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CONGENITAL UPPER LIMB DEFECTS IN FINLAND 1993-2005

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”All the effort in the world won’t matter if you’re not inspired.”
Helen Keller

To My Family

ABSTRACT

Eeva Koskimies: Congenital upper limb defects in Finland 1993-2005
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Background: Interest in limb defects has grown after the thalidomide tragedy in the 1960s. As a result, congenital malformation registries, monitoring changes in birth prevalence and defect patterns, have been established in several countries. However, there are only a few true population based studies on birth prevalence of upper limb defects. The burden of hospital care among these children, specifically in terms of the number of admissions and total time spent in hospital, is also unknown.

Aims and Methods: This study is based on information gathered from the Finnish Register of Congenital malformations (FRM) and the Finnish Hospital Discharge Register (FHDR). A total of 417 children born between 1993 and 2005 with an upper limb defect were gathered from the FRM. The upper limb defects were classified using the International Federation of Societies for Surgery of the Hand -classification that enables comparison with previous and future studies. Birth and live birth prevalence, sex and side distribution, frequency of associated anomalies as well as the proportion of perinatal and infant deaths according to the different subtypes were calculated. The number of hospital admissions, days spent in hospital, number and type of surgical operations were collected from the FHDR. Special features of two subgroups, radial ray defects (RRD) and constriction band syndrome (CBS), were explored.

Results: Upper limb defects were observed in 417 of 753 342 consecutive births and in 392 of 750 461 live births. Birth prevalence was 5.5 per 10 000 births and 5.2 per 10 000 live births. Multiple anomalies or a known syndrome was found in 250 cases (60%). Perinatal mortality was 139 per 1000 births and infant mortality 135 per 1000 live births (overall Finnish perinatal mortality <5 per 1000 births and infant mortality 3.7 per 1000 live births). Altogether, 138 infants had RRD and 120 (87%) of these had either a known syndrome or multiple major anomalies. The proportion of perinatal deaths in RRD group was 29% (40/138) and infant deaths 35% (43/123). Fifty-one children had CBS in upper limbs. Fifteen of these (29%) had other major anomalies associated with constriction rings. The number of hospital admissions per year of children with congenital upper limb defects was 11-fold and the time spent in hospital 13-fold as compared with the general paediatric population.

Conclusions: Birth prevalence of congenital upper limb defects was 5.5 per 10 000 births and 5.2 per 10 000 live births. RRD was especially associated with other major anomalies and high mortality. Nearly one third of the children with CBS also had other major anomalies suggesting different aetiologies inside the group. The annual burden of hospital care of children with congenital upper limb defects was at least 11-fold as compared with the general paediatric population.

Key Words: congenital upper limb defect, limb anomaly, limb deficiency, birth prevalence, hospital care, radial ray defect, constriction band syndrome, incidence

TIIVISTELMÄ

Eeva Koskimies: Synnynnäiset yläraajapuutokset Suomessa 1993-2005
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Tausta: Kiinnostus raajaepämuodostumia kohtaan kasvoi 1960-luvulla talidomidi-tragedian seurauksena. Moniin maihin perustettiin epämuodostumarekisteri seuraamaan epämuodostumien esiintyvyyttä vastaavien onnettomuuksien estämiseksi. Suomen epämuodostumarekisteri on aloittanut toimintansa vuonna 1963. Yläraajapuutosten syntymäesiintyvyydestä on aiemmin tehty vain muutamia väestöpohjaisia tutkimuksia. Yläraajapuutoslasten sairaalahoidon määrä ei ole tiedossa.

Tavoitteet ja menetelmät: Tutkimuksen tavoitteena oli selvittää Terveyden ja hyvinvoinnin laitoksen (THL) ylläpitämän epämuodostumarekisterin ja hoitoilmoitusrekisterin (HILMO) tietojen pohjalta yläraajapuutosten syntymäesiintyvyys, liitännäisepämuodostumat, kuolleisuus ja sairaalahoitopäivien sekä tehtyjen toimenpiteiden määrä. Yläraajapuutokset luokiteltiin kansainvälisen käsikirurgiyhdistyksen (IFSSH) luokituksen mukaisesti jotta tulokset olisivat vertailtavissa muiden maiden aineistojen kanssa. Tutkimukseen otettiin mukaan kaikki vuosina 1993-2005 Suomessa syntyneet lapset. Epämuodostumarekisteristä poimittiin yhteensä 417 ylärajapuutosdiagnoosilla rekisteröityä lasta. Kahteen alaryhmään, radiaalisäteen puutoksiin (RRD) ja amnionkurouma–oireyhtymään (CBS) perehdyttiin tarkemmin.

Tulokset: Yläraajapuutos todettiin 417 syntyneellä ja 392 elävänä syntyneellä lapsella. Syntymäesiintyvyys oli 5.5/10 000 syntynyttä ja 5.2/10 000 elävänä syntynyttä lasta. Valtaosalla (60%) oli liitännäisepämuodostumia tai jokin tunnettu oireyhtymä. Perinataalikuolleisuus oli 139/ 1000 syntynyttä (Suomessa yleisesti <5/1000). Imeväiskuolleisuus oli 135/1000 elävänä syntynyttä (Suomessa yleisesti 3.7/1000). RRD todettiin 138 lapsella ja näistä lähes kaikilla (87%) oli joko jokin tunnettu oireyhtymä tai muita epämuodostumia. Perinataali- ja imeväiskuolleisuus oli erityisesti RRD-ryhmässä korkea (29% ja 35%). Korkea kuolleisuus liittyi 18-trisomiaan ja muihin vaikeisiin epämuodostumiin. CBS yläraajoissa todettiin 51 lapsella. Näistä 29%:lla oli kuroumarenkaiden lisäksi muita epämuodostumia. Yläraajapuutospotilailla oli sairaalahoitojaksoja 11-kertainen ja hoitopäiviä 13-kertainen määrä verrattuna keskimääräiseen lapsiväestöön Suomessa.

Päätelmät: Synnynnäisten yläraajapuutosten syntymäesiintyvyys on 5.5/10 000 syntynyttä ja 5.2/10 000 elävänä syntynyttä. Erityisesti radiaalisäteen puutoksiin liittyy muita epämuodostumia sekä 58-kertainen perinataali- ja 95-kertainen imeväiskuolleisuus verrattuna lapsiväestöön keskimäärin. Lähes kolmasosalla CBS-lapsista on muiden elinryhmien epämuodostumia viitaten mahdollisiin erilaisiin syntymekanismeihin ryhmän sisällä. Sairaalahoitojaksojen määrä oli yläraajapuutoslapsilla 11-kertainen verrattuna keskimääräiseen lapsiväestöön.

Avainsanat: yläraajapuutos, raaja-anomalia, raajapuutos, syntymäprevalenssi, sairaalahoito, radiaalisäteen puutos, contriction band- oireyhtymä

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ABBREVIATIONS AND GLOSSARY

ABS	Amniotic band syndrome
ADAM	Amniotic deformity adhesion mutilations
Amelia	Absence of a limb
Anomaly	Something that deviates from what is standard, normal, or expected
Aplasia	Absence of a specific bone or bones
ARS	Amnion rupture sequence
ART	Assisted reproductive technology
Birth	A process resulting in a foetus or a child of at least 22+0 weeks of gestation or weighing at least 500 grams. The process of a child being born alive is always a birth. An induced termination of pregnancy is not a birth, in spite of the gestational age or the weight of the foetus.
Birth prevalence	The number of cases of a disease in a given population at birth
Brachydactyly	A condition in which fingers or toes are abnormally short
CBS	Constriction band syndrome
Cleft hand	Ectrodactyly, lobster-claw deformity, split hand: characterized by a cutaneous cleft in central part of the hand with or without absence of one or more central digits/rays of the hand
CMC	Carpometacarpal
Congenital	A condition present at birth, whether inherited or caused by the environment, especially the uterine environment
CVS	Chorionic villus sampling
Deformity	A deformed part, especially of the body
EEC	Split hand-split foot syndrome
ELBW	Extremely low birth weight (<1000g)
EUROCAT	“European Concerted Action on Congenital Anomalies and Twins”, European Surveillance of Congenital Anomalies
FDS	Flexor digiti superficialis tendon

