Archives of the Balkan Medical Union
vol. 58, no. 2, pp. 99-106
June 2023
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ORIGINAL PAPER

A CLINICAL-EPIDEMIOLOGICAL STUDY OF A COHORT OF 105 PATIENTS WITH CONGENITAL LIMB ABNORMALITIES

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Received 30th March 2023, Accepted 04th May 2023
https://doi.org/10.31688/ABMU.2023.58.2.02

Abstract

Introduction. Limb abnormalities are a heterogeneous group of congenital malformations defined as an incomplete development of a fetus limb during pregnancy. Limb abnormalities are spread worldwide, also in our country, with potentially severe complications in terms of patient functionality and aesthetic appearance. In Romania, there is not enough data regarding the impact of these abnormalities.
The objectives of this study were to analyze the epidemiological, clinical, and genetic data and to evaluate the psychosocial consequences of patients with limb abnormalities in Bihor County, Romania.
Materials and methods. We performed a retrospective study on a cohort of 105 patients with congenital limb malformations (CLM), selected using the database of the Bihor Regional Center for Medical Genetics.
Results. Most patients (48) presented only upper limb anomalies. Twenty-nine patients had lower limb anomalies and 28 suffered from both upper and lower limb anomalies. Polydactyly was the most common upper limb anomaly, and complete syndactyly was found in only one case. Syndactyly was the most common lower limb anomaly. There was only one case of phocomelia. Thirty-three cases were diagnosed in the context of a genetic syndrome.

Résumé

Étude clinico-épidémiologique d'une cohorte de 105 patients avec des anomalies congénitales des membres

Introduction. Les anomalies des membres sont un groupe hétérogène de malformations congénitales définies comme le développement incomplet d'un membre fœtal pendant la grossesse. Les malformations des membres représentent une pathologie répandue à travers le monde, y compris notre pays, avec des potentielles complications graves en ce qui concerne la fonctionnalité du patient et l'aspect esthétique. En Roumanie, il n'y a pas assez de données sur l'impact de ces malformations.
Les objectifs de cette étude étaient d'analyser les données épidémiologiques, cliniques et génétiques et d'évaluer les conséquences psychosociales des anomalies des membres chez les patients du Bihor, Roumanie.
Matériels et méthodes. L'étude est portée sur une cohorte de 105 patients à partir de la base de données fournie par le Centre Régional de Génétique Médicale de Bihor.
Résultats. La majorité des patients (48) ont présenté seulement des anomalies des membres supérieurs. 29 présentaient des anomalies des membres inférieurs

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Conclusions. The most commonly diagnosed cases were the upper limb anomalies. Monogenic etiology was the most frequently identified (32 cases) and polygenic was the rarest cause (3 cases).

Keywords: congenital malformation, limb, genetic anomalies.

List of abbreviations:
CLM – congenital limb malformation
EUROCAT – European Registration of Congenital Anomalies
ICD-10 – 10th International Classification of Diseases
AER – apical ectodermal ridge
FGF – fibroblast growth factor
ZPA – zone of polarizing activity
SHH – Sonic Hedgehog gene
BhRCMG – Bihor Regional Center for Medical Genetics

et 28 avaient des anomalies des membres supérieurs et inférieurs. La polydactylie était l'anomalie la plus fréquente du membre supérieur, et la syndactylie complète a été retrouvée dans un seul cas. La syndactylie était l'anomalie la plus fréquente des membres inférieurs. Il n'y a eu qu'un seul cas de phocomélie. 33 cas ont été diagnostiqués dans le cadre d'un syndrome génétique.
Conclusions. Les cas les plus fréquemment diagnostiqués étaient des anomalies des membres supérieurs. L'étiologie monogénique était la plus fréquemment identifiée (32 cas), et l'étiologie polygénique était la cause la plus rare (3 cas).

Mots-clés: malformation congénitale, membres, anomalies génétiques.

Introduction

Limb abnormalities are a heterogeneous group of congenital malformations defined as an incomplete development of a foetus limb during the intrauterine life. Congenital limb malformations (CLM) are spread worldwide, also in our country, with an estimated prevalence of 7.9/10,000 live new-borns[1]. CLM can vary from minor ailments, such as syndactyly (the partial or total union of several digits), to serious malformations, such as the absence or shortening of a limb.

