[Poster Session]

Internal Anomalies in Thalidomide Embryopathy: Common and Uncommon Findings on CT and MRI

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Background

- Thalidomide was developed as a sedative in 1957 in West Germany. Because of its teratogenic effects, thalidomide was withdrawn from the market in the early 1960s.
- It was reported that there were 3,900 patients with thalidomide embryopathy (TE) throughout the world.
- Immunomodulatory effects of thalidomide were discovered in the late 1980s and it has been used for the treatment of several diseases, including multiple myeloma and erythema nodosum.
- Schuler-Faccini L, et al. reported 3 new cases of TE in Brazil.
- It is not well-known that thalidomide causes not only limb deformities but also various internal anomalies (IAs).

Subjects and Methods

- In Japan, a total of 309 individuals were registered as a patient having TE for the national database.
- Among them, 22 individuals (9 men and 13 women: mean age, 49 years; range, 47-51 years) became involved in this study (Single Center Study of TE in Japan: SCSTJ); they underwent thorough medical examinations and image screening using CT and MRI to detect an IA in our institute.
- Whole body CT: 320-MDCT scanner (Aquilion ONE, Toshiba Medical Systems) and 128-dual-source MDCT scanners (SOMATOM Definition Flash, Siemens Healthcare) were used. For scanning parameters, slice thickness was as follows: body, 5 mm; neck, 1 mm; temporal bone, 0.5 mm. Sagittal and coronal reconstruction of the neck and temporal bone, and high resolution reconstruction of the temporal bone were routinely used.
- Head MRI: a 3T MRI scanner (MAGNETOM Verio, Siemens Healthcare) and two 1.5T MRI scanners (MAGNETOM Avanto, Siemens Healthcare; EXCELART Vantage Powered by Atlas, Toshiba Medical Systems) were used. The MRI sequences were T1WI, T2WI, FLAIR, T2*WI, Thin-slice T2WI, and MRA (head and neck).
- Image Analysis: The CT and MR images were analyzed in consensus by five radiologists (experienced neuro-, thoracic, abdominal and general radiologists and a radiology resident). Abnormal findings which seemed to be congenital were determined as an IA, while obvious acquired abnormalities such as cerebral aneurysm, liver and kidney cysts and uterine leiomyoma were excluded.

Results

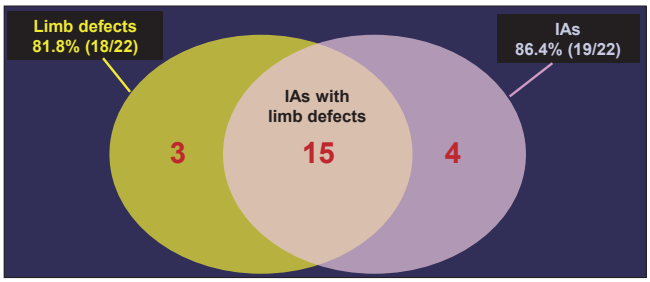


Figure 1. Relationship between IAs and Limb Defects (n=22)

Among the 22 individuals, limb defects and IAs were seen in 81.8% (18/22) and 86.4% (19/22), respectively. Fifteen individuals (68.2%) had both limb defects and one or more IAs.

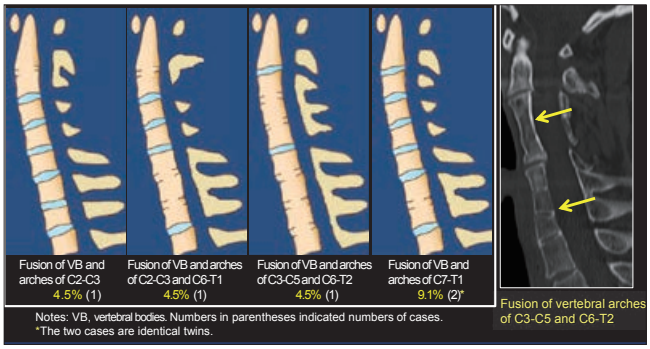
IAs	No. of cases
Block vertebrae	5 (22.7%)
Anomalies of the vascular system	6 (27.3%)
Hypoplasia or aplasia of the 7th/8th cranial nerves	5 (22.7%)
Anomalies of the auditory organ	10 (45.5%)
Agenesis of the gallbladder	6 (27.3%)
Fusion of the left lobe and quadrate lobe of the liver	2 (9.1%)
Others	5 (22.7%)

Table 1. The prevalence of radiological findings of IAs based on the data among the SCSTJ-registered victims

1. Block Vertebrae (Partial or complete fusion of adjacent vertebral bodies)

Prevalence of radiological findings in SCSTJ: 22.7% (5/22)

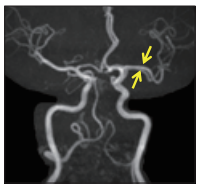
- Etiology: Result of locally decreased blood supply during the 3rd-8th week of fetal development.



2. Anomalies of the Vascular System

Prevalence of radiological findings in SCSTJ: 27.3% (6/22)

Double SVC	13.6% (3)
Carotid bifurcation level discrepancy	9.1% (2)
MCA duplication	4.5% (1)
Anomalous origin of the middle meningeal artery	4.5% (1)
The middle meningeal artery arising from the internal carotid artery	
Aberrant right subclavian artery	4.5% (1)
Anomalous course of the azygos vein	4.5% (1)
The azygos vein flowing into the SVC through the highest intercostal vein without forming the arch of azygos vein.	

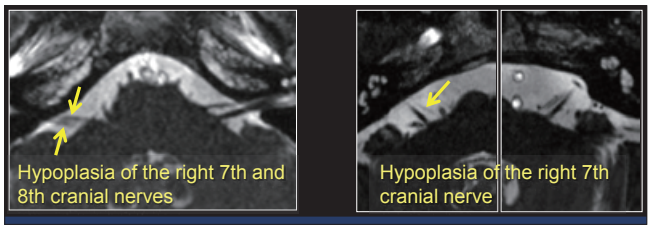


Duplication of MCA

3. Hypoplasia or Aplasia of the 7th and/or 8th Nerves

Prevalence of radiological findings in SCSTJ: 22.7% (5/22)

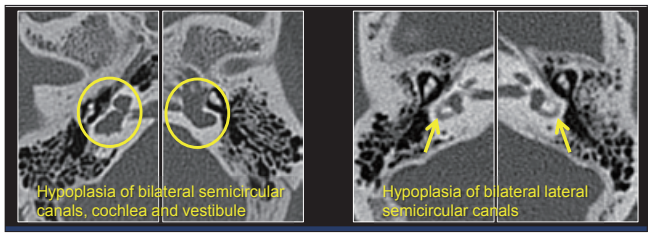
Hypoplasia	18.1% (4)
Unilateral 7th cranial nerve	13.6% (3)*
Unilateral 7th and 8th cranial nerves	4.5% (1)*
*Narrow internal auditory canals were found in these cases.	
Aplasia	4.5% (1)
Bilateral 7th and 8th cranial nerves	4.5% (1)*
*Internal auditory canal defect is found in this case.	



