UNIVERSITY OF MEDICINE AND PHARMACY "CAROL DAVILA"
BUCHAREST
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HAEMANGIOMAS IN CHILDREN - MEDICO-SOCIAL AND FAMILY IMPLICATIONS

ABSTRACT OF THE PhD THESIS

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CHAPTER I

Introduction

According to the International Society for the Study of Vascular Anomalies (ISSVA), childhood vascular anomalies are classified into two categories: vascular tumours and vascular malformations (1). Infantile haemangioma is the most common vascular tumour, caused by abnormal proliferation of endothelial cells, with a prevalence ranging from 4-5% (2-4) to 10-12% in Caucasian children, affecting mainly female children (5), preterm infants, those with phototype I (6, 7), etc. and most commonly located in the cephalic extremity (5).

Haemangiomas are further divided into two types: "infantile" and "congenital". Congenital' haemangiomas are rarer, less understood and present from birth. It either involutes rapidly, in a very short period of time (rapidly involuting congenital haemangioma (RICH)) or never involuting (non-involuting congenital haemangioma (NICH)).

Infantile haemangiomas usually develop during postnatal period and go through three phases of development: proliferative, when growth is accelerated, up to the age of one year, the stationary or plateau phase and the involution or regression phase, which lasts until the age of 4-5 years according to some authors and 7-12 years according to others.

The vast majority of haemangiomas are small lesions, easily recognisable by their clinical features. They most commonly occur in the dermal region, but they can also affect the viscera (most commonly the liver). Facial haemangiomas can be impressive in appearance, disfiguring, sometimes causing impaired visual function, eating disorders (those of the lips and tongue), and those of the airways can be life-threatening, especially in the proliferative phase. They may develop as unique or multiple lesions, may be single or part of syndromes (e.g. PHACE syndrome).

Treatment of childhood haemangiomas includes a wide range of modalities, from a conservative watch - "wait and see" to emergency surgery due to severe morbidity and complications. One must understand the different phases of HI growth and foreseeable morbidity for each phase. Reason being that the appropriate treatment has to be initiated at an optimal time.

Researchers have described criteria which must be listed in order to start a defined type of treatment. They have focused their attention on developing instruments to aid physicians

who first come into contact with a patient with infantile haemangioma to assess the severity of the lesion and what management steps need to be taken. They list instruments such as:

- The Haemangioma Severity Scale (HSS) and for longitudinal use of childhood haemangioma complications,
- Haemangioma Dynamic Complication Scale (HDCS),
- IHReS - Infantile Haemangioma Refferal Score developed in 2020 (8, 9).

Indications for treatment are absolute and relative. Absolute indications include: ulceration, disfigurement and impairment of vital organ function (10); relative indications include: improvement of aesthetic appearance, even if the affected body part is not an exposed one (e.g. scalp, posterior thorax, gluteal region, etc.).

Quality of life assessment

Current studies have shown that the location, size and appearance of haemangiomas would be mostly considered for this condition when comparing them with other dermatological conditions.

Skin conditions often remain a hidden affliction and the impact on quality of life of patients and their families is often underestimated. Pain is not a main feature and they are rarely life-threatening. These may be sufficient reasons for having been less considered in health and social impact assessments.

Unlike many serious diseases which can also be entirely 'hidden', this condition is carried by patients 'in plain sight', at all times. This aspect can have a very profound psychological and social impact and patients often learn to hide it. As a result lesions escape unnoticed. An accurate and extensive assessment of quality of life in these patients and their families is an essential therapeutic step in order to be able to formulate specific treatment schemes which deal with the condition, both at individual and social levels.

Many studies have already been carried out for quality of life of dermatological patients but there are few evaluations on the patients' families and very few assessing the impact of childhood haemangiomas on families. Generic instruments may overlook major characteristics of the condition, hence the development of specific ones which take into account the condition characteristics and the impact it has on the quality of life of patients and their families.

CHAPTER II

Personal research

The aim of research

To assess the medico-social and family implications of haemangiomas in children.

Working hypothesis

There is limited access of children with haemangiomas to appropriate therapy and this is mainly due to insufficient knowledge about the condition and its medico-economic and social implications as well as the lack of instruments and tools for practitioners, such as: case management guidelines, disease specific quality of life instruments, known mechanisms in facilitating the introduction of innovative therapies in the health services market, therapies aimed at enhancing positive benefits for patients.

Research objectives and sub-objectives

1. To develop and validate a tool to assess the quality of life of families of children with infantile haemangioma;

1.1. Specific objective 1: literature review

1.2. Specific objective 2: development and validation of the questionnaire

2. To describe the demographic characteristics and therapeutic approaches in the Romanian paediatric population with infantile haemangioma.

3. To evaluate the quality of life of patients with infantile haemangioma and their families in the Romanian population.

4. To evaluate the financial impact of this disease on i) the children's families and ii) on the health care provider (outcomes: cost of the disease from the perspective of the family of the child with haemangioma and costs incurred by the health care provider);

4.1. Specific objective 1: to evaluate the financial impact on the family

4.2. Specific objective 2: to evaluate the financial impact on the health service provider.

5. To develop case management framework and guide for treatment of children with haemangioma. This includes access to innovative treatments of childhood haemangiomas

defined by the i) pathway of a pharmaceutical product from market authorisation to its compensated regime and ii) the effective and equitable access to such treatments;

5.1. Sub-objective 1: to develop a case management algorithm

5.2. Sub-objective 2: to evaluate patient access to innovative therapies.

Research stages

The outline of the general methodological approach of the research includes:

Each research objective is addressed by considering:

- A literature review
- One or more methods to achieve the (SMART) objective,
- A data analysis plan,
- Reporting on obtained results
- Discussion (with focus on limitations) and conclusion.

