology and speech pathology. All participants were examined by me and including full clinical examination and the measurement of range of motion of the large joints. All participants were also examined by the spiral computed tomography on the lower extremities including the pelvic, and the examination was in spine position, so we didn't have any way bearing on the lower joints. CT scan was used to describe the malforma-



THE SAHLORENSKA ACADEMY
STUDY I

Computer tomography

All participants were also examined by Spiral Computed Tomography (CT) of the lower extremities including the pelvic, in supine position. The CT scans used for description of malformations.

For classification of OA the following scale was used:


- Grade "0", no signs of OA
- Grade "1", mild signs of OA with reduced cartilage height and/or a few osteophytes
- Grade "2", severe signs of OA with osteophytes and cysts.

For occurrence of OA:

The hip joint evaluated as one complete joint

The knee joint evaluated in three parts, medial, lateral and patello-femoral parts.

2016-06-17
15



THE SAHLORENSKA ACADEMY
STUDY I

Patients


Thirty-one participants, including 13 females and 18 males with a mean age of 45.8 (SD 1.1) years were examined.

The participants came from all parts of Sweden, except 3; two who lived in Norway and one in USA.

The study was multidisciplinary, and included in addition to the orthopaedic part, ophthalmology, neuropsychology, radiology, dentistry, otolaryngology and speech pathology.

All participants were examined by one orthopaedic surgeon (SG), including a full clinical examination and measurement of range of motion (ROM) of the large joints.

2016-06-17
13




THE SAHLORENSKA ACADEMY
STUDY I

Outcome Questionnaires

- Validated questionnaires were used for evaluation of:
 - Upper limb function: DASH: Disability in Arm Shoulder and Hand. (Atroshi 2001)
 - Lower limb function: RAOS: Rheumatoid Arthritis Outcome Score. (Bellamy 1988)
- Questions on previous treatment and surgical procedures

2016-06-17
17

tions. Because of not having weight-bearing, we had to follow a special scale. So grade 0 was no signs of osteoarthritis, grade 1 was mild signs of osteoarthritis with reduced cartilage height and or a few osteophytes. And grade 2 was severe sign of osteoarthritis (??@00:57:23). And for evaluation of the hip joint, we had a hip joint as a complete joint and the knee was divided in three parts. Lateral, femur and patellofemoral parts. All outcome questionnaires used are evaluated questionnaires for upper limb function disability dash all shoulder and hand. And lower limb function, RAOS: Rheumatoid and Arthritis Outcome Score. Also questions on previous treatment and surgical procedures were asked. We found as a result, 15 individuals had other diseases, such as asthma, hypertension, sleep apnea and migraine. And allergy was not considered any disease. Malformation of the upper limbs and I hope you can see. Anyway, number of extremities up on the top. I need exact number of individuals. 8 percent of shoulder malformation. 26 percent of elbow and 4 percent of malformation. And almost 70 percent had a malformation on the hands. And the lower one is the number of individuals. 27 had two functional full arm, not full arm, so the functional hand was considered



THE SAHLORENSKA ACADEMY
STUDY I

Results

Other conditions

Fifteen individuals had other diseases such as asthma, hypertension, sleep apnoea syndrome and migraine.

2016-06-17
19

THE SAHLORENSKA ACADEMY STUDY I

Malformations of the upper limb

Location of malformation	No of extremities (%)
Shoulder	5 (8.1)
Elbow/forearm	16 (25.8)
Hand	43 (69.4)

Number of fully functional arms/hands (=palm with ≥ 2 fingers with a grip function)	No of individuals (%)
2	27 (87.1)
1	2 (6.5)
0	2 (6.5)

2016-06-17 21

THE SAHLORENSKA ACADEMY STUDY I

Malformations of the lower limb

Five individuals (16 %) had Proximal Focal Femoral Deficiency, PFFD:

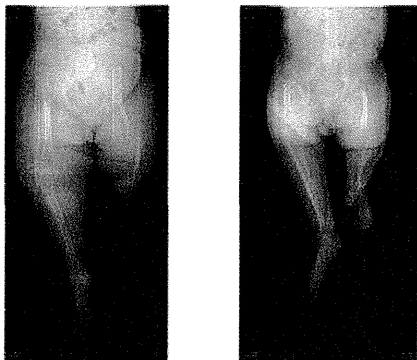
- 2 using wheel chair constantly
- 1 using wheel chair occasionally
- 2 walking with prostheses