FHDR=HILMO	Finnish Hospital Discharge Register
FRM	Finnish Register of Congenital Malformations
Hemimelia	Absence of one of the paired bones of a limb
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
ICD	International Classification of Diseases
IFSSH	International Federation of Societies for Surgery of the Hand
Incidence	The rate, at which new cases occur in a population during a specific period
Infant mortality	Deaths during the first year of life per 1000 live births
Intercalary defect	Absence of the middle portion of a limb, when proximal and distal parts are present
JSSH	Japanese Society for Surgery of the Hand
LBW	Low birth weight (<2500g)
Live birth	Birth of a child that, irrespective of the duration of the pregnancy, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord or movement of the voluntary muscles, whether or not the placenta is attached or the umbilical cord has been cut.
Longitudinal	Extending parallel to the long axis of a limb
Major anomaly	An unusual anatomic feature that is of serious medical or cosmetic consequence to the patient
Malformation	An abnormally formed part of the body
Minor anomaly	An unusual anatomic feature not of serious medical or cosmetic consequence to the patient
MCP	Metacarpophalangeal
MTP	Metatarsophalangeal
NCSP	Nordic Classification of Surgical Procedures
Perinatal mortality	Stillbirths and deaths during the first week of life (<7days) per 1000 births
Phocomelia	Absence of long bones with terminal parts present
PIC	Personal identity code

Postaxial	Ulnar (or in lower limb fibular) side of a limb
Preaxial	Radial (or in lower limb tibial) side of a limb
Prevalence	The proportion of a population that is affected by the disease at a specific time
RRD	Radial ray defect
Stillbirth	Birth of a foetus, or a child, that shows no evidence of life typical of a live birth, but complying with the definition of a birth
Syndactyly	A union of two or more digits
Symbrachydactyly	A union of two or more abnormally short digits
TAR	Thrombocytopenia-absent radius syndrome
THL	Terveyden ja hyvinvoinnin laitos; National Institute of Health and Welfare in Finland
Transverse deficiency	Absence of the entire width of a limb
VACTERL(S)	Vertebral-Anal-Cardiac-Tracheo-Esofageal-Renal/Radial-Limb (single umbilical arterial) defect
VLBW	Very low birth weight (<1500g)
WHO	World Health Organisation

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the bolded numbers **1-4**.

1. Koskimies Eeva, Lindfors Nina, Gissler Mika, Peltonen Jari, Nietosvaara Yrjänä. Congenital upper limb deficiencies and associated malformations in Finland: A population-based study. J Hand Surg Am 2011;36:1058-65.

2. Pakkasjärvi Niklas, Koskimies Eeva, Ritvanen Annukka, Nietosvaara Yrjänä, Mäkitie Outi. Characteristics and associated anomalies in radial ray deficiencies in Finland -A population-based study. Am J Med Gen 2013;161A:261-7.

3. Koskimies Eeva, Syvänen Johanna, Nietosvaara Yrjänä, Mäkitie Outi, Pakkasjärvi Niklas. Congenital constriction band syndrome with limb defects. A population based study. J Pediatr Orthop 2014 Apr 29 [Epub ahead of print].

4. Koskimies Eeva, Helenius Ilkka, Pakkasjärvi Niklas, Nietosvaara Yrjänä. Hospital care and surgical treatment of children with congenital upper limb defects in Finland. Submitted for publication.

1. INTRODUCTION

Several national registries were established in the 1960s with the aim of monitor changes in birth prevalence and defect patterns of congenital malformations. At present data is collected internationally (Stoll et al 1986, Stoll et al 1998, Nippert et al 2002).

There are only a few population-based studies on birth prevalence of upper limb defects (Birch-Jensen 1949, Rogala et al 1974, Aro et al 1982, Källen et al 1984, Froster and Baird 1992). It has been difficult to compare the results of these studies, since the investigators have used variable classifications.

In 1964, Alfred Swanson proposed a classification system for congenital upper limb deformities, which allows international and institutional comparison. This classification is accepted and later updated by the Congenital Anomalies Committee of the International Federation of Societies for Surgery of the Hand (IFSSH).

Upper limb defects, especially RRD, are strongly associated with other anomalies such as VACTERL association and Trisomy 18 (Goldfarb et al 2006, de Graaff and Kozin 2009). The burden of hospital care among these children, specifically in terms of the number of admissions and total time spent in hospital, is currently unknown. Factors, such as the type of the limb defect and additional anomalies, are likely to influence the number of hospital admissions and the length of treatment. Access to comparable data on congenital upper limb defects is essential for the allocation of health care and surgical resources.

In this thesis the population-based birth prevalence, mortality, number of hospital admissions, and surgeries of children with upper limb defects as classified by the IFSSH system are presented. The special features of RRD and CBS are presented in detail.

2. REVIEW OF THE LITERATURE

2.1. Thalidomide tragedy

Thalidomide (alpha-phthalimido-glutarimide) was first developed as an anticonvulsant drug by the German company Chemie Grunenthal in the 1950s. Thalidomide was widely used in many countries for a variety of indications. One of the indications was emesis during the first weeks of pregnancy (Nippert et al 2002). Quite quickly paediatricians and geneticists began to see new-born children with gross limb malformations of a most unusual pattern (McBride 1961, Lenz 1963, Ryöppy and Sulamaa1963, Sulamaa and Ryöppy 1964). The long bones of the limbs were extremely short or absent. The palm and the fingers could be present and thus the limb resembled a seal fin. The anomaly was named phocomelia (Greek Phoke = seal, melos= limb). Phocomelia was associated with other anomalies: eyes, ears, the heart, the gastrointestinal canal and urogenital organs could also be affected (Lenz 1963).

In December 1961, William McBride, in his letter to The Lancet, suggested that these anomalies resulted from the use of thalidomide during pregnancy (McBride 1961). Thalidomide was withdrawn from the market even before the letter was published (McBride 1961, Smithells and Newman1992, Saano 1996). Over 10 000 children were born severely handicapped in at least 46 countries (Saano 1996, Nippert et al 2002).

The embryonic sensitivity to thalidomide was recognised to be 34 to 50 days after the beginning of the last menstrual period (Smithells and Newman 1992). Today thalidomide is used in the treatment of leprosy and multiple myeloma under strict control (Burkholz 1997, Amadio 2005, Ito et al 2010 and 2011). The teratological mechanism of thalidomide is still unknown (McBride 2004, Hansen and Harris 2013).

2.2. Monitoring birth defects

Modern legislation requires extensive testing of all pharmaceutical products before approval (Burkholz 1997). Registries are monitoring changes in birth prevalence and defect patterns of congenital malformations in several countries: Czech Republic since 1961, Hungary 1962, Finland 1963, Sweden 1964, Canada 1966, Israel 1966, Norway 1967, USA (Atlanta) 1967 and France (Rhone-Alps) 1973 (Greenlees et al 2011, ICBDSR web page).

Today, data on birth defects is gathered on an international basis (Stoll et al 1986, Stoll et al 1998). Altogether 45 programmes in 31 countries collaborate in monitoring 40 types

of birth defects via the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) founded in 1974 in Helsinki, and maintained by WHO (ICBDSR web page, Botto et al 2006).

EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies, with a common protocol and data quality review, which was started in 1979, and funded by the European Commission since 2004 (Eurocat web page, Dolk et al 2010).

The Finnish Register of Congenital Malformations (FRM) has gathered information since 1963. The FRM is maintained by the THL (THL web page). Monitoring the national incidence of limb defects is an important part of early detection of potential new teratologic factors. Population-based registries are powerful tools for evaluation of prenatal screening practice, the effect of primary prevention strategies such as periconceptional folic acid supplementation, and vaccination against rubella (Eurocat web page). Completeness of the FRM has been validated and estimated to be 95% (Leoncini et al 2010, Sund 2012), for the Swedish Register of Congenital Malformations the figure has been estimated to be 94% (Hermansson et al 2001).

2.3. Birth prevalence of upper limb defects

According to previous population-based studies, the birth prevalence of upper limb defects is 3.25-6.7/10 000 births (Birch-Jensen 1949, Rogala et al 1974, Aro et al 1982, Källen et al 1984, Froster and Baird 1992). Table 1. In Finland Aro and co-workers (1982) has reported the total incidence rate of three selected congenital limb anomalies: reduction limb deformities, polydactyly, and syndactyly from 1964 to 1977. Due to heterogeneous populations, classification systems, and inclusion criteria it is difficult to compare the results of these previous studies.

Table 1. Comparison of birth prevalence of congenital upper limb defects in previous studies.