4. Anomalies of the Auditory Organ

Prevalence of radiological findings in SCSTJ: 45.5% (10/22)

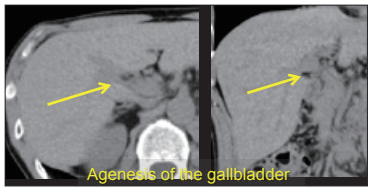
Hypoplasia of the semicircular canals	36.4% (8)
Hypoplasia of the auditory ossicles	22.7% (5)
Hypoplasia of the vestibule	22.7% (5)
Hypoplasia of the cochlea	18.2% (4)
Internal auditory canal abnormality	18.2% (4)
Bilateral narrow: 13.6% (3), bilateral absence: 4.5% (1)	
External auditory canal abnormality	13.6% (3)
Unilateral narrow: 9.1% (2), bilateral narrow: 4.5% (1)	
Narrow facial canal	4.5% (1)



5. Agenesis of the Gallbladder

Prevalence of radiological findings in SCSTJ: 27.3% (6/22

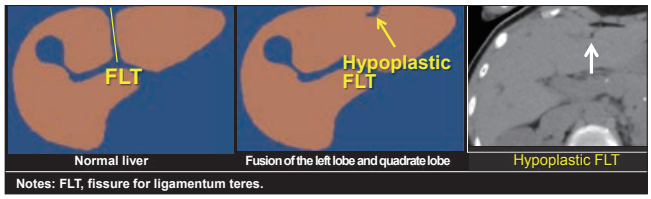
- There are two patterns in etiology.
- Failure of the formation of the gallbladder from the hepatic diverticulum during the 3rd-5th week of fetal development.
- Failure of the development of the lumen of the gallbladder during the 7th week of fetal development



6. Fusion of the Left Lobe and Quadrate Lobe of the Liver

Prevalence of radiological findings in SCSTJ: 9.1% (2/22)

- Agenesis of the umbilical portion of the left portal vein and gallbladder was also complicated in one of these two cases.
- There are few reports mentioning this anomaly in TE.



7. Other Anomalies

Prevalence of radiological findings in SCSTJ: 22.7% (5/22)
Transection of the pituitary stalk (1); Hypoplasia of unilateral thorax (1); Right-sided ligamentum teres hepatis (1); Vaginal atresia (1); and Unilateral congenital hip dislocation (1)

Discussion

- The limitation of our study is the small number of subjects.
- We thus cannot estimate the precise rates of IAs such as vascular anomalies and right-sided ligamentum teres hepatis, which was found in only one in our study.
- On the other hand, some IAs that are thought to be relatively common among individuals with TE, such as anomalies of the eyes, alimentary tract and urinary tract, were not found in our study. This may be because the prevalence of these anomalies is not so high; alternatively, the prevalence

may change as the age of the subjects advances.
- In addition, many of the subjects with IA in the previous studies were children or young people, whereas the mean age of the subjects in our results was 49.

Conclusion

- Various IAs were demonstrated by image screening using CT and MRI. As far as we know, block vertebrae and hypoplasia of FLT were new findings in TE.
- Understanding these characteristic radiological findings may help radiologists detect wide range of radiological findings of IAs associated with TE.

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[Poster Session]

Psychological and Mental Health Problems in Patients with Thalidomide Embryopathy in Japan

Koubun Imai, MD, Hanae Sone, MA, Ken Otomo, MA, and Yuki Nakano, MA

1. Introduction

Pathological characteristics of thalidomide embryopathy (TE) include not only mesodermal system abnormalities, such as limb hypoplasia, but also various degrees of ectoblast abnormality, including nervous system effects. Assessment of the actual psychological and mental status of TE patients in Japan is important because the study of autism in TE patients has been reported in other countries, but never in Japan, and the study of mental status, time has passed since the last research on patients with TE in Japan was conducted in 2004.

2. Aim

The aim of the study was to examine the presence of mental health problems and to assess the presence of autism in patients with TE in Japan in order to develop and build future support systems.

3. Methods

3-1. Participants

Participants were 22 patients with TE who were admitted to a hospital for medical examination during the period from September 2011 to February 2012. There were 9 male and 13 female patients aged 47 to 51 years. Among the 22 patients, 16 had limb deformities (4 male, 12 female), 2 had hearing impairment (both male), and 4 had both limb deformities and hearing impairment (3 male, 1 female). (Figure 1).

3-2. Procedure

Each patient first had an individual interview regarding their background information, including age, marital and educational status, and work experiences. After the interview, an electroencephalograph was administered. Experienced psychotherapists administered psychological tests, and the Mini-International Neuropsychiatric Interview (M.I.N.I.).

3-3. Instruments/Measures

(1) Electroencephalographic (Neurofax EEG-1524 by Kodensha).

Waking brain waves, including light stimulation and over-breathing load, were measured for 20 minutes for all patients.

(2) The Wechsler Adult Intelligence Scale Third Edition (WAIS-III; Japanese Version)

Differences in the mean scores of each IQ (full-scale IQ, verbal IQ, performance IQ), index score values, and mean subtest scores between the two groups (TE patients group and healthy subjects group) were evaluated by t-test.

(3) The Autism-Spectrum Quotient (AQ)

Differences of the mean scores of the total AQ score and each of the 5 subscales (communication, social skills, imagination, attention to detail, and attention switching) were analyzed by t-test.

(4) The General Health Questionnaire-28 (GHQ-28)

The total and mean scores on the subscales of two groups were compared using t-tests. The differences in mean scores were analyzed according to the presence/absence of a spouse, employment status, and locus of physical disability.

(5) Mini-International Neuropsychiatric Interview (M.I.N.I.)

The TE patients who fell under a certain diagnostic module were classified according to their disorder.

4. Result

(1) Electroencephalographic (Neurofax EEG-1524 by Kodensha)

Of the 22 patients, 18 were determined to be normal and 4 to be abnormal. 1 of 4 patients was diagnosed as epilepsy.