According to the European Registration of Congenital Anomalies (EUROCAT)[2], these are some of the most frequent congenital disorders. CLM may present a high degree of severity through their negative impact on functionality and aesthetic appearance.

Despite their high prevalence, there are few studies conducted in Romania on this topic. This article focuses on the presentation of a clinical-epidemiological study of a cohort of 105 patients with CLM of the limbs, from Bihor County, Romania. The results of this study could lead to a better diagnosis, management, and prevention of CLM, as well as raising awareness of the importance of eliminating factors that could lead to CLM.

The etiology of CLM can be attributed to determinant (genetic or teratogenic) and favouring factors (risk factors). Genetic factors can be genetic mutations in the family, for several generations, or arising *de novo*. Teratogenic factors include the pharmaceutical agents like thalidomide, warfarin, valproic acid, misoprostol, phenytoin[3]. Also, the chorionic villus sampling was identified as a risk factor[4].

Isolated congenital defects were associated with low birth weight (<2499g), premature birth, upper respiratory tract infection of the mother during the first 3 months of pregnancy, smoking, parents' level of education[5].

Embryological development of the limbs

The embryological development of the limbs occurs during weeks 4-8 from the upper and lower limbs` buds. The limb buds appear in week 4 on the ventral side of the trunk in the lower cervical and lower lumbar regions and are formed by a core of mesodermal tissue (originating in the lateral somato-pleural plate) and an ectodermal covering. The first one exerts an inductive action on the second one so that the apical ectodermal ridge (AER) is formed[6,7]. The AER itself induces the differentiation of the underlying mesodermal tissue and is responsible for growth along the proximal-distal axis (shoulders to digits) and limb differentiation; fibroblast growth factor (FGF) signaling is involved [8]. The second important region is the zone of polarizing activity (ZPA) which is at the base of the limbs and involved in the growth on the anterior-posterior axis (from digit 1 to digit 5); the ZPA belongs to the posterior mesodermal tissue and is regulated by the Sonic Hedgehog (SHH) gene[8,9]. The final region involved in the limb development process is located in the underlying ectodermal tissue, being under the control of the WNT7A signalling pathway. This ensures growth on the dorsal-ventral axis (from the back of the hand to the palm)[6,10]. For a proper development of the upper or lower limb, the coordination of these three growth axes is essential, process that takes place with

Table 1. Genetic syndromes associated with limb abnormalities.

Apparent etiology	*OMIM Numbers*	*Associated genes*
Cornelia de Lange Syndrome[11]	122470, 300590, 610759	NIPBL, SMC1A
Fanconi anemia[12]	227650	FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM
Holt-Oram Syndrome[13]	142900	TBX5
Nager acrofacial dysostosis[14]	154400	AFD1
Okihiro Syndrome[15]	607323	SALL4
Smith-Lemli-Opitz Syndrome[16]	270400	DHCR7

Legend: NIPBL – Nipped-B-like protein cohesin loading factor; SMC1A – structural maintenance of chromosomes 1A; FANCM – Fanconi anemia complementation group A-M; TBX5 – T-box transcription factor 5; AFD1 – acrofacial dysostosis 1, Nager type; SALL4 – Spalt-like transcription factor 4; DHCR7 – 7-dehydrocholesterol reductase.

the help of a large number of genes, which in turn are regulated by numerous promoters, enhancers, inhibitors and repressors.

Classification of CLM

There are several classifications of CLM, based on the affected limb and the degree of severity: multiplication, failure of separation or even failure of formation of a certain segment. According to the 10th International Classification of Diseases (ICD-10), osteoarticular congenital malformations correspond to codes Q67-Q78. These codes are used to classify also CLMs, noting that there are different codes for polydactyly and supernumerary pollex/hallux (thumb/great toe), and for complete and incomplete syndactyly, respectively, with different mechanisms of production or different therapeutic options. They include supranumerary thumbs, great toes or digits (polydactyly), syndactyly, absence of hand or foot, absence or shortening of the forearm or calf, absence of the entire limb, phocomelia, achondroplasia etc.

The clinical diagnosis is often possible by simply inspecting the affected limb. Plain radiography and ultrasonography are useful to confirm the imaging diagnosis. Monogenic causes of CLM can be identified, in certain cases, by genetic testing. Some of the conditions that can be tested are shown in Table 1.