	Birch-Jensen 1949	**Rogala et al 1974**	**Aro et al 1982**	**Källen et al 1984**	**Froster and Baird 1992**
Country	Denmark	United Kingdom	Finland	Sweden	Canada
Period	1910-1945	1964-1968	1964-1977	1965-1979	1952-1984
Type of study	Hospital- based	Population of city of Edinburgh, UK	Population of Finland	Population of Sweden	Population of province of British Columbia, Canada
Syndromes	Included	Included	Excluded	Excluded	Excluded
Stillbirths	Excluded	Included	Included	Included	Excluded
Population sample	151 648	52 029	964 878	1 368 000	1 213 913
Number of cases	34	35	314	553	659
Incidence	2.2/10 000 live births	6.7/10 000 births	3.3/10 000 births	4.0/10 000 births	3.4/10 000 live births
Classification system	Subjective classification	Temtamy and McKusick 1969	Franz and O´Rahilly 1961	Subjective classification	Losch et al 1984

2.4. Classification of upper limb anomalies

Traditionally, various descriptive terms such as hemimelia, peromelia, ectromelia, phocomelia, acheiria, adactylia, aphalangia, and dysmelia have been used to categorize limb anomalies (Frantz and O´Rahilly 1961, Burtch 1966). In 1961, Frantz and O´Rahilly proposed a classification based on anatomical terminology. They divided limb defects under two basic headings, terminal and intercalary, with subgroups of transverse and longitudinal (Frantz and O´Rahilly 1961). The classification system, presently accepted by the IFSSH, is the one Alfred Swanson proposed for limb anomalies in 1964. It was initially composed of six and subsequently expanded by the seventh basic category (Swanson 1976). The categories are: I failure of formation of parts, II failure of differentiation of parts, III duplication, IV overgrowth, V undergrowth, VI congenital constriction band syndrome, and VII generalized skeletal abnormalities. Subgroups I, V, and VI represent upper limb defects. Table 2.

The morphology- but not aetiology -based IFSSH classification does not permit full categorization of the most complex cases. It is occasionally difficult to differentiate between cases of symbrachydactyly, atypical cleft hand, transverse arrest, and CBS based on morphologic features only (Cheng et al 1987, De Smet et al 1997, Tonkin 2006).

The Japanese Society for Surgery of the Hand (JSSH) proposed in 2002, in the light of embryological evidence, a significant modification where central ray defects, syndactyly and central polydactyly are placed under an additional subgroup called "Abnormal induction of rays" and symbrachydactyly becomes a type of transverse arrest (Tonkin 2006). An updated classification scheme based on molecular pathways, named OMT-Classification, has also been proposed (Manske and Oberg 2009, Oberg et al 2010, Tonkin et al 2013, Ekblom et al 2014). The FRM uses the ICBDSR classification that divides limb anomalies into four groups: 1. Deficiencies, 2. Supernumerary structures, 3.Fusion/separation defects and 4. Combined anomalies (Stoll et al 1998).

Table 2. IFSSH Classification of congenital upper limb deformities (Ezaki et al 1993).

I Failure of formation of parts A. Transverse arrest 1 Shoulder 2 Arm 3 Elbow 4 Forearm 5 Wrist 6 Carpal 7 Metacarpal 8 Phalanx B. Longitudinal arrest 1 Radial ray deficiency 2 Ulnar ray deficiency 3 Central ray deficiency 4 Intersegmental deficiency (Phocomelia)	III Duplication
	IV Overgrowth
	V Undergrowth 1 Whole limb 2 Whole hand 3 Metacarpal 4 Digit a Brachysyndactyly b Brachydactyly
II Failure of differentiation of parts A Soft-tissue involvement B Skeletal involvement C Congenital tumorous conditions	VI Congenital constriction band syndrome
	VII Generalized skeletal abnormalities A. Chromosomal 1. Madelung´s deformity

2.4.1. Classification of upper limb defects

In IFSSH-classification subgroups IA1-8, IB1-4, V1-4 and VI represent upper limb defects. Table2.

I Failure of formation of parts

Upper limb defects regarding failure of formation are subdivided into transverse (IA1-8), longitudinal (IB1-3) and intercalary defects (phocomelia IB4). The existence of true intercalary deformities has been questioned and cases previously classified as

upper-extremity phocomelia have been proposed as representing a spectrum of severe longitudinal dysplasia (Goldfarb et al 2005).

IA 1-8 Transverse arrest

Shoulder IA1 (Amelia), Arm IA2, Elbow IA3, Forearm IA4 (Congenital forearm amputation), Wrist IA5 (Acarpia), Carpal IA6, Metacarpal IA7, Phalanx IA8

In the IFSSH classification, only congenital amputations are placed in this category. Recently, it has been suggested that symbrachydactyly is most likely a distal manifestation of a transverse deficiency. This is supported by the fact that 93% of extremities with transverse arrest, at the level of forearm, have rudimentary manifestations of digits (Manske and Oberg 2009). Amelia is associated with high mortality (Froster-Iskenius and Baird 1990, Bermejo-Sanchez et al 2011). Other types of transverse arrest are rarely associated with other anomalies (Evans et al 1994).

IB 1-4 Longitudinal arrest

IB1 RRD, Radial club hand

In RRD, skeletal and soft-tissue structures of the entire radial (preaxial) aspect of the upper limb are affected. The characteristic features are thumb hypoplasia/aplasia (Table 3) and different grades of radius deficiency (Table 4) (Heikel 1959, James et al 1999, Buck-Gramcko 2002, Manske and Oberg 2009, Riley and Burgess 2009). Most ulnae are secondarily involved. The ulna may gain only 50-75% of its normal length (Heikel 1959, Flatt 1994b, Sestero et al 2006). The features of RRD include radial angulation of the hand at the level of the wrist, active elbow flexion can be absent, and fingers 2-5 may have limited motion and function. Radial musculotendinous structures often form a firm fibrous band that tethers the wrist and hand (Manske and Oberg 2009). Goldfarb and co-workers (2005) extended the RRD classification further to include proximal radial longitudinal deficiency (type V) that has previously been considered a form of phocomelia. Simo Vilkki (2014) presented a functional scoring method to grade the usefulness and quality of the upper limb in congenital radial dysplasia.

Table 3. Blauth´s modified classification of thumb hypoplasia (Manske and Oberg 2009)

Type I: the thumb is small with mild hypoplasia of most anatomic structures
Type II: hypoplastic thumb has a tight web space between thumb and index finger and instability of MCP joint due to ulnar collateral insufficiency
Type III: the thumb shows all characteristics of type II with additional skeletal hypoplasia and deficiencies of extensor pollicis longus and flexor pollicis longus muscles. In type IIIA the metacarpal base is present and CMC-joint is stable and reconstructive surgery therefore justified (Flatt 1994b). In type IIIB the metacarpal base is absent and CMC-joint is unstable. Such an inadequate thumb is better removed and pollicisation planned except in culturally unfavourable populations (Flatt 1994b, Foucher et al 2001, McDonald et al 2008, Chow et al 2012).
Type IV: a floating thumb
Type V: the thumb and radial carpal bones are absent (Manske and Oberg 2009, Riley and Burgess 2009)

Table 4. Classification of radius deficiency (James et al 1996 and 1999)

Type N: normal length radius and normal carpus, thumb hypoplasia
Type 0: normal length radius, radial side carpal abnormalities
Type 1: >2mm shortening of the radius
Type 2: hypoplastic radius
Type 3: partial radius with absence of distal physis
Type 4: complete absence of radius

IB2 Ulnar ray deficiency

Ulnar longitudinal deficiency represents a spectrum of abnormalities that affect the ulnar border of the upper limb. Table 5. Both the ulnar and radial side of the hand may be affected. Syndactyly, thumb and first-web abnormalities are common (Ogden et al 1976, Cole and Manske 1997, Manske and Oberg 2009). Despite the significant radiographic and morphologic abnormalities these patients often function well (Blair et al 1983). Ulnar ray deficiency is seldom associated with anomalies in other organ systems than the musculoskeletal system (Evans et al 1994, Flatt 1994g, Bednar et al 2009).