(2) The Wechsler Adult Intelligence Scale Third Edition

The mean average of FIQ for the TE patients group was 92.3 (SD 20.4). The mean average of VIQ and PIQ for the TE patients group was 91.8 (SD 20.6) and 94.4 (SD 21.4). No significant differences were found between TE group and healthy group on FIQ, VIO and PIQ. For the Indices and the subtests, TE patients group had substantially lower Working Memory (WM) and Processing Speed (PS) scores than the healthy group ($p < .01$). Also TE patients group scores were lower on Arithmetic and Symbol search ($p < .01$) and on

Vocabulary, Digit span, Information, and Picture completion ($p < .05$). (Table 1)

(3) The Autism-Spectrum Quotient (AQ)

The average AQ score of the TE patients group was 18.95 (SD 5.95). When a cut-off point of 32 out of 33 points was applied to the groups of TE patients, none met the criterion of autistic pathologic standard. No significant differences were found between TE patients group and the healthy subjects group.

(4) The General Health Questionnaire-28 (GHQ-28)

13 of 22 (59.1%) patients were judged as having some kind of mental health problem. Nine of 16 patients with limb deformities were judged as having a mental health problem (56.3%). Of the 2 patients with hearing impairments, 1 had a mental health problem. Of the 4 patients with both limb deformities and hearing impairment, 3 were judged as having some type of mental health problem.

When the scores compared, GHQ full score and subscales scores (somatic symptoms, anxiety and insomnia, and social dysfunction) in the TE patients group were significantly higher than healthy subject group ($p < .01$; Table 2).

Results of GHQ were also examined for each attribute of patient groups (by locus of disability, marital status, and employment status). In the present study, higher depression scores in single/divorced subject than in married subjects ($p < .01$). Moreover, scores for impaired social activities were significantly higher in the group without spouses than those in the group with spouses ($p < .00$).

(5) M.I.N.I.

From the M.I.N.I., 19 diagnostic modules of psychiatric disorders were found to be applicable to nine of the 22 patients with TE (40.9%). The applicable diagnostic modules included major depressive episode, dysthymia, suicidality, hypomania episode, panic disorder, agoraphobia, post-traumatic stress disorder, alcohol abuse, and psychotic disorders. Five of 9 patients fell under more than one diagnostic module (Table 3).

5. Discussion

(1) Comparison of electroencephalograph Test and AQ / WAIS

No relationship was observed between WAIS-III score, or the AQ score and the presence, or absence of electroencephalographic abnormalities.

(2) Comparison of WAIS-III results of patients and healthy subjects

The results of comparing the indices and subtests of patients and healthy subjects have three main implications. First, TE patients showed slowness in PS. However, this could be because most patients in the TE group had limb deformities, producing functional limitations that made it difficult for them to solve these problems. Second, the TE group showed a reduced ability to process information effectively, while maintaining attention to visual and auditory information. Finally, it is possible that differences in participants' educational backgrounds may have affected the results. Many TE patients graduated from special schools for children with disabilities, and thus their learning environments and experiences were more limited than those of healthy individuals.

(3) Mental health problems

The GHQ-28 results implied that the mental status of the TE patients was poorer than that of healthy subjects. Specifically, TE patients showed evidence of suffering from somatic symptoms, anxiety, and insomnia, as well as social dysfunctions. The results of the M.I.N.I. suggested that 40.9% of the TE patients had some psychiatric disorder. This is a percentage that is comparatively high.

The present results are important from academic, social, and international perspectives. As noted earlier, few previous studies have examined the psychological and mental health problems of TE patients, either in Japan or in other countries. The present study has therefore contributed to the general understanding of the actual situations of patients with TE. Although the results of the present study have significant implications for patients with TE, the number of the patients was small. Future studies will require a larger number of patients to investigate more thoroughly the psychological and mental problems of TE patients.

Future outlook of research

We are researching the factors affecting QOL and mental health in TE patients. Our purpose is to examine the relationship between pain, coping, time perspective, social support, QOL and mental health in TE patients. Identifying the psychosocial problems and needs of support is necessary to consider the future support systems.

Note: This is the revision of the paper published in the Psychiatry and Clinical Neurosciences 2014; 68: 479-486.

Figure 1 Participants

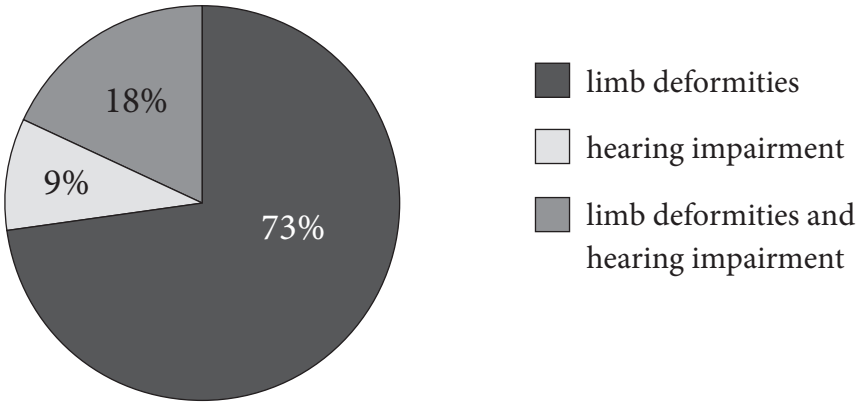

Table 1 Comparison of average scores (SDs) for WAIS-III Subtests

	Patient group (*N*=22)		Healthy group (*N*=120)		t-test		
	Average score	SD	Average score	SD	*t* value	degrees of freedom	*p* value
Verbal Scale							
Vocabulary	8.68	3.60	9.80	3.40	**2.26**	**52.79**	**0.03**
Similarities	9.68	4.11	9.90	2.90	0.24	24.97	0.81
Arithmetic	7.59	3.70	10.00	3.00	**3.36**	**140.00**	**0.00**
Digit Span	8.45	3.10	10.10	2.90	**2.42**	**140.00**	**0.02**
Information	8.45	3.42	10.00	3.10	**2.12**	**140.00**	**0.04**
Comprehension	9.64	4.69	9.90	3.10	0.25	24.48	0.80
Letter-Number Sequencing	9.64	3.43	10.20	2.90	0.81	140.00	0.42
Performance Scale							
Picture Completion	8.68	3.43	10.10	2.80	**2.11**	**140.00**	**0.04**
Digit Symbol Coding	8.27	3.68	10.00	3.00	**2.39**	**140.00**	**0.02**
Block Design	9.41	4.20	9.90	3.20	0.52	25.65	0.61
Matrix Reasoning	9.68	4.64	9.90	3.10	0.21	24.54	0.83
Picture Arrangement	9.41	4.18	10.10	3.10	0.74	25.40	0.47
Symbol Search	7.55	3.32	10.00	3.00	**3.47**	**140.00**	**0.00**
Verbal	52.50	19.15	59.70	14.20	1.68	25.40	0.11
Performance	45.45	16.30	50.00	10.40	1.26	24.23	0.22
Full	97.95	32.31	109.70	22.90	1.63	25.01	0.12
Verbal Comprehension	26.82	10.05	29.70	8.40	1.43	140.00	0.15
Perceptual Organization	28.50	11.34	29.90	7.00	0.56	24.01	0.58
Working Memory	25.68	8.71	30.30	7.00	**2.74**	**140.00**	**0.01**
Processing Speed	15.82	6.51	20.00	5.40	**3.23**	**140.00**	**0.00**