Psychosocial consequences of CLM

CLM are associated with a significant impact on the mental state of patients and their families. Children with CLM, especially hand anomalies, compared to control groups, are at significantly higher risk of social isolation, increased anxiety and low self-esteem[17]. Moreover, the parents or guardians of these children also have frequent feelings of guilt, isolation and perceive a lack of resources to support their children[18].

The upper member is essential in terms of social integration and human interaction and is therefore extremely important for the psycho-social development of children. Unlike other malformations, those of the upper limb are generally visible to both patients and people in the entourage. It has been shown that obvious congenital conditions are commonly associated with negative body image, low self-esteem, poor quality of life, and difficulties in social interactions[19].

According to Goffman's stigma theory[20], children with congenital limb abnormalities have difficulties in integrating into society. Their disability vulnerabilities are frequently exposed and analysed because society perceives people with congenital anomalies as "others", "outside the group", without various social privileges that are normal for the "normal" group. For example, patients may be excluded from many activities for children involving the use of both limbs. Having fewer opportunities than children without malformations and feeling stigma, they internalize these limitations imposed by society through cognitions such as: "I cannot play the violin, I do not have two hands". Thus, out of the desire to integrate into the "normal" group, children with disabilities either try to hide their deficit in order not to look different or internalize the social and functional limitations that are projected on them and identify with the group of "different ones."

The objective of the study was to obtain a more accurate knowledge of the clinical, genetic, epidemiological and psychosocial impact of CLM in Bihor County, Romania. We performed an epidemiological, clinical, and genetic data analysis of a cohort of patients with CLM, selected from the period 2005-2022, and the longitudinal analysis of the psychosocial consequences of CLM.

Material and methods

We performed a retrospective study on a cohort of 105 patients with CLM, selected using the database

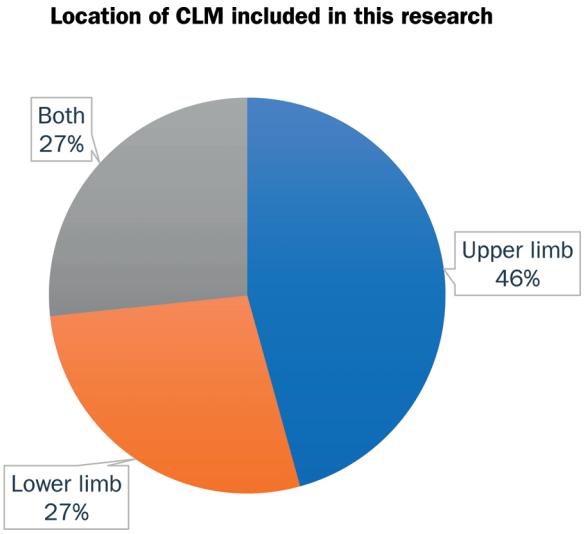


Figure 1. Locations of limb malformations

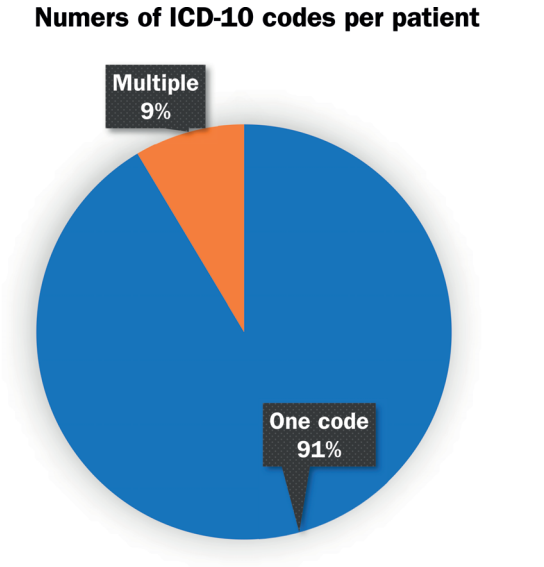


Figure 2. Proportion of isolated and associated CLM

of the Bihor Regional Centre for Medical Genetics (BhRCMG). We collected demographic data, clinical data, genetic testing results and evolution of the disease. Data from the patients' medical documents were used (CLM and genetic disease records, observation sheets, medical records, laboratory, imaging, and genetic analysis results). The study included 983 patients.

The criteria for inclusion in the study were the following: patients with a confirmed diagnosis of CLM encountered in the BhRCMG database in the period 2005-2022.

The exclusion criteria were the following: patients with uncertain diagnosis, not falling within the time frame set for the study (2005-2022).