Table 5. Bayne classification modified by Goldfarb et al 2005 and Havenhill et al 2005

Type 0: Normal length ulna with ulnar-sided hand deficiencies
Type 1: Hypoplastic ulna with distal and proximal epiphyses present
Type 2: Distal ulnar aplasia
Type 3: Complete ulnar aplasia
Type 4: Radial-humeral synostosis
Type 5: Proximal ulnar longitudinal deficiency

IB3 Central ray deficiency (cleft hand, lobster claw, central oligodactyly)

There are two types of cleft hand: typical and atypical. The presentation of a typical cleft hand varies from a simple soft-tissue cleft between the long and ring finger to suppression of all osseous elements of the hand except the little finger ray (Manske and Oberg 2009). In one third of cases, the cleft hand is associated with a cleft foot (EEC split hand-split foot syndrome). It is possible that pathogenesis of a typical cleft hand is related to that of syndactyly and central polydactyly (Ogino 1990). A cleft hand is often not functionally limited, but aesthetically unsightly (Manske and Oberg 2009). Atypical cleft hand demonstrates features of symbrachydactyly, where the anomaly is always unilateral and the central finger rays are hypoplastic, but the metacarpals are present (Flatt 1994a).

IB4 Intersegmental deficiency (Phocomelia)

In phocomelia, the proximal part of the limb is absent or markedly hypoplastic with the distal parts of the limb present. Phocomelia is one of the most characteristic defects produced by thalidomide (Bermejo-Sanchez et al 2011). Phocomelia is part of at least 25 syndromes or clinical entities (Bermejo-Sanchez et al 2011). It has been proposed that phocomelia represents the most severe form of longitudinal deficiencies (Goldfarb et al 2005).

V Undergrowth 1-4a/b (Whole limb V1, Whole hand V2, Metacarpal V3, Digit V4: brachysyndactyly V4a, brachydactyly V4b)

Poland syndrome is classified in this category as characterized by undergrowth of the whole limb starting with partial absence of the pectoralis major muscle and ending with a brachysyndactylic hand (Flatt 1994h). Brachymetacarpia is often not diagnosed until teenage. The ulnar metacarpals 4-5 are those most commonly affected. The functional deficit is minimal (Flatt 1994c, Kato et al 2002, Volpi and Fragomen 2011). A recent molecular study supports the idea that both symbrachydactyly and brachydactyly belong to the transverse deficiency category (Manske and Oberg 2009).

VI Constriction band syndrome (CBS) (amnion rupture sequence ARS, amniotic deformity adhesion mutilations ADAM, amniotic band syndrome ABS, Streeter´s dysplasia)

CBS compose a wide spectrum of congenital deformities ranging from simple constriction bands to major craniofacial and visceral defects (Walter et al 1998). Aetiology of constriction bands seen around extremities is still obscure. In 1930, George Streeter suggested there was an intrinsic defect of the subcutaneous germ plasm that caused the soft tissue to slough and the resultant external healing to lead to the constriction bands (Streeter 1930, Wiedrich 1998). In 1961, Thomas Patterson stated that histologically constriction rings look very much like the normal creases present on the hand and suggested that constriction rings

were abnormal creases (Patterson 1961). In 1965, Richard Torpin proposed an extrinsic condition, where an early amnion rupture forms adherent bands that constrict and amputate limbs (Torpin 1965, Walter et al 1998). Torpin´s theory has later been supported by other authors (Light and Ogden 1993, Kiehn et al 2007). Yoshitake Kino (1975) reproduced CBS in rats by amniocentesis and concluded that CBS is produced by environmental factors. Van Allen (1987) suggested that vascular disruption could lead to both internal and external defects. The significant rate (36-50%) of additional anomalies such as cleft lip and palate, body wall defects, anencephaly, and clubfoot support intrinsic theories (Bamforth 1992, Czeizel et al 1993, Foulkes and Reinker 1994, Wiedrich 1998, Robin et al 2005, Hunter et al 2011). Each theory has its limitations. It is possible that constriction band anomalies have more than one aetiology (Goldfarb et al 2009).

Table 6. Patterson´s classification of cbs.

Type I: simple constriction bands
Type II: constriction bands with distal soft tissue deformity
Type III: distal osseous syndactyly
Type IV: terminal amputation (Patterson 1961, Manske and Oberg 2009)

2.5. Associated anomalies and mortality

Associated major anomalies are most often seen in infants with amelia, RRD, phocomelia, or central ray defects and rarely in infants with transverse defects or ulnar ray defects (Heikel 1959, Froster and Baird 1992, Evans et al 1994, Rosano et al 2000, de Graaff and Kozin 2009). Radial ray defects are part of several syndromes and associations such as Trisomy 18, Thrombocytopenia-Absent Radius syndrome (TAR), VACTERL, Holt-Oram Syndrome and Fanconi Anemia (Garcia-Barcelo et al 2008, de Graaff and Kozin 2009). Acronym VACTERL represents a non-random association of congenital anomalies that include Vertebral defects, Anal atresia, Cardiovascular anomalies, Tracheoesophageal fistula, Renal anomalies and Limb Defects. Aetiology of VACTERL association still remains largely unknown (Kim et al 2001, Keckler et al 2007, Aguinaga et al 2010, Solomon 2011, Ngan et al 2013). Definition of VACTERL typically relies on the existence of at least three malformations of the VACTERL association (Rittler et al 1996, Solomon 2011). The risk of neonatal death is highest in cases with amelia followed by radial ray defects (Källen et al 1984, Froster and Baird 1992).

2.6. Risk factors and inheritance

Several genetic disorders and a few environmental factors are known to cause upper limb anomalies (Carli et al 2013). Rogala and co-workers (1974) stated that all reduction

defects appeared to be sporadic. With the progress of molecular medicine, a genetic background has been found in an increasing proportion, up to 17% (Evans et al 1994) and 31% (Carli et al 2013), of upper limb defects. For example, the true cleft hand is usually inherited as an autosomal dominant trait (Flatt 1994a). Nowadays, genetic counselling has become a routine part of diagnostics in upper limb defects.

Potent human teratogen thalidomide has been discussed earlier. There is increased incidence of congenital anomalies, including RRD, in new-borns of mothers suffering from epilepsy (Clayton-Smith and Donnai 1995). This may be due both the occurrence of seizures leading to hypoxia during pregnancy and teratogenic effects of anticonvulsant drugs. Valproate is a potent human teratogen causing Fetal Valproate Syndrome (FVS) (Clayton-Smith and Donnai 1995).

A young maternal age (Bower et al 1993, Werler et al 2003) and living at high altitudes (Orioli et al 2003) are both associated with constriction band syndrome.

Assisted reproductive technology (ART) is associated with a 30-40% increase in the risk of birth defects (Hansen et al 2005). Chorionic villus sampling (CVS) is associated with an increase in terminal transverse defects and CBS-type defects (Golden et al 2003).

2.7. Diagnosis and management

In spite of the success of routine antenatal sonographic screening, the sensitivity rate of isolated limb defects has remained at 25% (Stoll et al 2000) and 31% (Gray et al 2013), whereas specificity is as high as 70% in longitudinal defects (Pajkrt et al 2012).

The precise classification of limb defects needs expertise. A thorough clinical examination, radiographic studies including x-ray pictures (thorax, spine), a renal ultrasound, and echocardiogram and hematologic studies should be done to screen for associated conditions. Genetic counselling of the family should be considered.

2.7.1. Surgical treatment

The first functional goal of surgery is to provide the ability to control the placing of the hand in space. Secondly, the hand needs good skin cover with adequate sensibility. The third aim is to give satisfactory power grasp and precision handling. The ideal objective would be to provide a hand that is normal in both function and appearance (Flatt 1994f). Surgical techniques are summarized in Table7.

Surgical reconstruction is not recommended for digits that have failed to develop metacarpals, with the exception of the thumb (James and Durkin 1998). Most surgeons recommend reconstructive surgery for a child with bilateral aphalangia (James and

Durkin 1998). It should be taken into account that general function in children with unilateral below elbow deficiency is within the normal range (James et al 2006).

In timing of surgery associated anomalies must be considered. Steven Bates (2009) recommends completing most of the surgeries before the age of 4, or at least before the child begins school.

After operations on young children, surgeons should not take all the credit for the observed improvements in functional dexterity, since they may also be at least partly due to the natural development of skills and maturation of the child (James and Durkin 1998). The follow-up results should be compared with normative values of normal children of the respective age (Gogola et al 2013).

Table 7. Summary of surgical techniques used in correction of upper limb defects.