Study population

The sample is represented by legal guardians of all patients with infantile haemangioma who presented to the hospital during the research period.

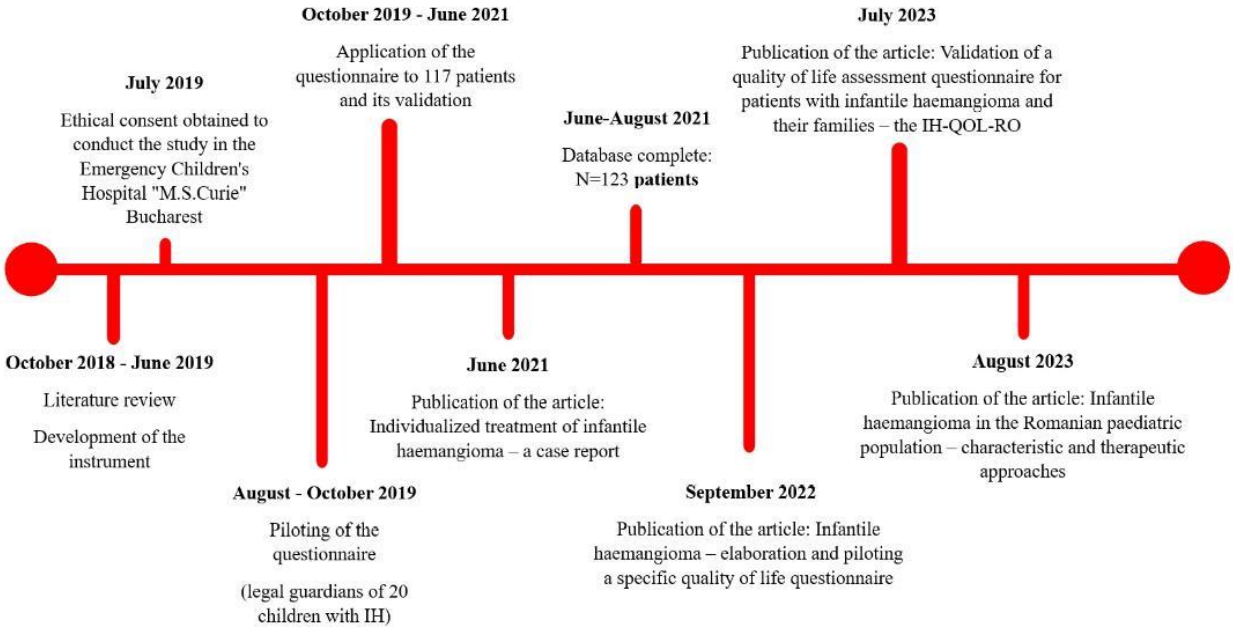
The *inclusion criteria* are:

- age of the child up to 24 months,
- the presence of an infantile haemangioma diagnosed by a medical specialist,
- parents' ability to read and understand Romanian, to sign the informed consent form and to answer the questionnaire.

The *exclusion criteria* are:

- patients older than 2 years at the time of presentation;
- patients with comorbidities unrelated to haemangioma or other major developmental disorders.

Methodological steps of the research



Addressing each objective includes:

Objective 1: Development and validation of a tool to assess the quality of life of families of children with infantile haemangioma

The methodological steps are:

- literature review,

- development of a questionnaire to assess the quality of life of the families of these patients:

- pilot of the questionnaire,

- application of the questionnaire,

- data collection and data analysis,

- validation of the questionnaire.

The result is a questionnaire with 58 questions. The questions in its structure include socio-demographic and clinical data, including the location of the haemangioma, size, stage of growth and treatment followed, as well as self-assessment of emotional status or physical condition.

Part 1 - general questions: 19 questions, covering:

- Relationship to patient (with response options: 1. mother, stepmother, foster mother; 2. father, stepfather, foster father; 3. grandmother; 4. grandfather; 5. legal guardian; 6. other-please specify which);

- Information about the child: patient's gender, patient's age, place of residence, county of residence;

- Information about the mother: age, education level, occupation, marital status;

- Father information: age, education, occupation, marital status.

Part 2 - questions specific to infantile haemangioma: 13 questions referring to the location of the haemangioma, number of lesions, size, type of treatment, age of the child at the time of diagnosis, what specialty the diagnosing doctor has, etc.

In case of more than one infantile haemangioma, the one with the most clinically involved (usually the most bulky or visceral) was considered with in depth clinical examination and case documentation (e.g. abdominal ultrasound for hepatic haemangioma, or trans-foontal ultrasound for intracerebral haemangioma).

Part 3 - IH QoL-Rom questionnaire: 26 questions. This section of the questionnaire was then validated.