The programs of the Office 365 package (Word, Excel) and MedCalc were used for data processing.

The patients were invited to participate in the study. Before deciding whether to participate, it was important that they understood the purpose of the study, what their participation involved, and any potential risks or benefits associated with it. They took the time to read the consent form carefully and ask questions before making any decisions.

There were no risks for the patients because their observation sheets and genetic disease records were checked, and they benefit from a re-evaluation. The confidentiality related to their identity was respected.

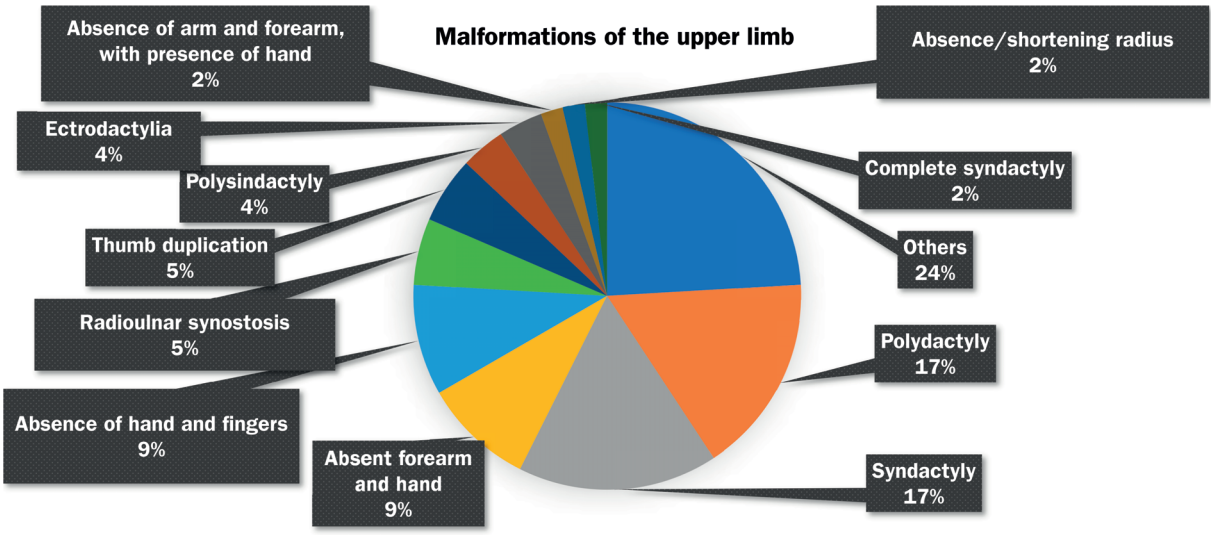


Figure 3. Malformations of the upper limb

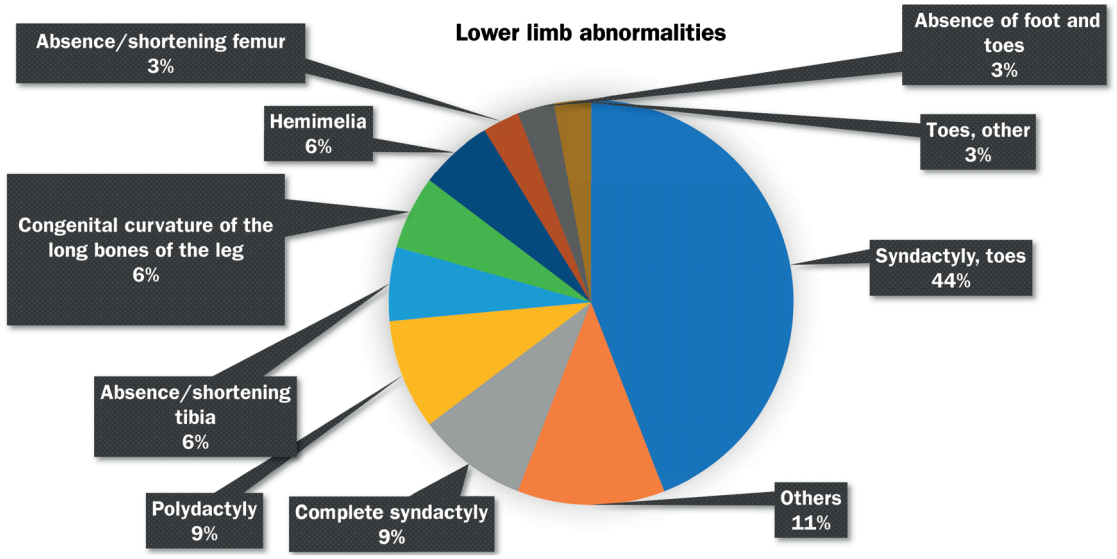


Figure 4. Malformations of the lower limb.