*WAIS-III scores and SDs of healthy groups are standardization data of 120 subjects aged 45 to 54 years old by Wechsler (2006).

Table 2 Comparison of average scores (SDs) on GHQ-28

	Patient Group (*N*=22)		Healthy group [1), 2)]		*t*-test		
	Average Score	SD	Average	SD	t value	Degrees of Freedom	p value
GHQ-28	7.36	5.48	2.76	2.31	**3.79**	**24.35**	**0.00**
Somatic Symptoms	2.86	2.24	1.02	1.09	**3.82**	**21.72**	**0.00**
Anxiety/Insomnia	2.41	1.87	1.24	1.4	**2.87**	**22.71**	**0.01**
Social Dysfunction	1.18	1.15	0.28	0.53	**3.64**	**21.64**	**0.00**
Severe Depression	0.91	1.90	0.28	0.79	1.54	21.52	0.14

Note. 1) GHQ-28 average scores and SDs of healthy groups are standardized data by Nakagawa & Daibo (1985).These data were collected from 50 healthy persons. 2) The average scores and SDs of Somatic Symptoms, Anxiety/Insomnia, Social Dysfunction, and Severe Depression of healthy groups are data by Nakagawa & Daibo (1985). These data were collected from 50 healthy persons and 307 university students.

Table 3 Number of patients diagnosed with disorder by M.I.N.I

		limb deformities (n=16)	hearing impairment (n=2)	both (n=4)
Disorder	Time Frame			
Major depressive	Past 2 wks	1(1)	0	0
disorder	Life time	1(1)	0	0
Dysthymic disorder	Lifetime	2(1)	0	0
Suicidality	Curent	5(4)	0	0
Panic disorder	lifetime	1(1)	0	0
Agoraphobia	Current	1(1)	0	0
Generalized anxiety disorder	Currebt	1(0)	0	0
Alcohol abuse	Current	1(1)	0	0
Psychotic disorder	Lifetime	2(2)	0	1(0)
PTSD		1(1)	0	0

Note: ( ) overlapping number

[Poster Session]

Thalidomide embryopathy: Common and rare differential diagnosis

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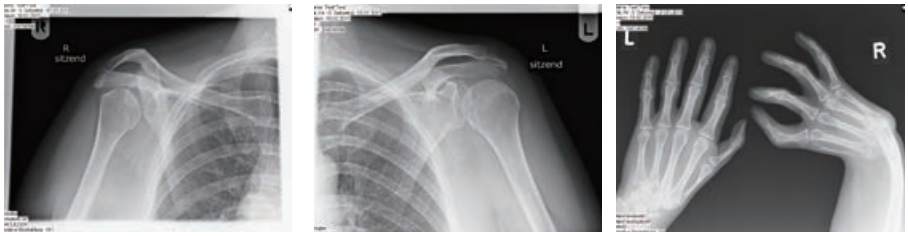
Dysmelia caused by Thalidomide intake of the mother during pregnancy has a certain pattern:

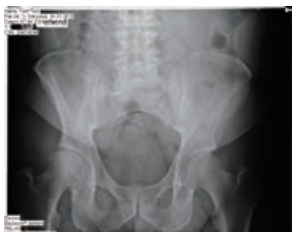
- Longitudinal reduction deformity
- Aplasia or hypoplasia of the radius and thumb
- Bilateral damage with relative symmetry
- Involvement of lower limbs always combined with dysmelia of upper limbs

Cases with Thalidomide-induced dysmelia of upper limbs

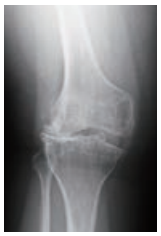


B.S. *1961 (Figure 1-3):
Longitudiual reduction deformity of upper limbs, right > left with absent right radius and thumb and triphanlangia of the left thumb.

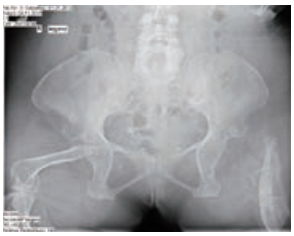
Cases with combined dysmelia of upper and lower limbs and sacrum



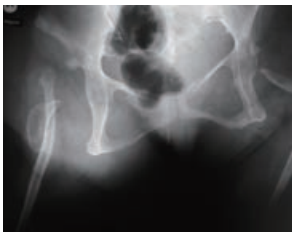
D. K. *1961 (Figure 4):
dysplasia of the sacrum with absent coccyx

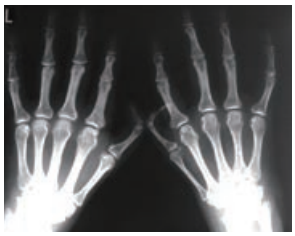


K. W. 1961 (Figure 5):
dysplasia of the right knee with severe secondary gonarthrosis



J. S. *1961 (Figure 6): severe reduction deformity of upper and lower limbs



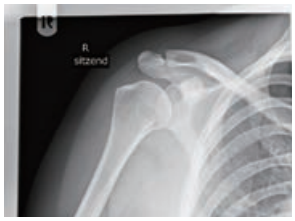
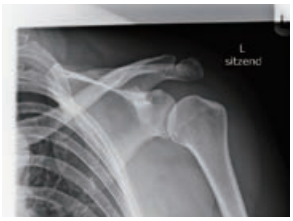
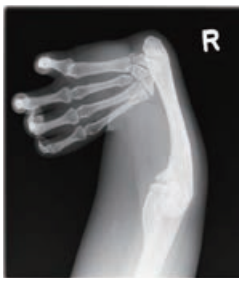