Results Objective 1

The IH-QOL-RO questionnaire included in the analysis has 26 items. It reports results with a total score on a range from 0 to 84, where 0 represents no effect and 84 substantial effect on QoL. The field validation of the Romanian version uses the following ranges for the subscale scores: CPS has the range 0-16, CSI has the range 0-12, PSF has the range 0-24 and PEF has the range 0-32. The same scale scoring and transformation was used, with scores from 0 to 100 for the items included in the Romanian language version.

Being a specific instrument, the scales defined from the 26 standardized items (loaded on subscales) and included in the analysis gave subscale values of Cronbach's alpha coefficient:

- 0.489 CSI subscale (child social interaction)
- 0.609 PSF subscale (psycho-social functioning for parents)
- 0.689 for the PEF subscale (emotional functioning for parents)
- 0.719 for the CPS subscale (expressed physical symptoms in child)

The 26-item version of HI-QOL-RO is ready for use including in a dynamic measurement of quality of life in children of up to two years of age with haemangioma and their legal guardians.

This research found that 21 items load on the four classical components of the instrument: CPS, CSI, PSF, PEF. The reduction of 5 items by cultural adaptation, from 26 to 21, gives optimal utility to the instrument. The Romanian validated version kept 14 items in the parent subscales (6 and 8 items respectively on the two subscales) and seven items in the child subscales (four and three items respectively).

A future study is needed to carry out the remaining psychometric quality, the test test-retest reliability (with redistribution for completion after 48 hours). It would also be recommended that at the same time the disease specific instrument is distributed, to also distribute it along with a generic instrument (either SF-36 or Euro-QoL) in order to allow for comparison of quality of life of families with children who do not have the condition.

This may detect the level of contemporaneous disease burden. The Romanian version of the HI-QoL-RO has moderate reliability, but shows high acceptability (100% accepted in the study participation).

Objective 2. Descriptive analysis: case studies and case series analysis

The methodological steps followed in achieving Objective 2 were as follows:

- selection of variables: was carried out when the questionnaire was drawn up;
- creation of the database template: in IBM SPSS v23.0;
- filling in the database as the data were collected (presentation of patients);
- recoding of some variables to facilitate the application of the statistical analysis plan. For example occupation: the free text filled in by relatives was coded according to the list of occupations in COR (Classification of Occupations in Romania); the 9 main classes were used, in ascending order, the last code being that of occupations with no qualification, practically that can go up to secondary school education or even up to high school education; no occupation was coded with 0 (students, unemployed, retired). The entry of codes for both mother and father was done with a double method of operation, with random checking of 12% of the files and by mirror analysis of the two lists of codes filled in. The inconsistency was analysed and corrected by review and arbitration with re-application of the values from the COR list. The recoding of the variables is an essential condition to facilitate not only the descriptive analysis plan (frequency distributions, correlations) but also the verification of hypotheses, a verification that requires an exclusively numerical listing of the codes used in the analysis.

- Analysis design and descriptive analysis: descriptive analysis was done for quantitative variables with central tendency indicators. For continuous quantitative variables the mean ±sd was used. For qualitative variables proportions were used. Statistical significance testing was done with Student's t-test (for continuous-type quantitative variables) and X^2 (for proportions). Instrument subscale scores used correlation analysis (non-parametric method) with obtaining and interpreting these coefficients showing either a direct correlation (+ sign of the coefficient) or an indirect correlation (- sign of the coefficient). Correlation analysis facilitates not only recommendations, but also the formulation of new hypotheses following the completion of the description of the information.

Results Objective 2

The average incidence of HI is 4% to 5% (2-4) and a maximum incidence of 10-12% found in non-Hispanic Caucasian infants. In terms of the gender distribution of patients, it has also been observed in this research that females are most affected (3, 5). Other factors associated with infantile haemangioma described in the literature are prematurity, low birth weight, multiple pregnancies, skin phototype I (5, 11).

Given the high heterogeneity of haemangiomas, deciding which patient needs treatment, and when to start treatment, requires a good knowledge of the natural history and a clinical assessment of the benefit/risk ratio, with particular emphasis on high-risk predictors for the development of complications. The choice of treatment will always take into account the potential evolution, tumour-induced damage, consequences or prognosis.

An important decision criterion for the therapeutic approach to IH is age at diagnosis and presentation. Seventy-two of the children diagnosed (or 62% of the group) were under five months of age (the upper limit of the window for initiating Propranolol treatment) at the time of presentation.

Although prematurity is one of the most cited risk factors for the development of infantile haemangiomas (3) and would be considered one of the most important risk factors for IH (3, 7, 12), only one third of the babies were born with a gestational age of less than 38 weeks: 34%, with a confidence interval (95% CI) of 26 to 43%). Gestational age was included and birth weight excluded because these two variables correlate strongly and positively: low gestational age, low birth weight (13).

Four out of five patients (79%) were diagnosed in the first month of life (mostly by neonatologists or paediatricians) and 62% were under 5 months of age at the time of examination and diagnosis. No other factors were related to the diagnosis of IH (e.g. if the mother had multiple pregnancies: less than 1% of the group had associated gynaecological pathologies.

Regarding another personal characteristic, it was observed a female predominance (68%), very similar to existing information in the literature; similarly, a slight predominance of children with phototype 1 (58%) was observed (2, 3, 5).