2016-06-17 22

more than two fingers with grip functional small palm. So it's not shortening of the arms or also other malformations just the function. Two had no functional arms and hands. And two had only one side. Malformation of the lower limbs, we found five individuals proximal focal femoral deficiency. Two were using wheelchair constantly, and one was using it only occasionally, and two were walking (00:59:36). These are the two going walking (00:59:40) at one side. The remaining 26 individuals had also some kind of odd malformations. Sixty-five percent had some

THE SAHLORENSKA ACADEMY STUDY I

Two patients with PFFD



2016-06-17 25

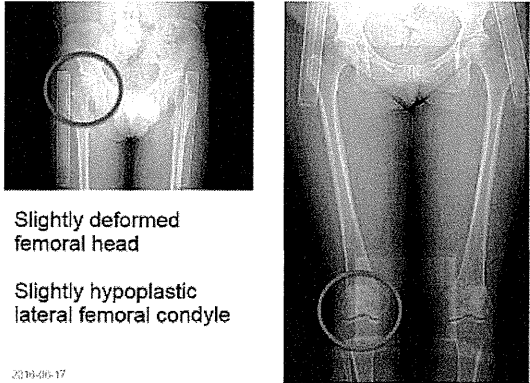
THE SAHLORENSKA ACADEMY STUDY I

Lower limbs of remaining 26 individuals

- All individuals had some kind of other malformations.
- 65% of the hips showed some deformity of the femoral head.
- 50% of the knees: hypoplastic lateral femoral condyle and hypoplastic intercondylar notch.
- All were independent walkers

2016-06-17 27

THE SAHLORENSKA ACADEMY STUDY I



Slightly deformed femoral head

Slightly hypoplastic lateral femoral condyle

2016-06-17 28

deformity of the femoral head. And 50 percent of the knees had hypoplastic lateral, femur condyle and also patellofemoral intercondylar notch which is associated with undeveloped or lack of anterior cruciate ligament. All will independent (01:00:14). And as you can see this is likely deformity of the femoral head, there is a picture. (00:00:24) doesn't cover. And this is the lateral, femur condyle, hypoplastic lateral, femur condyle. These two what you can see is to draw the arms using for doing CT in superimposition. Lower extremity function, we could compare the group it 26, we don't any P50 and 5 we P50 and they had significantly lower score for activity of daily life also sport and recreation was quite

UNIVERSITY OF GÖTHEBURG THE BAHLORENSKA ACADEMY STUDY 1

RAOS: lower extremity function

	N	All	Occurrence of PFFD *		p-value
			No n=26	Yes n=5	
Pain	31	79 (21)	80 (20)	68 (24)	n.s. (p=0.31)
Symptoms	31	79 (18)	80 (18)	70 (17)	n.s. (p=0.26)
ADL †	30 ‡	83 (20)	87 (17)	56 (13) ‡	p=0.0076
Sport & Recreation	31	62 (36)	72 (30)	9 (10)	p=0.0007
Quality of Life	31	66 (26)	71 (25)	40 (17)	p=0.016

ADL score significantly lower for those with OA (79) compared with those without OA (94) in any of the hip joints (p=0.036).

2016-06-17 31

UNIVERSITY OF GÖTHEBURG THE BAHLORENSKA ACADEMY STUDY 1

DASH: upper extremity function

- Patients with severe deformities, i.e. more than one limb with major malformation (n=15), had significantly lower DASH-scores than those with no extremities with major malformations (n=16). (25.5 vs. 14.3, p=0.0015).
- Existence/non existence of pincer grasp, did not affect the overall function of the upper limbs.

2016-06-17 33

low and quality of life. Activity daily life also was quite low for those with osteoarthritis at one side comparing those we don't osteoarthritis also significantly statistically significant. Upper extremity function was measured by DASH. We could also see severe deformities those with at least one limb with major deformity and we are not considering hand anomalies. If you not considering finger anomalies but major deformities at least one limb had significantly lower DASH score than the others with not major deformities on any limb. Existence or nonexistence of the pincer grasp was not affected in this function measurement. As also as a result we found sign of osteoarthritis in 40 percent of the hips and 60 percent of the knees, and this is also despite of the low sensibility of CT for diagnosis of osteoarthritis comparing with healthy Swedish population at the same with age is only 2 percent. So it's quite high. A great variety of malformation on the lower extremities were found. Five individuals P50 with severe malformation of the lower limbs and also have malformation of upper limbs. They had significantly reduced function of the lower limbs. And it affected the activity daily life, sports recreation and also quality of life.