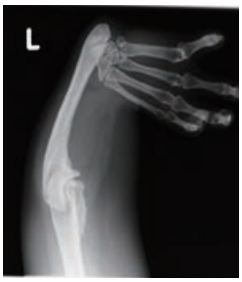
D. H. *1961 (Figure 7 + 8): quadruple limb damage: only slight changes in both hands and severe pelvic malformation

Differential diagnosis of Thalidomide-indured dysmelia:

• HOLT-ORAM syndrome (Heart-hand-syndrome type I)

Dysmelia of upper limbs, cardiac defect, aplasia of M. pectoralis major
Mutation in TBX5-gene

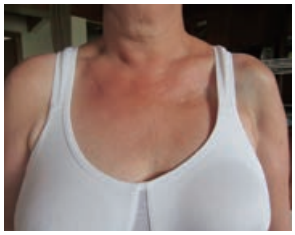
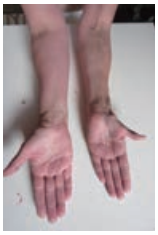
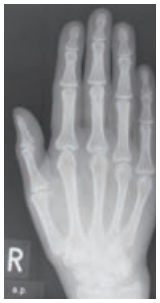




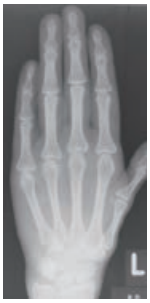


N. F. *1977 (Figure 9-12): bilateral symmetric reduction deformity of upper limbs with abcent radius and thumbs

• Poland syndrome

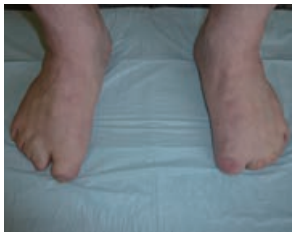
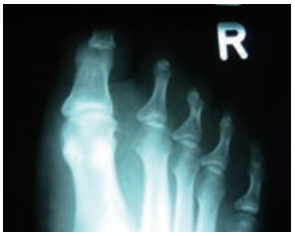
Unilateral aplasia of M. pectoralis major and mammary gland and unilateral dysmelia of upper limb

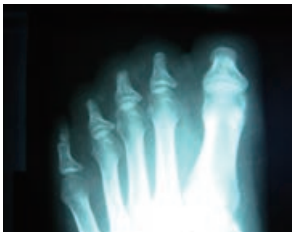






M.H. *1959 (Figure 13-16): dysmelia of the left upper limb combined with hypoplasia of M. pectoralis major and M. deltoideus

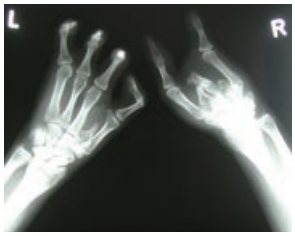
• All transversal reduction deformities

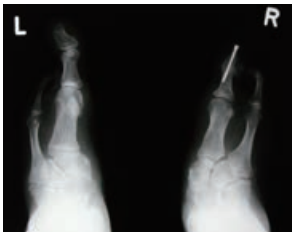


F. I. *1967 (Figure 17-19): transversal reduction deformity of both feet with "amputation" of the toes, no dysmelia of upper limbs

• EEC-syndrome (Ectrodactyly-ectodermal dysplasia clefting syndrome)



D. A. *1961 (Figure 20-21): reduction deformity of both hands and feet



[Poster Session]

Blood pressure (RR) measurement in patients with TE and limb defect technical problems, consequences and possible solutions

Dr. Jan Schulte-Hillen
Notfallzentrum Klinik St. Anna, Luzern

Pathologically elevated blood pressure is a major risk factor for long-term multi-organ compromising diseases (heart, brain, kidneys, eyes). It is considered as an important cardiovascular Risk Factor (CVRF) and has been surnamed "the silent killer" due to lack of primary symptoms.

Correct (self) measurement of blood pressure is mandatory for prophylaxis of these diseases and is part of all modern health programs.

Due to anatomic reasons thalidomiders with upper extremity defects show problems in measuring a valid arterial blood pressure. This may result in severe complications for the patients.

Problems with blood pressure measurement was not in the focus of rehabilitation programs for thalidomiders.

Correct Blood pressure measurement depends on (*):

1.) Correct diameter of cuff in relation to arm / hand diameter
2.) Cuff must be snugly fixed and arm must be held in the height of the heart
3.) Upper arm with normal anatomy must be patent
4.) Diameter of arm artery must be in normal relation to diameter of upper arm
5.) a. brachialis at normal anatomical location
6.) a. radialis on the radial side of the wrist in case of wrist RR measurement devices

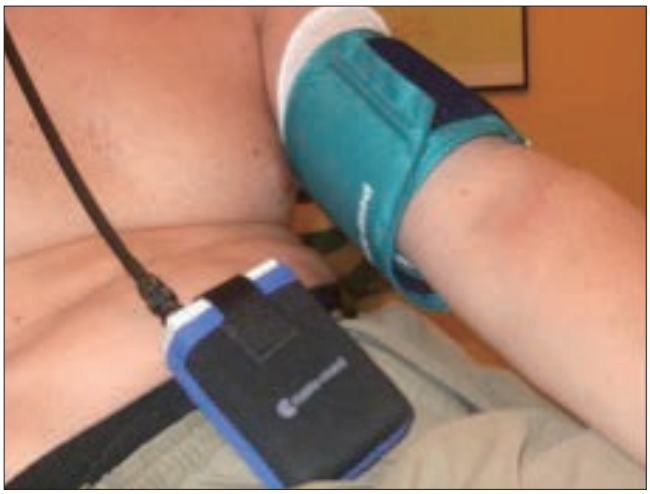
"Normal" arms

1.) yes
2.) yes
3.) yes
4.) yes
5.) yes
6.) yes

Upper arm defect

1.) often not possible
2.) often not possible
3.) no
4.) no data available
5.) questionable
6.) generally missing
(*) application of calibrated device and unimpaired hearing of doctor is also necessary...

Conclusion: 6 of the 6 patient related conditions for a reliable and valid blood pressure measurement with arm - or wrist-cuff do not apply in thalidomiders with upper arm defect.



picture source: Wikipedia

A) General physiologic / technical considerations for correct blood pressure measurement:

In thalidomiders with upper arm defect the following problems in measurement of blood pressure is to be expected:

1) Problems in handling the RR device:

Dysplasia of both arms leads to problems with manipulation of the device which cannot be applied correctly by the handicapped person. Someone else is needed. This seriously impairs compliance towards blood pressure measurement on a regular base as considered advisable in today's prophylactic medicine.