The mean age of the child at the first hospital visit was 6.25 months (±5.5 months), and the median was four months (with age limits specified in the inclusion criteria of minimum 0 and maximum 24 months). This variable is all the more important nowadays because treatment can only be compensated if initiated before 5 months of age.

Age at diagnosis ranged from 0 to 72 weeks, with a mean of 3.9 (±7.9) weeks and a median of two weeks. A proportion of 79% of children (four out of five) were diagnosed with HI during the first 4 weeks of life; only three cases were diagnosed after more than 4 months of life. This defines the observed distribution of age at diagnosis as strongly left-skewed.

Although the diagnosis was established early, in the first month of life, only one case presented immediately to the hospital for confirmation of the diagnosis and specialised treatment.

It can be seen that although the diagnosis was made at almost the same age in all patients, those with complications presented on average 8 weeks later; and the differences are statistically insignificant.

Regarding pregnancy and maternal factors that could influence the occurrence of IH, we found that seven mothers (6%) had received hormonal treatments during pregnancy, and none of them had been exposed to accidents or gynecological pathologies during pregnancy.

The number of lesions (isolated tumours) was limited to one or two haemangiomas in 92% of the children (108 out of 123), estimated with a 95% CI confidence interval from 86 to 96%, with most being located in the head and neck (53%). Only one case of a hepatic haemangioma was recorded.

Given the haemangioma's size, 45% of children had a lesion with a maximum size of two cm, and in the case of multiple haemangiomas, the largest of these was considered.

Since the occurrence of complications, in the course of haemangiomas, is an absolute indication for initiating a therapeutic scheme, we investigated this aspect thoroughly at the time of presentation. The 12 cases (10%) that developed complications consisted of: ulcerations (nine cases) and haemorrhages (three cases).

In all cases the presence of complications was the real reason why parents sought medical attention and were immediately referred to the paediatric surgeon. Complications were mostly present in girls. There were nine girls and three boys, so in a 3:1 ratio. All 12 cases were treated orally with Propranolol for up to 12 months, and only one case was treated longer (18 months), all with good tolerance. All patients responded very well to drug treatment and progressed to remission with minimal sequelae. For selected cases, depending on the local appearance at treatment discontinuation, laser therapy was recommended.

According to the clinical guidelines, the available therapeutic options are: oral Propranolol, topical beta-blocker (Timolol gel), topical steroids, surgical excision and "wait and see". Laser therapy, which could not be performed in our hospital, was only recommended for the remaining skin lesions.

All 123 patients have been followed up since presentation. Only 13% of patients did not require any treatment (wait and see group, N = 16). All other patients needed either a single treatment (64%) or a combination treatment: oral Propranolol and local Timolol - 23%. 64 (52%) of the patients were treated with oral Propranolol, 35 (28.5%) of the 123 children received local treatment with Timolol, 7 children underwent surgical excision of the haemangioma, and only 1 case was treated with local corticosteroid.

Therapeutic management was done according to the characteristics of each patient: patient age, absence/presence of complications, lesion location and lesion size.

At this point it must be emphasised that the present research was carried out before the competent authority decided to place the oral Propranolol solution under a compensation regime. Therefore treatment costs were almost entirely covered by the family (except for the period of initiation of treatment, if this was carried out by continuous hospitalisation). When asked whether the choice of the form of administration of Propranol was influenced by the price (approx 900 RON/120 ml vial), 73% of the children's legal guardians answered that the price "was not the most important reason taken into account for their decision". This response characterises the expression of a preference or utility. Around 19% (one in five legal guardians) said that they "had difficulties with the investigations necessary to commence the child's treatment". Almost all (11 out of 12 relatives) described the difficulties as "problems with access to heart ultrasound and cardiology examination".

Furthermore the descriptive analysis of family background and socio-economic characteristics shows that most respondents are mothers (85%).

In terms of mean age, fathers are older (33.2±6.8 years) than mothers (29.9±6.3 years), with a difference of 3.3 years, which is statistically significant in favour of the older age of fathers (95% CI from 3.1 to 3.5 years).

From the recorded statements 76% of the parental couples are married, 22% live in a consensual union and 2% have recorded a response of divorce or single parent situation.

The socio-economic position within families noted that a high proportion of mothers (46/123 = 37%) self-report of being housewives. This category is considered as occupation in class 9. Moreover, the most frequently self-reported occupation for fathers is driver

(10/123 = 8%).

Given the level of education, 29% mothers report high school education level and 47% of fathers; the difference of 18% (18 percentage points) or, the difference of 58/123 versus 36/123 = 0.179 has a standard error of 0.071 which gave a confidence interval (95% CI) of 0,04 to 0.32% and this difference for the level of instruction as shown by the middle level of education (high-school) is statistically significant.

In terms of residency, due to easier access to specialized medical services, the majority of children (69%) presented came from urban areas, and a high proportion (39% or n = 48) of patients were from Bucharest.

In the study we considered the income of the family, relative to the member, in order to see to what extent it influences the decisions made regarding the type of treatment followed and what could be the impact that the investigations, treatment and travel to the hospital (both in terms of absenteeism from work and means of transport to the hospital) have on the family financial component, as well as affecting the quality of life of the family.

Self-reported income was more than 1500 RON per household member for 57% of respondents. This is mirrored by the observation of about half of the parents of children who followed the oral Propranolol treatment who responded that "the decision on the type of treatment (oral solution vs. tablets) was influenced by price".