Most individuals with all P50 and also some kind of minor deformity in the lower extremities. We could see by CT scans. But the walking ability was not affected. So upper extremity function was significantly lower in those with major deformity in at least one limb. And DASH doesn't cover the fine motor skills. That's why we didn't consider the pincer grasp actually. The difference was in this part will be low the clinical relevance. So the sign of osteoarthritis was quite high, 40 percent of the hips and 60 percent of the knees comparing with the general Swedish population. I'm going to show a very short summary on study two which is submitted this article submitted. The general these change in the (#####@01:03:45) in the final

UNIVERSITY OF GÖTHEBURG THE BAHLORENSKA ACADEMY STUDY 1

Results OA

- Signs of OA were found in:
 - 40 % of hips
 - 60 % of knees
 despite the low sensibility of CT for diagnosis of OA

Healthy Swedish population: OA in 2%

2016-06-17 35

UNIVERSITY OF GÖTHEBURG THE BAHLORENSKA ACADEMY STUDY 1

Conclusion

- A wide variety of malformations of the extremities was found.
- Five individuals with PFFD (severe malformations in the lower limbs) also had malformations of the upper limbs, including the hands.
- They had significantly reduced function of their lower limbs, affecting ADL, sport/ recreation and QoL, compared with those without PFFD.

2016-06-17 37

THE SAHLORENSKA ACADEMY
STUDY I

Conclusion

- Most individuals without PFFD (n=26) had some kind of minor deformity in the lower limbs as visualized by CT scans.
- Ambulation was not affected, though.

2016-06-20 36

THE SAHLORENSKA ACADEMY
STUDY I

Conclusion

- Upper extremity function (i.e. total DASH score) significantly lower in those with major deformity in more than one limb
- BUT; this score does not evaluate fine motor skills
- The differences were below the level of clinical relevance

2016-06-20 41

THE SAHLORENSKA ACADEMY
STUDY I

Conclusion

Signs of OA were more frequent in TE patients (40% hips and 60% knees) compared with general Swedish population (2%)

2016-06-17 43

THE SAHLORENSKA ACADEMY
STUDY II

Study II

Degenerative changes in the cervical spine are more common in middle-aged patients with thalidomide embryopathy than in healthy individuals

Ghasseml Jahani SA et al., Submitted

more common in middle age patient with thalidomide embryopathy than in the healthy individuals. The aim of this study was to investigate presence of mal-formation and subsequent disease in this generation of the cervical spine in a group of middle age individual with thalidomide embryopathy and comparing

THE SAHLORENSKA ACADEMY
STUDY II

Aim

To investigate the presence of malformations and subsequent disc degeneration (DD) of the cervical spine in a group of middle-aged individuals with TE and to compare with a healthy group of controls.

2016-06-17 47

THE SAHLORENSKA ACADEMY
STUDY II

Material and methods: Patients

```

graph TD
    A[Invited 31] --> B[27 performed MRI]
    A --> C[One had metal clips in the head]
    A --> D[Two had claustrophobia]
    A --> E[One rejected]
    B --- F[27 healthy controls, age- and sex-matched]
  
```

2016-06-17 48

to health group. All study group was 31 participants from the study one. One rejected MRI, two had claustrophobia, and one had (???) in operated in the head from 80s. So it was 23 remained and DP form and MRI. The result was compared with 27 healthy controls age and sex matched. In the group of the study, 56 percent had deformities up to 4 extremities. All had some kind of function of the upper

THE BAHLORENSKA ACADEMY
STUDY II

Results
Malformations

- 15 (56%) patients had deformities on 1-4 of the extremities.
- All had some function of the upper limbs, despite short arms in some individuals.
- 81% had some degree of hand anomalies
- 8 (30%) patients had a bilateral pincer grasp.

2016-06-17 51

THE BAHLORENSKA ACADEMY
STUDY II

Degenerative changes

- Disc degeneration (DD) on ≥ 1 level:
89% of the TE and 67% of CTR ($P < 0.001$)
- Segments with DD:
10 patients in TE had DD on ≥ 4 levels
None of controls group had DD on ≥ 3 levels ($P < 0.001$)
- In both groups majority of DD were located at C5-C6, C6-C7.
- Only TE group had DD of the upper segments.