Radialisation (or centralisation)
Indication: Radial club hand
Technique: Preoperative distraction with an external fixator, fixation of ulna under radial carpal bones, along the axis with index finger metacarpal with a K-wire
Contraindications: Children with stiff elbows, older patients who have adapted to their deformity, and children with severe associated anomalies significantly decreasing life expectancy (Flatt 1994b, Buck-Gramcko 2002, Bates et al 2009)
Considerations: The mean focus of this procedure is to correct the angulation of the wrist. However, in radial longitudinal deficiency, the total range of motion of digits and wrist may be more important to the child (Ekblom et al 2013).
Vascularised Joint Transfer
Indications: Radial club hand
Technique: Preoperative distraction, maintenance of correction with a vascularised MTP II joint transfer, thus forming a Y-shaped ulna and providing radial half of the wrist with a mobile joint (Vilkki 1998)
Outcome: A demanding procedure with over 50% complication rate (Bauer et al 2013) and steep learning curve for the surgeon (Vilkki 1998)
Syndactyly separation and web space widening
Indications: Symbrachydactyly, CBS, cleft hand, ulnar ray deficiency, thumb hypoplasia
Technique: Numerous skin flap techniques. The optimum gain in length with the least tension on the flaps is provided by four-flap Z-plasty (Flatt 1994h)
Outcome: Syndactyly release enhances function and appearance. Surgical treatment of the narrowed thumb web is functionally important (Manske and Oberg 2009, James and Durkin 1998, Buck-Gramcko 2002)
Pollicisation
Indications: Congenital hypoplasia of the thumb with absence or instability of the CMC joint
Technique: Index finger is transferred to thumb position
Outcome: Good range of movement, power, appearance, and sensation (Flatt 1994d, Clark et al 1998, Kozin 2012)

Tendon transfer (opponens plasty)
Indications: Type II (-IIIA) thumb hypoplasia
Technique: Transposition of either FDS IV tendon or abductor digiti minimi muscle (Huber transfer) to restore opposition, stabilization of the MCP I joint. Index finger extensor can be used to restore extension and FDS III for flexion
Outcome: Opponens plasty improves pinch power (Buck-Gramcko 2002, Bates et al 2009)

Toe to hand transfer
History: The first successful microsurgical toe-to-hand-transfer to reconstruct a congenital anomaly was done in 1978 (O'Brien et al 1978).
Indications: Adactylous hand, absent thumb, symbrachydactyly, CBS, transverse deficiency of the thumb
Technique: Second toe (or great toe) is microsurgically transferred to the hand
Outcome: Improvement in the use of the defective extremity, linear growth observed (Lister 1994, Vilkki 1995, Bates et al 2009, Jones and Kaplan 2013)

Free phalangeal transfer
Indications: Adactylous hand, symbrachydactyly
Technique: Proximal phalanx of a toe is transferred to the hand and attached either on the top of a metacarpal or a hypoplastic proximal phalanx
Problems: Resorption, growth problems, stiffness, foot problems (James and Durkin 1998, Buck-Gramcko 2002, Bates et al 2009)

Correction/rotational osteotomy
Indications: Cleft hand, correction of bowed ulna in radial club hand, 1st metacarpal rotational osteotomy and radial osteotomy in ulnar ray deficiency
Technique: In cleft hand transposition of the second ray to the position of 3rd ray (Miura and Komada1979, Ogino 1990)
Outcome: Usually good (Buck-Gramcko 2002, Bates et al 2009)

Arthrodesis
Indication: Severe and fixed radial club hand, type II-III thumb hypoplasia
Technique: Ulno-carpal arthrodesis, MCP-desis (Buck-Gramcko 2002)

Distraction lengthening (and one-stage elongation)
Indication: Symbrachydactyly, ulnar ray deficiency, RRD, brachymetacarpia
Technique: Lengthening with external fixator (Buck-Gramcko 2002, Kato et al 2002, Matsuno et al 2004, Bozan et al 2006) or one-stage elongation with iliac bone grafting (Saito et al 2001)
Outcome: Lengthening is found to disturb the remaining growth in a radial club hand (Bauer et al 2013)

Amputation
Indication: Rudimentary digits or digital parts, floating thumb
Technique: Removal (Flatt 1994e, Bates 2009)

Direct closure of constriction rings
History: Former technique was Z-plasty for decades (Patterson 1969)
Indication: CBS
Technique: Simple excision of the constriction ring, direct closure, two-stage approach
Outcome: Good aesthetic result with no scar contraction in follow-up (Choulakian and Williams 2008)

Anlage excision
Anlage excision in longitudinal deficiency is no longer recommended because of questionable functional benefit (Cole and Manske 1997)

2.8. Hospital admissions of children with upper limb defects

The burden of hospital care among these children, specifically in terms of the number of admissions and total time spent in hospital, is currently unknown.

3. AIMS OF THE PRESENT STUDY

The purpose of this thesis was to calculate the birth prevalence of upper limb defects in Finland, to classify upper limb defects in the FRM in a manner that enables comparison with other studies, to clarify associated anomalies and special features of certain upper limb defects, and to review hospital admissions and surgical treatment of these patients.

The specific aims were:

1. To evaluate birth prevalence, mortality, and associated anomalies (**1**)
2. To determine the special features of RRD (**2**)
3. To determine the special features of CBS (**3**)
4. To summarize the various types of hospital admissions and surgeries of children with upper limb defects (**4**)

4. MATERIALS AND METHODS

4.1. Study design

This study consists of four original publications (**1**, **2**, **3**, **4**). Data were obtained from population-based longitudinal registers maintained by the National Institute of Health and Welfare in Finland (THL): publications **1**, **2** and **3** were based on records of the Finnish Register of Congenital Malformations (FRM) and data in publication **4** was obtained from the Finnish Hospital Discharge Register (FHDR).

4.2. Data sources

Individuals in the FRM and FHDR are coded using the Finnish personal identity code (PIC), which was introduced in the 1960s. The Finnish PIC consists of the date of birth (DDMMYY), a separator digit indicating the century of the birth (+, 19th; -, 20th; A, 21st), a running number for persons with the same date of birth (odd, male; even, female), and a check digit calculated with a modulo-31 algorithm (Population Register Centre web page)

4.2.1. The Finnish Register of Congenital Malformations (FRM)

The register contains national-level data on congenital chromosomal and structural anomalies, detected or suspected in stillborn and live born infants and foetuses with a gestational age of ≥ 22 weeks or birth weight of ≥500g, and in foetuses from elective terminations of pregnancy for severe foetal anomaly and from spontaneous abortions. Data on about 5000 new cases with congenital anomalies is annually reported to the register (Register description, available at thl- web-page)

Cases with at least one detected major congenital anomaly are included. Minor anomalies are excluded from the statistics according to the exclusion list of the European Surveillance of Congenital Anomalies (EUROCAT) (eurocat web page, Greenlees et al 2011). The FRM collects nationwide data from multiple sources, including hospitals, health-care professionals, and cytogenetic laboratories. It also obtains data on cases with malformations from the Medical Birth Register, the Register on Induced Abortions, the FHDR and the Register of Visual Impairments, which are all nationwide registers, maintained by THL, and from the Cause of Death Register, maintained by Statistics Finland. The children born with malformations are followed up to the age of two years by the FRM. Data on foetal anomalies diagnosed prenatally and confirmed after elective

termination of pregnancy are received from hospitals and from the National Supervisory Authority for Welfare and Health (Valvira); this authority is responsible for nationally granting permissions to all terminations of pregnancy for severe foetal malformations or diseases, up to 24 completed gestational weeks.

The database and the data compilation method were transformed into an electronic form in 1993. All the data is double-checked by a medical geneticist who is in charge of the register. This medical geneticist contacts the maternity and children's hospitals and confirms the data given in the "Declaration of malformation"-forms and the data of the diagnosis listings obtained from the FHDR and other previously mentioned data sources. Copies of the patient's hospital records, radiographs, photographs, specialist consultations (radiologist, hand surgeon etc.) are requested as deemed necessary.

Information on both the child and the mother is entered into the register. This includes the date of birth (and date of death when relevant), gender, birth weight, length of the pregnancy, type of birth (live born, stillborn, spontaneous abortion or legal abortion), karyotype of the child if tested either during pregnancy or after delivery, and all of the infant's diagnoses.

The main purpose of the FRM is to monitor the prevalence and type of congenital anomalies for early identification of any new teratologic factors. The diagnoses of cases in the register follow the 9th revision of the International Classification of Diseases (ICD-9) of the World Health Organization (WHO). The country-coverage of the Finnish Register of Congenital Malformations is 100% (Greenlees 2011).