Regarding absenteeism from work, 25 of the respondents stated that they had missed at least one day in order to attend the hospital (for investigations or for the initiation of treatment), one person answered that they had to miss work on 16 occasions over two months and as a result they "were forced to take unpaid leave".

A large proportion (78%) of respondents said they travelled to the hospital by their own car, 9% by taxi, 4% by public transport, 3% by rented car, and 6% by other means of transport which they did not mention. Families living outside Bucharest (60.9%) had the greatest difficulty in travelling to attend the hospital visit(s).

Specialty of doctors who diagnosed IH: 54% of cases were diagnosed by neonatologists and paediatricians, 21% were diagnosed by family doctors and 25% by other specialists (dermatologists, paediatric surgeons, ENT specialists, ophthalmologists, etc.).

In order to see if the diagnosing doctor is also the one who refers the patient to a specialized service, we asked the legal guardians which is the specialty of the doctor who referred them to the hospital and we found that the pediatrician is still in first place, followed by the dermatologist. Of note, although the neonatologist was second in terms of diagnosis, none referred the patient for investigation and treatment.

No relationship was found between the occurrence or presence of complications and the location or size of the haemangioma. Ulcerations which are common complications in areas prone to mechanical friction, e.g. the perianal region, where areas are susceptible to bleeding, pain and local infection, were observed in a small number of cases (n=12). The only observation made during this research was that all complications were observed in female patients.

The description of the group is completed with the analysis of the quality of life responses according to personal, socio-economic and IH characteristics.

Objective 3. Quality of life measurement

The methodological steps followed in achieving Objective 3 were as follows:

- literature review: quality of life
- data collection with the validated instrument
- creation of the database: in IBM SPSS v23.0 and data entry;
- quality of life analysis: after the pilot study and validation of the scale with its subscales in Romanian, the analysis of the scores was carried out to assess the quality of life with the comparison of the response levels obtained by using the original scale with published results (Chamlin, 2015) (14). In this sense, the results obtained from the correlational analyses, which allow the development of informational benchmarks, support the recommendations made in the thesis.

The analysis plan includes:

- description of total score and subscale scores;
- exploration of the relationship of subscale scores and their items to selected variables (socio-economic status, in particular the instrumental variable income, the variable related to education and occupation, of both parents; income was collected as the response variable "income per family member");
- score analysis was performed with total score and subtotal scores on the 4 subscales for the whole group (N=123) and cases presented with complications (n=15) and without

complications (n=108);

- score analysis was also performed according to the location of the haemangioma: for "other locations" (extremities, trunk, pamper area the responses were recoded as category 0) and craniofacial location (recoded as category 1); the analysis also included the size of the haemangioma.

To explore the relationship between location, size and subscale score values, we conducted correlation analyses between scores and these independent variables (Chamlin, 2015);

Differences between means were interpreted with estimated and confidence interval (95% CI) for statistical significance.

Results

The analysis revealed an asymmetric distribution and left shift of the score curves on the 4 subscales.

The total score amplitude reaches the upper value of only 29 (out of a maximum of 84) in the subgroup with complications, compared to 52 (out of a maximum of 84) in the group without complications; this is noted in this group, and the difference between the mean total score of the group without complications versus the group with complications is statistically insignificant. This observation does not preclude an important interpretation of the clinical significance of this difference, namely, that the quality of life score obtained with this instrument is significantly lower in those presenting with complications at the time of diagnosis, but this does not mean that there is a less important subjective perception of quality of life in those presenting without complications.

The analysis of the total score (mean values) of both mother's and father's level of education shows that: the maximum value of the mean score is recorded at the mother's secondary school education level and the father's at primary school level. This aspect points to the fact that a lower educational level may indicate a lower perception of a given quality of life at that particular level of education. Moreover, the value of the total score recorded for post-secondary education is higher for fathers than for mothers (14.5 compared to 10), but the frequency of the number of observations is low, which confirms the absence of post-secondary vocational qualifications from the economic scene. As a general observation, the lower the average total score recorded, the higher the educational level but the differences recorded at the category level are not statistically significant. One of the limitations is the number of participants, knowing that sample sizes are important when interpreting statistical significance in differences

of results. This is even more true for the scores obtained for the complicated and uncomplicated subsamples, where the number of those presenting with complications was extremely small (n=12).

Daily routine and ability to function as unaffected at work paradoxically show a higher mean total score in the response categories "sometimes/often" or, "almost always a problem". This observation may launch the hypothesis of the ubiquity of the situation in which the family finds itself, a situation to which the family is accustomed, at least declaratively; another hypothesis is that they are or have reached the position of considering daily work-related challenges as something 'normal'. A research with qualitative methodology could better describe what the family understands by these two terms. Such issues are usually clarified also in situations where quality of life is measured not only with a specific instrument but also with a generic one that gives the opportunity to compare the results with norms obtained from samples taken from the general population.

Regardless of haemangioma location only the CSI subscale correlates directly with location, although not strongly, but statistically significant (r=0.191; p=0.034). This subscale also correlates with the "absence of sadness or depression" item when it relates to the child haemangioma (r=0.31; p=0.000).