2) Arm cuff RR devices generally do not fit properly:

Arm diameter changes in a very short distance from shoulder to "elbow" in patients with upper extremity deformation leading to a "conical" arm profile. This may result in "slipping

down" of the upper arm cuff blood pressure devices. Correct measurement depends on correct ratio of diameter of the arm and width of the cuff. With regard to the picture **on the left**: Which diameter should be chosen? That of the "upper" arm or that close to the hand?

3) Wrist cuffs often yield invalid data

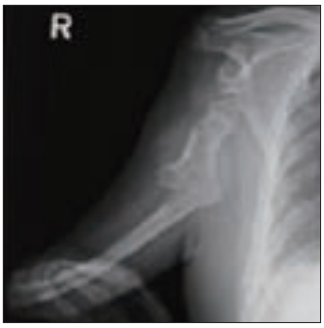
Accuracy of wrist cuff measurement devices highly depend on correct position of the pulse sensor over the radial artery. Where in the corresponding x-ray **on the right** do you expect the radial artery to be? There is none. The strongest signal that is received from the sensor of the RR wrist measurement device derives from the a. ulnaris which is at a different place than the sensor. The consequence are inconsistent and false measurement - or none at all. An absent radial artery is very common with severe defect of upper extremity defect (like in the picture on the left). Thalidomide causes a longitudinal limb defect with emphasis on the radial side. Apparently all tissues are involved. On top of that, we see cases with complete absent radial artery in spite of otherwise only very mildly affected arms (only thenar hypoplasy).

4) Thalidomiders with lower (and upper) extremity defect may have an intrinsically elevated blood pressure

While there are no publications regarding this issue, there is scientific evidence (1) of higher blood pressure (and increased mortality risk) in patients with **acquired** extremity defect (amputations).

The pathomechanisms behind this has not been properly identified. It is discussed that reduced general body vessel diameter / volume in patients with amputations of the lower limbs may lead to an impaired blood pressure regulation. If this observation is also valid with patients with congenital reduction defects like thalidomiders and if this also applies for patients with isolated upper extremity defect remains to be elucidated.

Furthermore, most of the thalidomiders with extremity defects are chronic pain patients due to arthrosis od the malformed limb joints or of the healthy limbs due to chronic overuse for non-physiological tasks like combing the hair with the feet. The pain caused elevated stress level and the chronic use of non stereoid anti-inflammatory drugs may be a risc factor for arterial hypertension in itself.



B) Special considerations concerning the necessity of measuring blood pressure in thalidomiders

Obtaining correct blood pressure data is mandatory for management of hypertension as a CVRF in every patient.

However, thalidomiders may be prone to generally elevated CVRF. There is no data available considering this subject but based on many conversations and contact with thalidomiders as applicants for acknowledgement of certain defects in the German thalidomide thrust it seems an educated guess to state that:

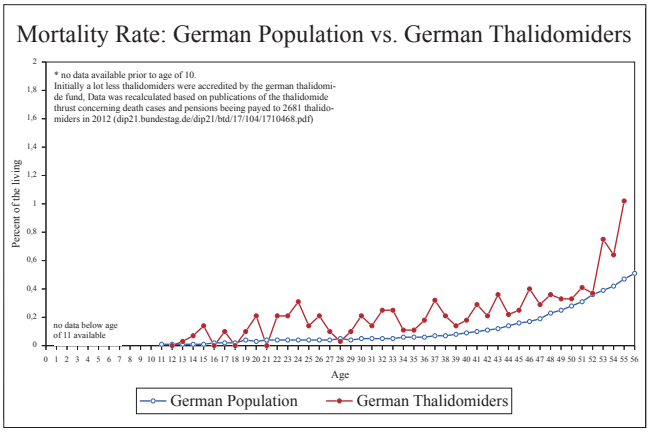
- Most of the thalidomiders are reluctant to go to the doctor because of difficulties of locomotion, getting dressed and undressed, syringe phobia, social phobia. Evading medical service itself is not considered a CVRF itself but since hypertension does not show primary symptoms it is evident that it can only be detected by having the blood pressure measured properly.
- Impaired locomotion, combined with often severe hyperhydrosis (reduced body surface in relation to body volume) often leads to a passive lifestyle, many of the thalidomiders being severely obese, many developing a metabolic syndrome and a diabetic condition.
- Abnormal arteries (dysplastic, absent, errant location) may present a risk factor of its own (e.g. very poor prognosis in case of a myocardial infarction in aplasia of single coronary arteries)
- As suggested above, limb reduction defects may pose an intrinsic risk factor for arterial hypertension itself.

Conclusion: Eliminating or treating hypertension as CVRF is mandatory in this patient group.

C) Possible evidence of a high prevalence of undiagnosed hypertensive disease in the thalidomide group in Germany

- Comparison of mortality rate of the German population with the group of the German thalidomiders may yield evidence of a higher per year mortality rate of the thalidomiders in Germany. This data has not been published yet and is based on personal enquiry (2). (Data and diagram on the right side....)
- Several cases are known where blood pressure measurement of thalidomiders had always yielded normal blood pressure but on ophthalmologic diagnosis, a fundus

hypertonicus was observed, thus being proof of a long-standing history of arterial hypertension and end-organ damage on one hand and for false blood pressure data obtained by the family physician for one of the reasons explained in A.)



Mortality Rate ()

year	Age	German Popul.	German Thalidom.	Thalido miders living	miders died
	Born 19(				
1961	0				
1962	1				
1963	2				
1964	3				
1965	4				
1966	5				
1967	6				
1968	7				
1969	8				
1970	9			*	
1971	10			2922	0
1972	11	0,01	0,00	2921	1
1973	12	0,01	0,03	2919	2
1974	13	0,01	0,07	2915	4
1975	14	0,01	0,14	2915	0
1976	15	0,01	0,00	2912	3
1977	16	0,02	0,10	2912	0
1978	17	0,02	0,00	2909	3
1979	18	0,02	0,10	2903	6
1980	19	0,04	0,21	2903	0
1981	20	0,03	0,00	2897	6
1982	21	0,04	0,21	2891	6
1983	22	0,04	0,21	2882	9
1984	23	0,04	0,31	2878	4
1985	24	0,04	0,14	2872	6
1986	25	0,04	0,21	2869	3
1987	26	0,04	0,10	2868	1
1988	27	0,04	0,03	2865	3
1989	28	0,05	0,10	2859	6
1990	29	0,04	0,21	2855	4
1991	30	0,05	0,14	2848	7
1992	31	0,05	0,25	2841	7
1993	32	0,05	0,25	2838	3
1994	33	0,05	0,11	2835	3
1995	34	0,06	0,11	2830	5
1996	35	0,06	0,18	2821	9
1997	36	0,06	0,32	2815	6
1998	37	0,07	0,21	2811	4
1999	38	0,07	0,14	2806	5
2000	39	0,08	0,18	2798	8
2001	40	0,09	0,29	2792	6
2002	41	0,10	0,21	2782	10
2003	42	0,11	0,36	2776	6
2004	43	0,12	0,22	2769	7
2005	44	0,14	0,25	2758	11
2006	45	0,16	0,40	2750	8
2007	46	0,17	0,29	2740	10
2008	47	0,19	0,36	2731	9
2009	48	0,23	0,33	2722	9
2010	49	0,25	0,33	2711	11
2011	50	0,28	0,41	2701	10
2012	51	0,31	0,37	2681	20
2013	52	0,36	0,75	2664	17
2014	53	0,39	0,64	2637	27
	54	0,42	1,02		
	55	0,47			
	56	0,51			