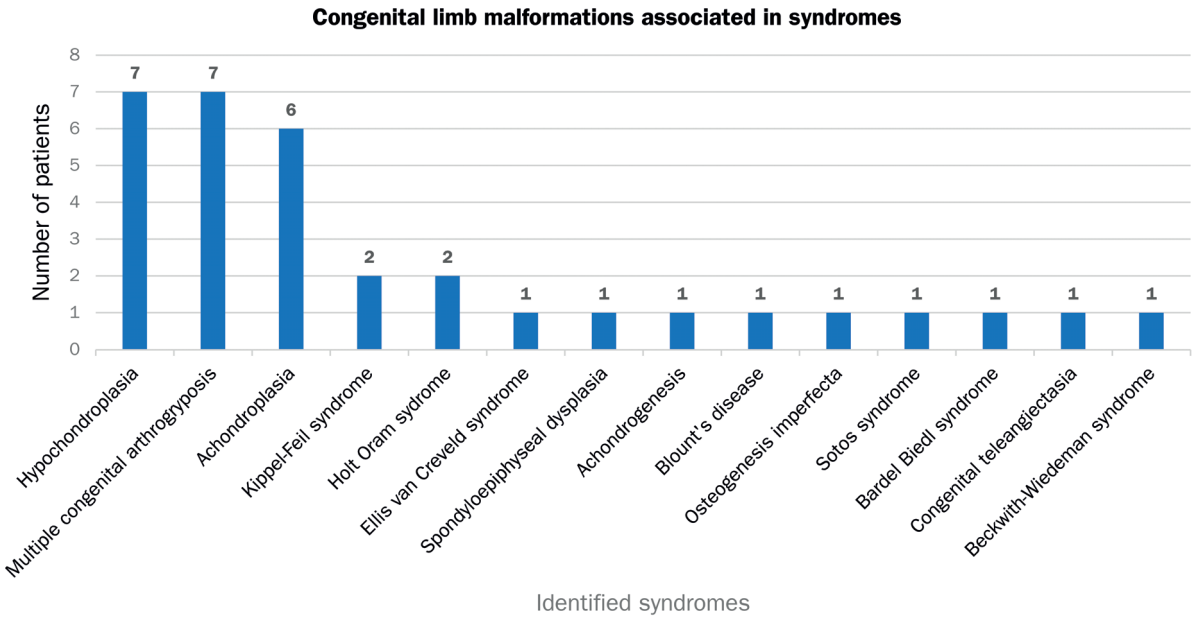


Figure 5. Congenital limb malformations associated in syndromes

This research study has undergone ethical review and received approval from the Ethics Committee of the University of Oradea, Faculty of Medicine and Pharmacy, before proceeding. The Ethics Committee has evaluated the study's design and protection of participants' rights and welfare.

Results

In this study, 105 patients were analysed, of which 49 were female and 56 male. Fifty-five of them lived in urban areas and 50 in rural areas.

A positive family history was identified in 27 patients (25.7%). Genetic consultation was performed in all patients, and genetic testing was proposed for some of them. The etiology of the malformations could be established in 44 (41.9%) of the cases. Of these, 32 (73%) were monogenic, 9 (20%) chromosomal, and 3 (7%) polygenic.

The most frequent limb abnormality was that of the upper limb (46%). The lower limb was affected in 27% of cases, while the other 27% of patients had both upper and lower limb malformations. The distribution of these CLM is shown in Figure 1.

Most of the patients (96) had an isolated limb malformation, according to ICD-10. Only 9 of the patients in this study were identified with more than one ICD-10 code (Figure 2).

Malformations of the upper limb were ICD-10 classified according to their location. Other malformations, corresponding to the Q71.8 code from ICD-10, were encountered most frequently (24%), and polydactyly and syndactyly were on the second place in frequency (17% each, of the total number of cases with upper limb anomalies). Figure 3 shows the distribution of malformations of the upper limb.