Regarding craniofacial location (n=69) vs other locations (n=54) vs sizes (4 ordinal classes): the correlation coefficient takes negative values, however this is explained by the very high proportion of small size tumours at craniofacial level. Larger sizes are found with higher frequency at other locations (logical counter proportionality); other results show that overall the total PEF subscale score correlates directly and statistically significant with size only regardless of location; this is not observed when considering craniofacial location which mostly has small sizes of the IH (r=0.215; p=0.076). The CSI subscale score also correlates directly only with location but not with haemangioma size. However, at the disaggregated level for the CSI and PEF subscales the following results show correlations of items in the subscales with size by location category: at craniofacial localisation size correlates with PEF for items 9 and 10 with a statistically significant direct correlation coefficient; and for other locations size correlates with items 8 and 24 (CSI) and 9 and 17 (PEF) with a statistically significant direct correlation coefficient; one observation is that item 9 of the PEF subscale, correlates significantly with both locations and its content refers to the emotional functioning component which is reflected in the reporting of the "presence of sadness or depression". All results are comparable with those reviewed from the literature which has published information obtained from the use of the

IH-QoL and variants of the instruments validated by those studies (Chamlin, Wang).

Socio-economic status does not show statistically significant influences on the total score or differences between categories (education, average income per family member, gender of child, residence, who filled in the instrument, treatment modality or whether it was single/multiple treatment). According to the results in the tables presented for the total score and for the subscales (CSP, CSI, PSF and PEF) "ability to concentrate at work" and "daily routine" were the only characteristics that recorded higher total score, scores on the CSP, PSF and PEF subscales for those who reported experiencing them "daily and frequently", statistically significant differences, compared to those who self-reported "not at all or rarely". However, these two items are not included in the scale and their individual results are reported individually.

In contrast to this list of socio-economic variables, it is the mother's occupational class - not the father's - that scores a higher score, which is statistically significant for the Child Functioning and Expression of Symptomatology (CPS) and Parental Psychosocial Functioning (PSF) subscales.

Objective 4. Financial impact

The methodological steps, qualitative methods, followed in achieving Objective 4 were as follows:

- data and information collection having explored secondary data sources (reports),
- reference to definition of economic concepts (utilities and preferences, costs, economic evaluations),
- performance of a synthesis of information in European region context.

Results

It has been estimated that the group of 123 patients included in this research who were referred to the "M.S.Curie" Hospital during the two years may represent one third of the IH cases in the whole of the country for the given period. Given the absence of specific clinical guidelines for IH, it can be concluded that the results of the study have a twofold importance: it has allowed a thorough description of the cases seen during this period in a reference centre; and the current clinical course and therapeutic management were

explored in depth, including financial data.

Although other studies (15) have reported that watchful waiting is most of the time the therapeutic attitude needed for IH, the results of this study showed that 86% of the patients observed needed at least one type of treatment and this incurs costs. These results are not surprising, given that patients were referred to this centre of reference for specialised treatment of IH, including by physicians who hold other specialties than recommended. Similar to other studies (7, 16), the majority of patients had haemangioma located on the head and neck (53%), followed by the thorax and abdomen (21%) and limbs (20%).

It should be noted that complications are usually not life-threatening, but have a significant emotional impact on the family as well as other lay people and/or medical staff. Even though there are effective treatments for complicated haemangiomas, these can be complex, require longer time and as a result, ulceration can also leave an unsightly scar. This raises the importance of a patient diagnosed with IH to be referred as soon as possible to specialised services with the management of this pathology.

Propranolol has been the gold standard for the treatment of proliferative and potentially complicated IH for some years (since 2008). The guidelines recommend initiation of treatment with oral Propranolol starting at 1 mg/kg/day, gradually increasing weekly to a maximum dose of 2-3 mg/kg/day, as tolerated, for a minimum of 6-12 months. Response rates of 82-100% to Propranolol treatment, rebound rates of up to 25% and adverse effects of 17-96% have been reported, with 3% requiring discontinuation (8; 16-19).

The results presented by this research demonstrate professional commitment to aligning with the most up-to-date clinical guidelines for HI management, despite the fact that from an administrative point of view, the National Social-Health Insurance Fund has not rushed the formal approval of a reimbursement scheme to allow an alleviation over the financial burden on affected families from 2008 to December 2022.

Detailed investigations and correct diagnosis of IH, established before initiating Propranolol treatment, are essential for a high success rate. The low recurrence rate (4%) in this research and the lack of severe side effects in the children in this selected group of patients could indicate an effectiveness of the already established therapeutic regimen for the management of IH. Patients were actively and continuously followed up and parents' feedback regarding the treatment effects for each patient was sought, even when the Propranolol dosage was still low. There were no situations requiring discontinuation of

treatment, although in a few cases sleep disturbances or agitation were mentioned, but these turned out to be one-off, mild episodes that could not be directly associated with the Propranolol administration, but rather were associated with age-specific abdominal pain or discomfort created by dental eruption.

Although it is a drug with clear indications for over 15 years in the treatment of IH, Propranolol is still considered an off-label prescription for this condition. Thus, administration requires very careful monitoring of paediatric prescriptions for Propranolol solution. Secondly, financial support through treatment compensated regimes, especially for low-income families, are also needed due treatment costs. These claims are supported by economic theories regarding the laws of demand and supply for health care.