4.2.2. The Finnish Hospital Discharge Register (FHDR)

The FHDR has contained nationwide linkable data on all inpatient hospital discharges with a personal identification code since 1969 (Dolk et al 2010). The therapeutic procedures from 1983 to 1996 were classified according to the National League of Hospitals classification, and from 1996 onwards according to Nordic Classification of Surgical Procedures (NCSP) (julkari web page).

4.3. Data collection

Publications **1**, **2** and **3** are based on records of the Finnish Register of Congenital Malformations between January the 1st1993 and December the 31st2005. All births with ICD-9 codes 754XX (Maleformationes systematis musculosceletalis), 755XX (Maleformationes extremitatum aliae) and 756XX (Maleformationes systematis musculosceletalis aliae) were included for evaluation. Spontaneous abortions and foetuses from elective terminations of pregnancy were excluded because of difficulties

in classification due to scarce case information. A total of 430 cases with defects in the upper limbs (**1**,**2**,**3**) were gathered from the registry. The cases were re-evaluated by an orthopaedic surgeon and a medical geneticist. In 52 cases the data was supplemented from the referring hospital. Among these, 11 cases had no upper limb deficiency whatsoever, leaving a total of 419 cases for further analysis, and a rate of 97 % for the positive predictive value (PPV) of the FRM. Patient records, x-ray pictures/radiologist's reports on x-ray pictures, family history, and clinical photographs, when available, were reviewed to allow accurate classification of the limb defect using the IFSSH-classification (Table 2). Difficulties were encountered when trying to differentiate between cleft hand, brachysyndactyly, and transverse arrest. In these cases we followed principles introduced in 2006 by Tonkin. The birth and livebirth prevalences, sex and side distribution, frequency of associated anomalies, as well as the proportion of perinatal and infant deaths according to the different subtypes were calculated.

Out of the 419 cases with an upper limb defect, there were 25 stillbirths, 30 new-born deaths at the maternity hospital and 2 elective terminations (2 foetuses with antenatal diagnosis of anomalies). These were all excluded, leaving a total of 362 live births (between January the 1st1993 and December the 31st2005) for the final FHDR analysis on hospital care of congenital upper limb defects **(4).**

The number of hospital admissions (excluding the birth episode), days spent in hospital, number and type of surgical operations from January 1st 1993 until December 31st 2009 were summarized. The average follow up time was 10.2 years (4-17 years).

The general paediatric (0-17 years) population, served as a control group. The size of the control population, number of hospital admissions, and days in hospital from January 1st 1993 to December 31st 2009 were obtained from the FHDR.

4.4. Statistical analyses

Statistics were calculated by the FREQ procedure using Chi-square with the SAS System for Windows, version 9.3. P-values below 0.05 were considered statistically significant.

4.5. Ethical considerations

This register-based study involved data from the Finnish Register of Congenital Malformations and Finnish Hospital Discharge Register. According to Finnish legislation, informed consent was not required, as the study objects were not contacted. Permission to use the register data in this study was granted by the Ministry of Social Affairs and Health (#111/07/1998), and approved by the data protection authority.

5. RESULTS

5.1. Birth prevalence, mortality and associated anomalies (1,2)

Upper limb defects were observed in 417 of 753 342 consecutive births and in 392 of 750 461 live births in Finland during 1993-2005. Birth prevalence was 5.5 per 10 000 births and 5.2 per 10 000 live births. The condition was bilateral in 41%, left-sided in 33% and right-sided in 23% of the cases. Information on the affected side was unavailable in 15 cases. The anomaly was associated with multiple anomalies or a known syndrome in 60% of the cases. Table 8.

There were 25 stillbirths, 33 deaths during the first seven days of life, and 20 additional deaths during the first year of life. Perinatal mortality was 139 per 1000 births and infant mortality 135 per 1000 live births compared with an overall perinatal mortality of < 5 per 1000 births and infant mortality of 3.7 per 1000 live births in Finland during 1993-2005 (www.childmortality.org).

Nine of these 417 children (2%) had relatives with known upper limb deficiency. In seven cases, the relative had the same type of defect as the index patient. Of these seven

Table 8. Upper limb deficiencies. Titles of the columns (IA-VI) refer to IFFSH-classification described in Table 2.

	Total **417**		IA **1**	IA1 **5**	**IA2 6**	**IA3 4**	**IA4 12**	**IA5 11**	**IA7 5**
male	233	56%		4	5	2	5	4	3
female	184	44%	1	1	1	2	7	7	2
right	94	23%		2	1	1	4	3	1
left	139	33%			2		6	6	3
bilateral	169	41%		3	2	3	1	1	1
unknown	15	4%	1		1	1	1	1	
isolated	167	40%	1		3	1	10	9	5
syndrome	104	25%				2	1		
multiple anomalies	146	35%		5	3	1	1	2	
stillbirths	25	6%		2		2			
died <7d	33	8%		3					
died 7d-1y	20	5%							

Table 9. Birth prevalence per 10 000 live births and infant mortality (n=417).

Classification	**N**
IA1-IA8 Transverse arrest	58
IB1 Radial ray deficiency	138
IB2 Ulnar ray deficiency	33
IB3 Central ray deficiency	41
IB4 Phocomelia	5
V1-4 Undergrowth	91
VI Constriction band sdr with amputation of part of the upper extremity	51

cases, three were brachysyndactyly, two were transverse deficiencies, and two were radial ray deficiencies. The birth prevalence of different subgroups, perinatal, and infant mortality are summarized in Table 9.

Subgroups of transverse arrest (IA1-IA8) comprised 14% of cases. An isolated anomaly was found in 41 cases, multiple anomalies in 14 and a known syndrome in 3. Three of the 14 children with multiple anomalies were stillborn and three died during the first day of life. Two children had relatives with the same type of upper limb deficiency.

Ulnar ray defects (IB2) comprised 8% of cases. An isolated anomaly was found in 19 cases, multiple anomalies in 10, and a known syndrome in four children. No infant mortality occurred and no relatives had an upper limb defect in children with ulnar ray defects.

Central ray deficiency (IB3) comprised 10% of the cases. An isolated anomaly was found in 27 cases, multiple anomalies in nine, and a known syndrome in five children. There were two stillbirths. No relatives with upper limb defects were recorded.

Some type of bilateral phocomelia (IB4) was found in five (<2%) cases. Of these five children three had a known syndrome and two a suspected syndrome (with multiple anomalies). There was no family history of upper limb defects.

IA8	IB1	IB2	IB3	IB4	V1	V2	V3	V4	V4a	V4b	VI
14	**138**	**33**	**41**	**5**	**15**	**3**	**4**	**1**	**21**	**47**	**51**
7	80	20	23	2	9	3	2		13	21	30
7	58	13	18	3	6	0	2	1	8	26	21
1	29	10	4		6	1	1	1	7	7	16
10	24	14	18		5	1	1		8	18	23
3	81	8	18	5	4	1			5	21	12
	4	1	1				2		1	1	
12	11	19	27		8	2	2		14	23	19
	68	4	5	3	3		2		1	15	
2	59	10	9	2	4	1		1	6	9	32
	15		2							1	4
	25			1	1					1	3
	18				1					1	

Birth prevalence per 10 000 live births	Infant mortality per 1000	Perinatal mortality per 1000
0.77 (1: 13 000)	55(3/54)	121(7/58)
1.64 (1: 6100)	350(43/123)	217(30/138)
0.44 (1: 22 800)	0/33	0/33
0.52 (1:19 200)	0/39	49(2/41)
0.07 (1: 143 000)	167 (1/6)	167(1/6)
1.19 (1: 8400)	44 (4/90)	33(3/91)
0.62 (1: 16 100)	64 (3/47)	137(7/51)

Undergrowth (subgroups V1-4) comprised 22% of the cases. An isolated anomaly was found in 49 cases, multiple anomalies in 21, and a known syndrome in 21 of these 91 cases. No family history was present. The largest subgroup of undergrowth was brachydactyly which was associated with a known syndrome in 15 out of 47 cases. Symbrachydactyly, on the other hand, was associated with a known syndrome in only one out of the 21 cases.

5.2. Special features of RRD (2)

Twenty-five of the 138 infants with RRD died within the first week, and additionally 18 children died during the first year. There were 15 stillbirths. Perinatal mortality was 29 % and infant mortality 35 %. The high mortality was associated with trisomy 18, and other severe major congenital anomalies.