Malformations of the lower limb were divided similarly to those of the upper limb. The most common congenital anomaly of the lower limb was partial syndactyly (44%), followed by other malformations corresponding to the ICD-10 codes (11%), complete syndactyly (9%) and polydactyly (9%). The distribution of these anomalies is highlighted in Figure 4.

CLM were part of a genetic syndrome in 33 cases. Congenital arthrogryposis multiplex and hypochondroplasia were the most common syndromes, 7 cases each, followed by achondroplasia, 6 cases. The distribution of the most common syndromes can be seen in Figure 5.

From a clinical point of view, associations of the analysed osteo-articular anomalies with other musculoskeletal (14.95%), cardiovascular (12%), and gastrointestinal (9%) conditions were observed more frequently. Complications such as limb fractures and non-specific changes in the blood count have been observed less frequently.

Regarding the psychosocial consequences of the CLM in patients included in the study, they all underwent genetic consultation, orthopaedic consultation, psychological evaluation, laboratory tests (blood count and general or specific biochemical tests depending on the suspected associated pathology).

In most cases (46.51%), the evolution of patients was unfavourable (depressive syndrome in 39.86% of patients, and 5 patients presented autolytic behaviours). Also, 19% had a stationary evolution, 18% sublethal and 16.49% lethal.

Discussion

In the present study, 105 cases of CLM were identified. Most patients (46%) presented a malformation of the upper limb, a result close to other studies. Most patients were male (53%). The largest percentage was represented by patients from the urban area (52%). According to these results, the male sex is slightly more prone to develop CLM and in the urban area CLM appear with a higher frequency, probably due to the exposure to different factors.

A study by Betard et al. carried out in Alberta[22] shows that the majority of patients were also male (61.8%) and the percentage of upper limb involvement was the highest (55.9%). These authors included 170 patients from 1980 to 2012 and identified the frequent association of limb anomalies with musculoskeletal (28.6%), cardiovascular (16.8%) and gastrointestinal (12.6%) anomalies. In our study, the most frequent associations were similar, but in a lower percentage (musculo-skeletal anomalies 14.95%, cardiovascular 12%, gastrointestinal 9%).

Within the anomalies of the upper limb, polydactyly was the most frequently identified, like a recent study conducted in Korea (23.3%) by Shin et al. on a group of 10,704 patients with upper limb malformations[23]. Another similarity with our study is the increased proportion of male patients (57.7%). Contrary to our study, more frequent associations with cardiovascular (24.9%), musculoskeletal (19.9%) and digestive (19.6%) disorders were identified.

Another similar study, conducted by Jurca et al. on 301 patients[24], highlights the presence of anomalies mainly among males (52%), the predominantly sporadic appearance of these anomalies (83.4% without family history), deformities to the upper limbs in most cases (60.8%), deformities of the lower limbs were less common (15.3%), with both upper and lower limbs affected in almost a quarter of the cases (23.9%). Polydactyly was most frequently found (27.9%).

A study conducted in New York by Goldfarb et al[25] identified polydactyly as the most common upper limb malformation, followed by syndactyly. Syndromic associations were relatively rare (0.44 per 10,000 live births). The results of our study, although on a much smaller group and in a different geographical area, are consistent with the results of this study.

Furniss et al. conducted a study on a group of 202 patients[26] and identified polydactyly as the most common CLM. Following indications and performing genetic testing, a cause could be identified in 23 patients. According to the findings of the genetic tests, the most frequent was the monogenic etiology, followed by the chromosomal etiology. In Furniss's study, 52% of patients who were genetically tested also had a family history of genetic involvement.

Goldfarb et al. also conducted a study in which they only looked at upper limb malformations[27]. The majority of those affected were male (51%), a proportion of 17% presented syndromic association, polydactyly was the most common CLM, followed by arthrogryposis.

A similar study was conducted in Pakistan on a group of 153 patients[28]. Male patients were affected approximately 2 times more frequently than female

patients. Polydactyly was present in 71% of the cases and the upper limb was more frequently affected than the lower limb. In most cases, no family history was identified (78%).

In our study, patients presented high rates of depression (39.86%), especially those whose disease progressed unfavourably. This result contradicts other studies, such as the one conducted by Andersson et al[29], who identified rather positive emotions in patients with malformations of the upper limbs and a general self-esteem as high as in the group of Swedish adolescents without a pathology of limbs.