The health services market is an atypical market. Information asymmetry and price inelasticity prevail. The aesthetic aspect of this condition is of utmost importance. The risk of complications (predominantly ulcers) cannot be underestimated and care incurs costs.

The 'new' therapeutic options, which are particularly useful for children with haemangiomas (oral and topical treatment with beta-blockers, laser therapy with high-performance devices, etc.), can have their effectiveness measured. Quality of life, as an outcome, can be evaluated by means of the questionnaire developed in Romanian to allow legal guardians to express concerns. The extent to which a particular treatment can also influence quality of life can also be captured, e.g. treatment with Propranolol, monitoring which requires regular visits to the doctor, daily administration for a minimum of 6 months, twice a day, regular measurements of IH (16), etc. Such a scale can be used in practice to identify parents who need support, either emotional (e.g. psychotherapy) or financial (compensation regime). Patients concerns which relate to limited access to certain health services or innovative therapies, including access to the appropriate prescription regime, could also be identified. These aspects have raised the importance of costing the care of the IH patient.

Objective 5. Development of the therapeutic management algorithm

The methodological steps, which includes qualitative methods, followed in achieving Objective 5 were as follows:

- a synthesis of good therapeutic practices (literature review),
- exploration of appropriate recommendations for the Romanian context: for the

patient and his family, and for the health service system involved in the therapeutic management of this condition.

Most of the other specialties, other than those directly involved in the specialist care of the condition will have to undergo 'refinement' in what is involved in the lean management of IH, generically referred to as 'good medical practice'. It is important to emphasise that in rare cases the therapeutic attitude has not been shown to be adopted in the benefit of children (l).

The importance of family physicians in the management of IH cases is paramount, hence the recommendation to use the IHReS Infantile Haemangioma Referral Score - IHReS (9). We noted the 20% proportion (of one in five cases) presented late to specialist care after referral issued by the GP.

Anecdotally, but consistent with the cultural norms observed in rural residency based on the sometimes not-watchful "wait and see" belief and attitude, such norms are found among medical professionals, too, even when the treatment indication is very clear. When it comes to medical colleagues, this research has identified the issue as a consequence of limited access to up-to-date medical information for continuing professional development (CPD). This will be explored in the future, once IHReS is also used in Romania. IHReS is a scoring tool, developed and validated by industry experts, tested by paediatricians and family doctors. It aims to improve the decision-making process of healthcare professionals regarding the referral of patients with childhood haemangioma.

Conclusions

Quality of life is important in the therapeutic evaluation of benign conditions such as infantile haemangioma which involves aesthetics (mainly the area of dermatology).

The Romanian version of the IH-specific QoL instrument has moderate reliability but very good acceptability.

Specific instrumentation can be used at diagnosis and post-therapy to allow for the detection of differences in the therapeutic impact of Propranolol on IH.

The financial impact at family level is important if the patient does not benefit from a compensated regime of their prescribed treatment; but this can also be owed to the absence of specialised territorial services (reduced access), which causes financial effort for repeated trips (unequal access), sometimes long distances from home (low access).

The financial impact on the health service system is considerable if cases requiring admission are not rigorously screened and clinically explored, especially if the department to which the patient is admitted is a surgical one.

Any therapeutic product follows several pathways in the post-marketing authorisation phase but all are linked to the mechanisms of the healthcare market. The market behaviour of the product becomes interesting when it goes generic and when research discovers that a drug can also be prescribed off-label. This is the case with Propranolol

According to economic laws of markets, if there is no demand of a product (treatment), at a minimum price, the quantity sold remains small; as demand increases so does supply; in this context one has to calculate the equilibrium price for the necessary quantity of the product to be supplied to the market; however, this does not exclude the unusual behaviour of products in the healthcare market when off-label prescribed generic products may become a "niche" product; pricing strategies could address this.

To have answered the present research question "how do families cope with everyday life when a child has been diagnosed with infantile haemangioma"? Before attempting an answer, another question can be asked: "What happens to a well established generic product when a restrictive clause is introduced in its marketing authorisation, introduced as a result of a change in the prescription modality from on-label to off-label?"

A first observation in the market, a change unapparent at first, is reflected in the role of the new restriction, i.e. the lack of a product that directly satisfies this demand, so

pressure will be put on the price and this can be raised above the equilibrium price (P1). The quantity supplied will initially be reflected in a reduced demand, process which will be 'masked' by the use of substitute or an alternative product, but which fulfil the same therapeutic role. The evolution of the market could also lead to a subsequent fall in price below the equilibrium price (P2). In the range created the market is now divided: those who can afford the alternative product at P1 (solution) and those who will turn to the alternative defined by P2 (tablet). With the emergence of P2 demand can be pushed onto a parallel path, i.e., actually allowing a fall in demand for product at P1.

While this may be encountered in the market for any generic product, when off-label prescribing appears, demand (for product at P1) may fall even more, but less noticeably, i.e. for a smaller segment, such as in the case of a rare pathology. Only cost analyses and pricing strategies can detect such changes.

The rolling average of the number of IH cases analysed over a period of 10 years is interpreted as a trend following and mirroring some regulations which appeared during the same period of observation. The trend analysis picks up what happens to the number of cases after 2008 and, although explanations for fluctuations in diagnosis, presentations and other elements defining access to specialist services can be numerous, it is noted that the period is marked by the entry into force of the cross-border Directive 2011/24 (October 2013) and the advent of topically applied gel (NICE England guide August 2015). The lowest number of cases recorded is observed in 2013. After 2015 the guideline has not been revised or renewed but, England has probably the largest market for alternative therapeutic products under Propranolol solution. They are marketed at much lower prices, shown to be below the price of the product that has monopolised the European (EU) market.