Conclusion:

There may be signs of undiagnosed arterial hypertension as clinically relevant in the population of German thalidomiders. Mortality rates of thalidomiders in Germany seem to exceed the mortality rate of the "normal" population. It is very important to obtain reliable and valid blood pressure data in the thalidomide population to identify arterial hypertension as a possible "silent killer".

D) Possible solutions in obtaining valid and reliable data in blood pressure measurement of thalidomiders with upper limb defect

There is very little literature concerning this issue. Yoshizawa (3) uses the arteria tibialis posterior for blood pressure measurement and recommends the formula ((systolic pressure of A. tibialis posterior + 8 mm Hg) × 0.88 mm Hg) for assessment of actual systolic blood pressure by measuring the pressure with a cuff over the arteria tibialis posterior.

- Patients with isolated leg defects should not require special handling and should be able to manage normal arm / wrist cuff devices. These devices should be expected to yield valid data. Special attention should be brought to patients with additional minor arm defects like thenar hypoplasy as these patients might have aplastic / dysplastic radial arteries. In these cases wrist cuff devices may yield invalid data and arm cuffs should be used instead.
- Patients with upper arm defect should have their blood pressure measured once on both legs and both arms. If the results yield much higher values (more than 20 mm hg) in the legs than in the arms, legs should be used for future blood pressure measurement (A. tibialis posterior, correction factor as mentioned above).

  Generally, in blood pressure measurement on the legs the two following considerations must be taken into account:
- Diabetic mediasclerosis leads to rigid blood vessels and to enormous resistance against pressure from outside and will yield false high blood pressure levels in measurement of blood pressure.
- Arteriosclerotic lesions as in "claudicatio intermittens" show reduced blood vessel diameter due to arteriosclerotic plaques leading to rapid occlusion of arteries by external pressure and yielding false low blood pressures in blood pressure measurements.

  The below described "measurement by proxy" might be exceptionally helpful in thalidomiders with upper extremity defects if we assume that thalidomiders do not have a generally different circulation system on the macroscopic and microscopic scale.

- Patients with defects of upper and lower extremity should have their intra-arterial blood pressure taken once as an equation base for a "personal ratio" between the "daily" blood pressure taken at a determined localization and the correct intra-arterial pressure. This can either be done with a planned surgical intervention or especially for this purpose.

  Generally and for all thalidomiders I suggest the 4 following procedures:
  - determine where you want to take the patients' blood pressure in the future
  - in all planned surgical interventions where invasive intra-arterial blood pressure is taken, have the intra-arterial pressure during surgery compared to a simultaneously taken non-invasive blood pressure measurement at your preferred localization to establish a "personal ratio" for this patient between intra-arterial blood pressure and cuff measurement.
  - measurement by proxy: If possible, find a "healthy reference person" not affected by extremity defects who matches the thalidomide patient in age, sex and leg circumference and take his blood pressure in legs and arms with cuffs of adequate size. If the reference patients' blood pressure obtained at his arms is normal and the blood pressure obtained on his legs is comparable to that of the thalidomider, it can be assumed that the thalidomider has a normal blood pressure too regardless of the blood pressure obtained at the thalidomider's legs. The ratio of the "reference persons" blood pressure between upper and lower extremities can be used as equation base for assessing the thalidomider's correct real blood pressure based on measuring the thalidomider's leg blood pressure.
  - all thalidomiders should see an ophthalmologist once per year to detect early signs of a fundus hypertonicus
  - creatinine clearance (lean body mass corrected for limb loss (4)) and microalbuminuria should be measured regularly to detect kidney impairment caused by hypertension.

Possible future of blood pressure measurement:

24 hour blood pressure monitoring with the cuff being inflated all 15 minutes has been perceived as disturbing to the extent of being insupportable by patients and a lot of investigative effort has been invested into finding alternative solutions. A recent publication (5) describes arterial blood pressure being assessed by an ultrasound device and one of the superficial arteries which is compressed from the outside by a small cushion. Being a very promising concept in itself, it remains to be elucidated if this can be applied to thalidomiders with an obviously varying anatomical vessel position. A possible solution may be the temporal artery. Technical approaches using a piezoelectronic device for measurement of pulse wave velocity undergo clinical evaluation in Germany at this moment.

1 Amputation and cardiac comorbidity: analysis of severity of cardiac risk. Nallegowda M, Lee E, Brandstater M, Kartono AB, Kumar G, Foster GP., PM R. 2012 Sep;4(9):657-66. doi: 10.1016/j.pmrj.2012.04.017. Epub 2012 Jun 13., PMID: 22698850

2 The data was obtained by comparing the mortality rate tables ("Sterbetafeln") in Germany (Statistisches Bundesamt) for the birth year of 1961 with the data published by the German thalidomide thrust. Unfortunately, there is no data available concerning the cause of death in the thalidomide group. Payment of thalidomide pensions depends on an official "proof of life" issued by German authorities. Pension payments are stopped when this document is not sent to the thrust every 2 years.

3 Atsuto Yoshizawa. Q&A on Thalidomide-Impaired People, Departments of Emergency Medicine and General Internal Medicine National Center for Global Health and Medicine (NCGM) 1-21-1 Toyama, Shinjuku, 162-8655, Online Publication http://www.ncgm.go.jp/eng/pdf/saridmaid_qa5-5_eng_20140613.pdf

4 e.g.: http://touchcalc.com/calculators/bmi_amputation

5 http://www.gesundheitsforschung-bmbf.de/de/4631.php

[Poster Session]

Adapting not Surrendering - The health and independence of thalidomide-affected people as they age

Ms. Elizabeth Newbronner
Firefly Research and Evaluation, York

1. Introduction

Thalidomide has become synonymous with 'medical' disasters and is frequently used as an example of how, in the past, the unchecked greed and arrogance of pharmaceutical companies led to tragic consequences.