A study conducted by Franzblau et al[30] demonstrated that these patients experience emotional stress more often related to functional limitations rather than aesthetic appearance, but adopt positive styles of overcoming stress, methods that increase self-esteem. It was concluded that the most important role in reducing the levels of depression and anxiety is the social support (family members, teachers, classmates). In Romania, it is very likely that this aspect is deficient.

The terminology of limb malformations takes on an important aspect, to which American medicine has paid much attention over the years. According to the study of Biesecker et al[21] on congenital malformations, an even broader classification can be used than ICD-10 to better understand and manage patients with such pathologies, but also their needs, especially from a therapeutic point of view.

A report by the Save the Children organization[31] stated that in general, children, parents and sometimes teachers have a hostile attitude towards the integration of children with disabilities in regular classes. In addition, despite the regulations on accessibility in public places, many local institutions do not have adequate access routes, which limits the leisure, education, and culture opportunities of these patients.

Conclusions

In the last 18 years, 105 patients with CLM were diagnosed in Bihor county, most of them being male patients, coming from the urban area. Most congenital malformations were identified in the upper limb; among these, polydactyly and syndactyly were the most common, and lower limb malformations were represented by syndactyly in most patients. Most CLMs had a monogenic etiology.

The most common genetic syndromes that were diagnosed, in which CLM were identified, were the following: arthrogryposis, hypochondroplasia and achondroplasia.

Many cases of depression have been identified in the course of the disease, especially in the group of patients with an unfavourable evolution.

Author Contributions:

Conceptualization, C.V.S. and M.B.; methodology, C.J.; software, C.V.S.; validation, C.V.S. and M.B.; formal analysis, C.V.S.; investigation, CVS; resources, C.D.P.; data curation C.V.S.; writing–original draft preparation, C.V.S.; writing–review and editing, C.V.S. and M.B.; visualization, C.V.S. and M.B.; supervision, M.B.; project administration, C.J. and C.D.P.

All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

"There was no funding for this study"

Acknowledgements:

None.

References

1. Boyd SAB. Congenital Limb Abnormalities. *MSD MANUAL Professional Version*. Available from: https://www.msdmanuals.com/professional/pediatrics/congenital-craniofacial-and-musculoskeletal-abnormalities/congenital-limb-abnormalities (Accessed March 12, 2023).
2. EU-Commission Public Health Directorate Programme of Community Action on Rare Diseases. 1986-1-3:2003-2004. *EUROCAT Guide 3 (2nd Ed) For the Description and Classification of Congenital Limb Defects*. Belfast: University of Ulster; 2004.
3. Alexander PG, Clark KL, Tuan RS. Prenatal exposure to environmental factors and congenital limb defects. *Birth Defects Research Part C – Embryo Today: Reviews*. 2016;108(3):243-73.
4. Golden CM, Ryan LM, Holmes LB. Chorionic villus sampling: A distinctive teratogenic effect on fingers? *Birth Defects Research Part A – Clinical and Molecular Teratology*. 2003;67(8):557-62.
5. Materna-Kiryluk A, Wisniewska K, Wieckowska B, et al. Maternal risk factors associated with limb reduction defects: Data from the Polish registry of congenital malformations (PRCM). *Children*. 2021;8(2):138
6. Mooney EK. Hand Embryology. *Medscape*. 2021. Available from: https://emedicine.medscape.com/article/1287982-overview. (Accesed February 10, 2021)
7. Mooney EK, Loh C. Lower limb embryology gross morphologic overview of lower limb development. *Medscape*.