As a recommendation, further research aims to analyse this generic product prescribed under off-label regimen. This is necessary because the therapeutic product marketed in Romania has a compensated prescription regime for only 6 months, during which time cure is not always guaranteed and discontinuation of treatment may lead to relapses. Thus, the remaining 6-9 months leave the family exposed to a very high cost of treatment, often prohibitive to cover other needs. This leads parents to seek and buy the treatment from other markets where the price of the recommended paediatric product is below the Romanian or EU purchasing price (recommended by EMA). These alternative markets may also be from outside the EU, where the pharmaceuticals market may be regulated differently from the EU one.

The issues discussed in this research are important for the contextual answer to the question that prompted the initiation of the present research and its approach through the lenses of a tertiary prevention service.

In conclusion a partial answer to the question of how insured and uninsured families cope with these costs and the cost of living is that they are finding it very difficult to cope with the fact that the marketing authorisation for off-label prescribing has established not only a high price (2 RON for one mg Propranolol DCI in solution) but also a shorter payback period for the compensation of the amount invested (maximum 6 months). This is despite the fact that in some countries the therapeutic recommendation is as long as 12-15 months. Families thus face an economic burden of 6-9 months, which directs them to alternative markets for substitute solutions with: either various other concentrations of the active substance, or they must resort to preparing the prescribed daily dose from tablets. More than half of those in the present research group come from families with unskilled occupations or occupations whose incomes are below the median income in the economy and this was noted by the questionnaire through higher scores for mothers in the unskilled occupational category. Not being able to afford a readymade product and resorting to making an ad-hoc treatment solution in the given socio-economic context poses risks in treatment administration.

Once being able to establish the clinical and treatment algorithm and this can be studied in a greater detail along with outcomes such as quality of life of patients and families, it is recommended to review the monopolistic price of this marketed product, to make the existence of alternative and substitute products on the market more transparent so that low-income families have a good part of the economic burden reduced. Price inelasticity, which is specific to the health services market, must not lead families in need to avoid access to specialist services, especially when the therapeutic recommendation is referred and endorsed by the specialist doctor.

A good starting point would be to address the economic situation of the unemployed: economically inactive, schoolchildren, pensioners. Although the research found very few in numbers, these categories could the first in which social inequalities could be identified and addressed.

Personal contributions

Considering that infantile haemangioma is the most common benign tumour of the child, which occurs most frequently immediately in the postnatal period (a period of high emotional vulnerability for the family in general and for the mother in particular) and which can have an unfavourable evolution by rapid growth in size or by the appearance of complications, the increased interest shown in recent years in this condition is highly justified, especially when it comes to outcome measurements such as assessing the quality of life of patients and their families.

The family implications of haemangioma range from financial difficulties to emotional disturbances and family dissolution. The lack of specialised local health services places a heavy financial and physical burden on the families of children with haemangioma, as well as overburdening existing specialised centres, at considerable cost to them.

Diagnosis, treatment and follow-up of these patients are available, and as with any health care service they are making use of resources: financial, medical and emotional, to mention just a few.

As a complex entity, haemangioma requires a multidisciplinary team for diagnosis and treatment, and the increased heterogeneity of the therapeutic approach makes case management difficult as it depends on the type of treatment chosen.

The paucity of studies or research on the evaluation of the quality of life of families of children with haemangioma, as well as the recommendations related to the diagnosis and treatment of this pathology in Romania and the lack of studies on the financial impact on the families of these children and service providers was the reason for choosing this topic for a doctoral research.

The elaboration of the PhD thesis "Haemangiomas in children - medical, social and family implications" was based on a complex review of the literature with an evaluation of the most recent bibliographic data. The first objective of the present research was to develop and validate a tool to assess the quality of life of the patient and family of the infantile haemangioma patient. The result is a questionnaire with 26 questions, with moderate reliability but high acceptability - IH-QoL-RO, the first HI-specific instrument adapted to the Romanian population. This disease specific instrument is easy to use, quick to administer and can identify and highlight the difficulties faced by patients with IH and

their families. If used repeatedly, over time, for the same patient it could provide supporting evidence of therapeutic benefit.

The detailed and in-depth description of demographic characteristics and therapeutic approaches allowed a comparison of results with current internationally published studies. This was achieved despite the fact that the research spanned over a longer period than expected and has also crossed a pandemic (COVID-19).

Policies/regulations or programmes to help families who find it difficult to access specialised health services, adapted to their needs and updated with the latest findings, are needed. A very important step is cost-plus compensation for the drug product that is currently considered the "gold standard". Decreasing the burden of diagnosis and treatment on tertiary centres by creating territorial centres (a great benefit also for patients' families, who do not have to travel long distances) is another conclusion of this study. The first condition in achieving this is accurate information for all the actors involved in this condition (parents, medical staff and third party payer). The approval of IHRes for use in Romania can be a first step and a good tool for family doctors who are the gatekeepers in the Romanian health care service.

The results of the study can be found in the four published articles (21-24).

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