However, as Abrams (2014) points out, Thalidomide is not just a historical tragedy, it is a contemporary disability issue. The first generation of Thalidomide-affected people have now been living with the consequences of the drug's damage for over 50 years. There are three distinct influences on their health as they age:

- The consequences of aging with an impairment
- The possible emergence of previously unknown effects of the drug
- The complications of managing unrelated health problems.

2. Purpose

To establish a much fuller understanding than currently exists, of the health problems and deterioration Thalidomide-affected people in the UK are experiencing as they age.
Specifically it is addressing three main research questions:

- What Thalidomide-related health problems are Thalidomide-affected people in the UK experiencing as they age?
- How do these Thalidomide-related health problems affect peoples' functioning and independence?
- What are the lived experiences of Thalidomide-affected people aging with impairment?

3. Methods

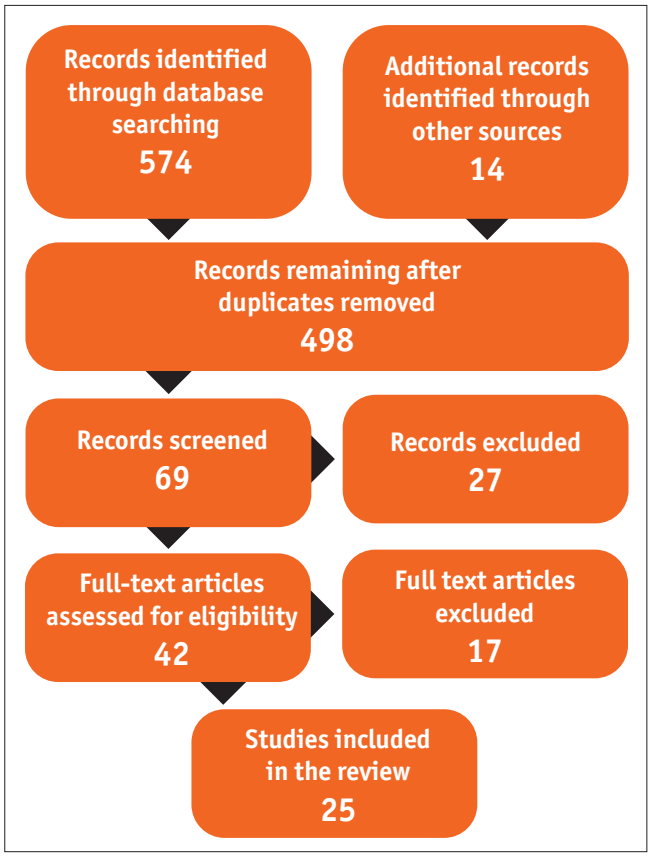
The research is being approached from a critical realist perspective, which recognizes both the fixed 'structures' that affect peoples' lives (e.g. their original Thalidomide impairments), and the fact that people have the ability to construct their own reality and influence change. This perspective has:
"Important implications for theorization of 'bodies and their impairments' because it suggests that there is a reality about human bodies and altered biological states, a reality that exists independently of societies categories of knowledge about these matters"

Thomas 2007
Grounded Theory is the overarching methodology for this mixed methods study. Specifically the study has four main elements:

- Literature review
- Semi-structured interviews with a representative sample of Thalidomide-affected people
- Health and wellbeing survey of all UK Thalidomide-affected people
- In-depth interviews with a small purposive sample of Thalidomide-affected people (2016)

4. Initial Results - Literature Review

- The literature on aging with Thalidomide impairment is limited and very diverse
- There are a small number of clinical studies focusing on specific aspects of aging with Thalidomide Embryopathy. For example - osteoarthritis
  (Ghassemi Jahani S A et at, 2014); psychological and mental health problems (Imai K et al 2014), neurological symptoms (Jankelowitz 2013)
- A few studies in Germany, Japan and the UK have looked more broadly at the health of Thalidomide-affected people (see Peters et al 2015; Kruse et al 2013; Kayamori R 2013; and Newbronner et al 2012)
- There are very few studies about the lived experience of ageing with Thalidomide impairment and the quality of them is mixed



5. Initial Results - Semi-structured interviews

The 40 participants for the semi-structured interviews were recruited via the Thalidomide Trust, and the make-up of the group in terms of level of impairment and gender was broadly representative of all UK Thalidomide-affected people. The interviews explored peoples' current and recent health problems. They revealed that many Thalidomide survivors feel that as they grow older their health is deteriorating more quickly than their peers in the general population. The health problems reported included:

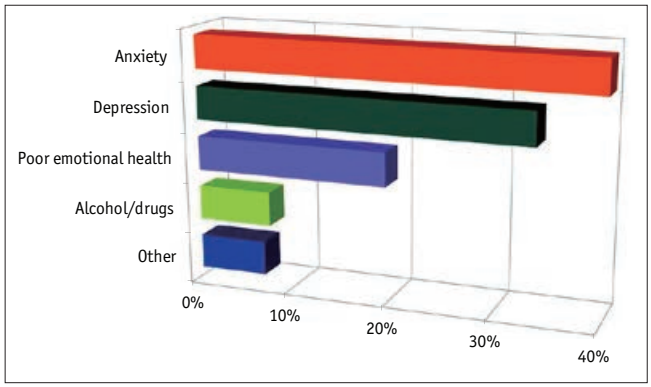
- Deterioration of joints and loss of flexibility and/or mobility
- Pain both in specific joints/limbs and generalized
- Loss of strength, numbness, tingling, partial paralysis
- General tiredness and lack of energy
- Weight gain (with wider implications for health and independence)
- Dental problems
- Deteriorating sight and/or hearing
- Changing mental and emotional health

6. Initial Results - Health and Wellbeing Survey

The survey was sent (via the Thalidomide Trust) to all 467 Thalidomide-affected people who were born in the UK. 351 people completed the survey either by post, on-line or on the telephone with support – a response rate of just over 75%.

The survey closed in October 2015. The data is still being analyzed but selected results are presented here:

- 93% were experiencing pain and/or loss of movement in one or more joint (including their neck and/or spine)
- 48% had generalized pain
- 73% reported experiencing neurological symptoms (tingling; loss of feeling; heat/cold)
- 50% had one or more mental health problems
- 62% reported that they had experienced problems with access to or the quality of health services



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