We identified 11 isolated cases of RRD. Only one of these had involvement of the radius, others were limited to the thumb. All isolated cases were unilateral. In the remaining 127 cases, RRD was part of a known syndrome (23% trisomy 18) or associated with multiple anomalies (20% VACTERL association).

5.3. Special features of CBS (3)

Sixteen of the 51 infants with upper limb CBS were born preterm (before the 37th week of gestation). Eight children were small for their gestational age (SGA) when referred to foetal growth curves in Finland (Pihkala et al 1989). Birth weight was low in fourteen infants (LBW, <2500g), very low in two (VLBW, <1500g) and extremely low in four (ELBW, <1000g) respectively. The distribution of maternal age was the same as with the normal population.

In nineteen cases, the defect was isolated and in one extremity only. In 15 of the 51 cases associated anomalies were found: club foot 7, cleft palate 3, congenital heart defect 3 and miscellaneous 10.

There was a clear distinction between the two phenotypes, children with and without associated anomalies: children with associated anomalies had shorter gestation, lower birth weight, and higher mortality.

5.4. Hospital admissions (4)

During the study period the general paediatric population (n=1 126 353) had an annual total of 126 243 (range 112 325-140 981) hospital admissions, and 563 245 (range 501

502-594 610) hospital days. The mean number was 0.09 admissions and 0.4 hospital days per child per year.

For the 362 children with an upper limb defect discharged from the maternity hospital, the number of hospital admissions was 3726 and the days spent in hospital 19 522. Annually the mean number of hospital admissions was one (range 0-36 admissions), and the number of days spent in hospital 5.3 (range 0-150 days). The length of a hospital treatment varied between 1 and 388 days per admission. The number of hospital admissions was 11-fold in these 362 patients with an upper limb defect as compared with the general population ($P<0.001$, crude rate difference 0.92, crude rate ratio 11.2) and the time spent in hospital 13-fold ($P<0.001$, crude rate difference 4.88, crude rate ratio 13.2). Table 10.

Table 10. Hospital admissions by subgroup.

	Children with upper limb defect	**Radial ray defect**	**Ulnar ray defect**	**No additional anomalies**	**Additional anomalies**	**Children in Finland**
population size	362	98	33	167	195	1 121 539
had hospital admission(s)	87%	100%	79%	78%	100%	
admissions/year/child	1.01	2.8	0.6	0.4	1.5	0.09
hospital days/year	5.28	15.0	3.5	1.6	8.6	0.4

Surgical admissions (4)

The majority (72%) of the 362 children with upper limb defects had surgical hospital admissions. Altogether 1535 surgical procedures were done, on average four procedures per child (range 0-45). Orthopaedic operations were the most common accounting for one third of all procedures. Most of these orthopaedic procedures (326/512) were directed to the upper limb and 295 to the hand. Table 11. Altogether 135 children (37%) had surgery directed to the hand. The mean number of hand surgical procedures per child was 1 (range 0 to 9).

Nearly half (44%) of the operations were performed in 1-4 year old children, 22% within the first year of life, 20% between 4-7 years and 13% between 7-16 years. The mean age at which the operation was performed by different specialities is presented in Table 12. The most common distinct hand surgical procedures were done before the age of four in most cases: syndactyly separation at median age of 18 months (range 1month to 9years), pollicisation at median age of 42 months (range 14 months to 7years) and toe to hand transfers at median age of 39 months (range 18 months to 6 years).

Table 11. Hand surgery.

Total	**295**
Complicated hand anomaly correction	75
Implant removal	56
Syndactyly separation	49
Pollicisation	38
Toe to hand transfer	18
Finger anomaly correction	18
Amputations and stump revisions	10
Muscle and tendon surgery	9
Fracture surgery	4
Arthrodesis	3
Osteotomies	3
Miscellaneous	12

Table 12. Timing of surgery.

	Median	**Range**
All surgery	2y7m (31m)	0-15y4m
Orthopaedics	3y3m (39m)	13d-14y6m
Pediatric surgery	2y5m (29m)	0-15y3m
Dental	3y5m (41m)	3m-14y3m
ENT	4y4m (52m)	47d-15y4m
Neurosurgery	1y8m (20m)	0-10y9m

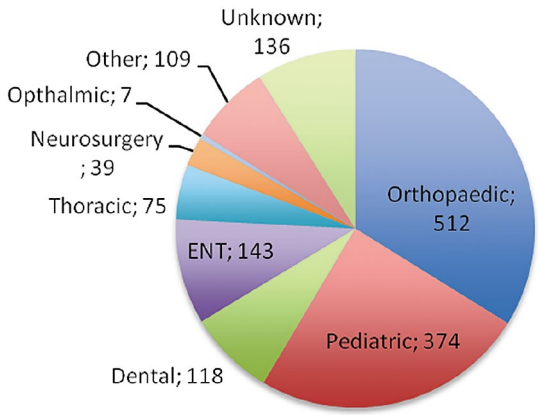

Figure 1. Surgical hospital admissions.

Non-surgical hospital admissions

Altogether 60% (2191/3663) of hospital admissions were non-surgical. The most common reason (32%) for these admissions was the congenital upper limb defect

itself or an associated congenital anomaly. Gastroenterological problems (20%) and respiratory tract conditions (13%) were the other most common reasons for non-surgical admissions. Figure 2

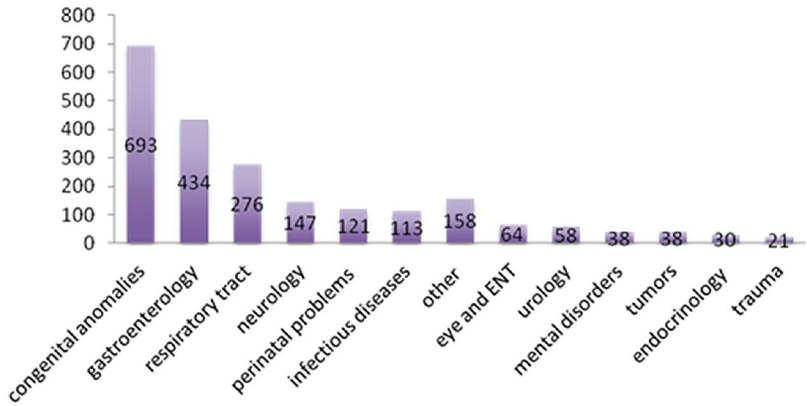

Figure 2. Non-surgical hospital admissions.

Children with no admissions

Forty-one children with an upper limb defect (11%) all without associated anomalies had no hospital admissions. The most common diagnoses in these children without registered hospital treatment were absent ulnar finger(s), Poland's syndrome, terminal defects of fingers and constriction band syndrome.

Subgroup analysis

130 of the 167 children with an isolated upper limb defect had hospital admissions (mean 0.4 hospital admissions and 1.6 hospital days annually). Table 10

Twenty-six of the 33 infants with ulnar ray defect had hospital admissions (mean 0.6 admissions and 3.5 hospital days annually). The seven children with an ulnar ray defect without registered hospital treatment did not have associated anomalies.

All 195 children with a syndrome or multiple organ anomalies and all 98 children with RRD had hospital admissions (annually mean 1.5 and 2.8 admissions, 8.6 and 15 hospital days respectively). Table 10

6. DISCUSSION

Congenital anomalies have been reported to cause 6.7% of deaths in the neonatal period in the world (WHO, GBD-report 2004). Congenital anomalies are also a significant component of the global burden of disease (GBD) among children, accounting for 25 million disability-adjusted life years (DALYs) worldwide (www.who.int).

There are only a few true population based studies on birth prevalence of upper limb defects. These defects are known to be associated with other anomalies and it can, therefore, be assumed that the need of hospital care is significant (Froster and Baird 1992).

Attitudes towards children with limb defects has changed with time. In 1990, the United Nations Convention on the Rights of the Child, Article 23, focused on disabled children, and stated that a disabled child has the same rights as other children and should enjoy a full and decent life and receive special care and assistance free of charge (Unicef web page).