2016-06-17 53

limbs. But still very short in some of the individuals. 81 percent had some degree if hand anomalies, but 30 percent had pincer grasp bilaterally. We found these degenerations in more than 1 level and 90 percent of group with TE comparing with 67 percent on the control statistically significant result. 10 patients with thalidomide embryopathy had up to 4 level and segment of this degeneration.

While in the control group, we didn't have anyone more than 3 levels, also statistically significant. In both groups majority of those degeneration were located at lower segment C5-C6, C6-C7. And only TE had in upper segments. These pathology and osteoarthritis were more often in TE than controls. Almost 90 percent in TE group has some affected for arm in comparing 44 percent in the controls. And the amount for affected for arm pair individuals TE group was also higher. So as in conclusion or finding support and earlier development of these degeneration in TE. Because

THE BAHLORENSKA ACADEMY
STUDY II

Degenerative changes

- Disc pathology and osteophytes occurred more often in TE than controls.
- 24 pat (89%) in the TE group had some affected foramina / (controls 44%)
- The amount of affected foramina per individuals was also higher in the TE group.

2016-06-17 55

THE BAHLORENSKA ACADEMY
STUDY II

Conclusion

- Our findings support an earlier development of DD in the TE group due to:
increased DD in the cervical spine
increased number of affected segments
- Most DD occur at the lower segments in TE, same as in norm or control group.
- If the presented results are due to the drug itself or only the unusual mechanical load on the cervical spine needs to be further studied.

2016-06-17 57

THE BAHLORENSKA ACADEMY
STUDY II



ありがとう
Thank
you



of increase of this degeneration is cervical spine also increase number of affected segments in TE. Most of this degeneration located in lower segments in both groups, both TE and same their control. And if these results are because of the drug itself or because of the unusual mechanical load on the neck and cervical spine. This is something to study more if you try hopefully. Thank you very much.

Hinoshita : Thank you very much, Dr. Ghassemi. She gave us a good insight into osteoarthritis and degenerative changes in the cervical spine. By the way, there are some orthopedists here from Japan and from Europe. They might have any other comment, any comment or question? Yes, Professor Kayamori.

Kayamori : Differential diagnosis this is aging process or this is particularly for thalidomide people. How to differentiate between aging and characteristic of thalidomide especially in the cervical spine? We can see the early sign of thalidomide, but aging process also we can see the same.

Ghassemi : Yes.

Kayamori : So any of the distinction between these two groups.

Ghassemi : Of course. It's also the aging process, of course. But comparing to the control at same age and sex, we also can see that thalidomiders have much higher prevalence and incidence of this degeneration. And I have to tell you that MRI done in this group is, I think, it is one of the actually first study read MRI, because ethically in Africa, he did just X-ray on the cervical spine because of the high load on the neck with the head bearing. But this is only X-ray, but MRI we use them, I don't know if you are familiar with the Pfirrmann classification tool to just see the disks and to see how early they actually changes and they get this degeneration. So comparing of course it is an ageing process but comparing to the controls we see differences. Thank you.

Hinoshita : Is there any other, OK. Dr. Beyer, please.

Beyer : Yeah, Rudolf Beyer from Germany. Is it possible to divide the control group in people who has lifelong hard body work like building workers. For example, find out whether it's you too overburden, overstress over the years?

Ghassemi : The control is actually was collected the whole control where collected from those MRI. We don't have any clinical problems with the, how do you say, with the sensibility or anything clinical referee. So it's picked of, picked thousand picked MRI but in other, because of other, how do you say, investigation or nothing. So they were not unusual on the load of their neck, they were not head bearing, they were, I mean this is done what on those they have whole spine MRI and we just took this cervical part.

Beyer : OK.

Ghassemi : So it's actually the very average people we don't have any problem, clinical problem. It's very, very relevant question.

Hinoshita : Anything else? Nobody has other question? OK? Thank you very much, Dr. Ghassemi.

Then according to the time table, next we will have some intermission. Now it's just 2:20 PM, then please take a rest during the intermission to 2:40. Then, close this discussion now. Let's come back here at 2:40.

(Intermission)