2021. Available from: https://emedicine.medscape.com/article/1291712-overview. (Accesed February 10, 2021)
8. Tickle C. How the embryo makes a limb: Determination, polarity and identity. *Journal of Anatomy*. 2015;227(4):418-30.
9. Tickle C, Towers M. Sonic hedgehog signaling in limb development. *Frontiers in Cell and Developmental Biology*. 2017;5(2):1-19.
10. Geetha-Loganathan P, Nimmagadda S, Scaal M. Wnt signaling in limb organogenesis. *Organogenesis*. 2008;4(2):109-15.
11. National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center. *Cornelia de Lange syndrome*. Available from: https://rarediseases.info.nih.gov/diseases/10109/cornelia-de-lange-syndrome (Accesed February 10, 2021)
12. National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center. *Fanconi anemia*. Available at: https://rarediseases.info.nih.gov/diseases/6425/fanconi-anemia (Accesed February 10, 2021)
13. National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center. *Holt-Oram syndrome*. Available from: https://rarediseases.info.nih.gov/diseases/6666/holt-oram-syndrome (Accesed February 10, 2021)
14. National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center. *Nager acrofacial dysostosis*. Available from: https://rarediseases.info.nih.gov/diseases/498/nager-acrofacial-dysostosis (Accesed February 10, 2021)
15. National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center. *Duane-radial ray syndrome*. Available from: https://rarediseases.info.nih.gov/diseases/9182/duane-radial-ray-syndrome (Accesed February 10, 2021)
16. National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center. *Smith-Lemli-Opitz syndrome*. Available from: https://rarediseases.info.nih.gov/diseases/5683/smith-lemli-opitz-syndrome (Accesed February 10, 2021)
17. Lumsdaine S, Thurston M. Growing up in a mainstream world: a retrospective enquiry into the childhood experiences of young adults with a physical disability. *International Journal of Disability, Development and Education*. 2017;64(2):182-197.
18. Ardon MS, Selles RW, Roebroeck ME, Hovius SE, Stam HJ, Janssen WG. Poor agreement on health-related quality of life between children with congenital hand differences and their parents. *Archives of Physical Medicine and Rehabilitation*. 2012;93(4):641-646.
19. Rumsey N, Harcourt D. Visible difference amongst children and adolescents: Issues and interventions. *Developmental Neurorehabilitation*. 2007;10(2):113-123.
20. Goffman E. *Stigma: Notes on the Management of Spoiled Identities*. London. PENGUIN BOOKS; 1963.
21. Biesecker LG, Aase JM, Clericuzio C, Gurrieri F, Karen Temple I, Toriello H. Elements of morphology: Standard terminology for the hands and feet. *American Journal of Medical Genetics Part A*. 2009;149(1):93-127.
22. Bedard T, Lowry RB, Sibbald B, Crawford S, Kiefer GN. Congenital limb deficiencies and major associated anomalies in Alberta for the years 1980–2012. *American Journal of Medical Genetics Part A*. 2018;176(1):19-28.
23. Shin YH, Baek GH, Kim YJ, Kim MJ, Kim JK. Epidemiology of congenital upper limb anomalies in Korea: A nationwide populationbased study. *PLoS One*. 2021;16(3):1-14.
24. Jurcă MC, Bembea M, Șandor MI, et al. Congenital anomalies of digits – a clinical-epidemiological study of 301 patients. *Romanian Journal of Morphology and Embryology*. 2019;60(4):1221-6.
25. Goldfarb CA, Shaw N, Steffen JA, Wall LB. The prevalence of congenital hand and upper extremity anomalies based upon the New York Congenital Malformations Registry. *Journal of Pediatric Orthopaedics*. 2017;37(2):144-8.
26. Furniss D, Kan SH, Taylor IB, Johnson D, Critchley PS, Giele HP, et al. Genetic screening of 202 individuals with congenital limb malformations and requiring reconstructive surgery. *Journal of Medical Genetics*. 2009;46(11):730-5.
27. Goldfarb CA, Wall LB, Bohn DC, Moen P, Van Heest AE. Anomalies in a midwest United States population: An assessment using the Oberg, Manske, and Tonkin classification. *The Journal of Hand Surgery*. 2015;40(1):127-132.e2.
28. Ullah S, Dasti JI, Malik S. Descriptive epidemiology of hereditary musculoskeletal and limb defects in the isolated population of Chitral, north-west Pakistan. *Pakistan Journal of Medical Sciences*. 2015;31(5):1047-52.
29. Andersson GB, Gillberg C, Fernell E, Johansson M, Nachemson A. Children with surgically corrected hand deformities and upper limb deficiencies: Self-concept and psychological well-being. *The Journal of Hand Surgery*. 2011;36(9):795-801.
30. Franzblau LE, Chung KC, Carlozzi N, Chin AYT, Nellans KW, Waljee JF. Coping with congenital hand differences. *Plastic and Reconstructive Surgery*. 2015;135(4):1067-75.
31. *Raport alternativ la cel de-al treilea și al patrulea Raport periodic înaintat de România Comitetului ONU pentru Drepturile Copilului*. Save the Children Romania. 2008. Available from: www.salvaticopiii.ro