The purpose of this thesis was to evaluate the birth prevalence and mortality of children with upper limb defects in Finland 1993-2005, to classify upper limb defects using an internationally widely accepted classification system that enables comparison with other studies, to examine possible associated anomalies, to explore special features of RRD and CBS, and to investigate hospital treatment of children with upper limb defects 1993-2009 in a population based manner, using the FRM and the FHDR. According to several studies, the coverage and data quality of the FRM is good (Leoncini et al 2010, Greenlees et al 2011). The validity of the FHDR was examined in 2012, and more than 95% of discharges could be identified in the register (Sund 2012). The positive predictive value (PPV) for common diagnoses varies between 75 and 99%. Completeness and accuracy in the register varies from satisfactory to very good (Sund 2012).

6.1. Main results and comparison with previous findings

Birth prevalence of upper limb defects in this study including syndromic cases was 5.5 per 10 000 births and 5.2 per 10 000 live births. In previous studies, the birth prevalence of upper limb defects was 2.24-6.7 per 10 000 (Birch-Jensen 1949, Rogala et al 1974, Aro et al 1982, Källen et al 1984, Froster-Iskenius and Baird 1989, Froster-Iskenius and Baird 1990, Froster and Baird 1992, Vasluian et al 2013). Comparison with previous studies is interfered by divergent study populations and different inclusion criteria. The lowest birth prevalence (2.24) is based on Danish hospital data (Birch-Jensen 1949)

and the highest (6.7) on the population of the City of Edinburgh, Great Britain (Rogala et al 1974). In a Swedish population-based register study, a birth prevalence of 4.0 per 10 000 was reported excluding syndromic cases (Källen et al 1984). From a previous Finnish study, also excluding syndromic cases, a birth prevalence of 4.0 per 10 000 can be calculated (Aro et al 1982). The slightly lower figures compared with our study are probably due to the inclusion of syndromic cases in our study. Our higher prevalence figures most likely also reflect improved detection and reporting of upper limb defects and an improved computer-based register. Detailed comparison with other studies is hindered by the different classification systems used. We decided to use the internationally accepted IFSSH classification, to allow future researchers to compare their results with our figures. Classification of hand anomalies using the IFSSH classification has been reported as straightforward in 86% of cases (De Smet et al 1997). The problems we encountered with the IFSSH classification were similar to those reported earlier (De Smet et al 1997, Cheng et al 1987, Tonkin 2006).

Perinatal mortality was 14.1% in the present study, which is practically the same as the 15.9% reported from Sweden (Källen et al 1984). Clear differences emerged between subgroups according to the IFSSH classification. Stillbirths and infant deaths accumulated in the RRD-group. The proportion of perinatal deaths in the RRD group was 29%, and infant deaths 35%. The high mortality among children with RRD was mostly associated with trisomy 18 and other severe major congenital anomalies.

The majority of children in our study (60%) had multiple anomalies or a known syndrome. Aro et al 1982 excluded known syndromes and reported 27% additional anomalies. Källen and co-workers also excluded known syndromes, but included stillbirths, and reported that over 30% of infants had non-limb malformations.

Only 2% of all children in this study had relatives with limb defects. Affected relatives may be underreported to the registry. Based on our subject pool, upper limb deficiencies appear to be sporadic, with no strong inheritance. This finding is supported by earlier studies (Birch-Jensen 1949, Rogala et al 1974, Froster and Baird 1992).

The largest subgroup in our study was RRD, the birth prevalence being 1.27 per 10 000 live births. In previous studies, the birth prevalence of RRD has been reported to be 0.38-0.86 per 10 000 live births (Aro et al 1982, Källen et al 1984, Froster and Baird 1992, Goldfarb et al 2006). Our higher birth prevalence is probably due to inclusion of stillbirths and infants with known syndromes. Excluding stillbirths and syndromic cases, the live birth prevalence of RRD in this study was 0.73 per 10 000.

Additional anomalies were found in 87% of our RRD-cases, which is in good agreement with a previously published population based study from Canada reporting additional malformations in 89% of RRD cases (Froster and Baird 1992). Only one of the eleven

infants that had isolated RRD in this study had radius aplasia (ten had thumb hypoplasia). All other 127 infants with RRD had additional anomalies. Previous reports have also indicated a strong association of RRDs with other major congenital anomalies, isolated RRDs accounting for only 8–30% of cases (Froster and Baird 1992, Goldfarb et al 2006, de Graaff and Kozin 2009).

Robert and co-workers characterized the epidemiology of preaxial limb malformations and observed an association of cardiac defects with upper limb malformations, especially with reduction defects (Robert et al 1997). In our study, a strong association between heart anomalies and RRDs was also found. Altogether 8.7% of RRD cases presented with defects limited to the radial ray, usually the thumb, and heart. Only four cases were primarily diagnosed with Holt-Oram syndrome, which is the most common heart-limb syndrome, with mutations in the TBX5 transcription factor present in 35 per cent of cases (Basson et al 1997, Li et al 1997). The phenotypes vary in both heart and limb anomalies (Basson et al 1995). It is possible that the clinical spectrum of Holt-Oram syndrome is wider than presently appreciated and that a more thorough genetic evaluation of the affected subjects could reveal underlying TBX5 mutations in some of the cases. The development of the heart and the limbs are dependent on common regulatory mechanisms, partially explaining their association (Wilson 1998).

We identified 51 children with upper limb CBS. We found no association of CBS with known syndromes, but in 29% of cases the CBS was associated with other major anomalies. We assume that CBS may well be several syndromes banded together as a result of a lack of understanding. Isolated cases are clearly the result of an extrinsic insult (Kiehn et al 2007), while others may be due to intrinsic defects. Thomas Patterson (1961) from England reported other congenital malformations than constriction bands in 27%, with the most common malformation being a clubfoot (Patterson 1961). Light and Ogden (1993) reported a 31% incidence of clubfoot in Chicago (USA), while our material revealed clubfoot deformity in 14% of the children with upper limb CBS.

We found phocomelia only in conjunction with a known or suspected syndrome. This indicates that without an exogenous teratogen, like thalidomide, the incidence of phocomelia in a population is near zero if children with a known syndrome, like Roberts syndrome, Nager syndrome and Cornelia de Lange syndrome, are excluded. This is in accordance with the Swedish findings (Källen et al 1984).

The number of hospital admissions of children with congenital upper limb defect was 11-fold and the time spent in hospital 13-fold as compared with the paediatric population. Population based studies focusing on hospital care of children with upper limb defects do not exist. A study in England analysed hospital admissions in the first two years of life among children with cleft lip and/or palate. Those who had additional

anomalies had a 5-fold number of hospital admissions and 11-fold number of days spent in hospital compared with all children (Fitzsimons et al 2013). A study from Western Australia clarifies the number of hospital admissions of all children with birth defects and they found 3-fold numbers in the age group up to one year compared with the normal child population (Colvin and Bower 2009). It seems that upper limb defects lead to a considerable amount of hospital care compared not only with general population, but also with other congenital anomalies.

6.2. Methodological considerations

Results of this study are minimum estimates, as some under-ascertainment always exists in a registry. Terminated pregnancies were not included and the presented birth prevalence figures may thus not be comparable with countries where prenatal screening and elective terminations differ significantly from Finland.

The rate of operative treatment calculated from the register data is also an underestimate, because the follow up time in study **4** was only four years in some patients. Furthermore, a greater difference in hospital care between children with upper limb defects and healthy children would most probably have been found if a direct comparison could have been made.

6.3. Clinical implications

This study gives detailed population-based information about upper limb defects in terms of birth prevalence, mortality, and associated anomalies. Upper limb defects, especially RRDs, can be regarded as isolated anomalies only after thorough assessment of the various organ systems in an affected infant. Treatment of these children requires teamwork by many specialities. This information is valuable in prenatal diagnostics, family counselling, and planning of health care services.

6.4. Implications for future research

The Finnish medical registers can be used for further studies (Gissler and Haukka 2004). A project to assess possible risk factors of limb defects by collecting information on medication used during pregnancy based on information from Social Insurance Institution has been initiated. We are also planning to investigate surveillance and participation of these children using registers of social benefits, of social assistance, of child welfare, and discharge registers of social institutions.

7. SUMMARY AND CONCLUSIONS

Around thirty-five infants with an upper limb defect are registered in Finland annually. Over half of the infants with an upper limb defect and all of the infants with a radial ray defect have other congenital malformations or their upper limb defect is part of a known syndrome. Nearly one third of the children with CBS have other major anomalies suggesting different aetiologies inside the group. Children with associated malformations and syndromic cases have an increased number of hospital admissions and their mortality rates are high.

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