Poznan University of Medical Sciences
Poland

JMS Journal of Medical Science

previously Nowiny Lekarskie

Founded in 1889

2020
Vol. 89, No. 4

QUARTERLY

Indexed in:
Polish Medical Bibliography, Index Copernicus,
Ministry of Science and Higher Education, Google Scholar

eISSN 2353-9801
ISSN 2353-9798

www.jms.ump.edu.pl

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PUBLISHER
Poznan University of Medical Sciences

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eISSN 2353-9801
ISSN 2353-9798

Publishing Manager: Grażyna Dromirecka
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Ark. wyd. x,x. Ark. druk. x,x.
Zam. nr x/19.

The Editorial Board kindly informs that since 2014 *Nowiny Lekarskie* has been renamed to *Journal of Medical Science*.

The renaming was caused by using English as the language of publications and by a wide range of other organisational changes. They were necessary to follow dynamic transformations on the publishing market. The Editors also wanted to improve the factual and publishing standard of the journal. We wish to assure our readers that we will continue the good tradition of *Nowiny Lekarskie*.

You are welcome to publish your basic, medical and pharmaceutical science articles in *Journal of Medical Science*.

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ORIGINAL PAPER

JMS Journal of Medical Science

Styles of coping in a stressful situation, social support and psychological consequences in emigrants from the Netherlands

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DOI: https://doi.org/10.20883/medical.e431

Keywords: emigration, stress, the Netherlands, styles of coping, social support

Published: 2020-12-29

How to cite: Bujek-Kubas I, Kopczyński P, Mojs E. Styles of coping in a stressful situation, social support and psychological consequences in emigrants from the Netherlands. JMS [Internet]. 2020Dec.29 [cited 2021Apr.3];89(4):e431. Available from:. doi:10.20883/medical.e431

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ABSTRACT

Emigration is an experience irrevocably associated with stress caused by leaving one's family home, changing one's social environment as well as living conditions, etc. The main aim of this study was to establish if and what correlations there are between different styles of coping with stress, social support and psychological consequences resulting from the emigration of a group of 96 Polish emigrants living in the Netherlands. The participants were clients of the Pomoc Nederland (the name reflects the company's objective to help the Poles living in the Netherlands) company, aged from 31 to 50 years and they had lived abroad for 1 to 20 years. The research tools applied in the study included the Social Support Questionnaire and the Inventory to Measure Coping Strategies with Stress Mini-COPE. The psychological consequences of emigration-related stress were evaluated using: the Scale of Positive and Negative Experience (SPANE), the State-Trait Anxiety Inventory (STAI) and the Satisfaction with Life Scale (SWLS). The findings showed that in the group of subjects, certain personal resources were significantly correlated with constructive strategies of coping with stress while living abroad. It was revealed that among the evaluated emigrants only emotional support was significantly correlated with certain psychological consequences resulting from emigration-related stress.

Introduction

Stress is a dynamic adaptive human reaction resulting from the difference between our abilities and the requirements of the situation, prompting taking remedial measures to restore the state of balance. We deal with stress when the challenge encountered makes us cope with it. Moreover, disregarded stress is the cause of many serious diseases [1].

Lazarus and Folkman defined coping with stress as "constantly changing [i.e. dynamic] cognitive and behavioural efforts to manage specific external and/or internal demands that are

appraised as taxing or exceeding the resources of the person" [2]. The ability to cope with stress may take two forms, either of management or self-defence. A common characteristic of defensive reactions to stress is their low efficiency and usually, such reactions lead to the abandonment of goals as a result of the experienced stress [3]. There are different forms of defensive reactions to stress ranging from escape and withdrawal from a stressful situation through aggressive behaviour (attack on the source of threat) to various symbolic actions, which assign the reality a new non-threatening meaning [4].

As regards subjectively experienced stressors, coping is a process, an attempt to manage specific demands appraised as taxing or exceeding the resources of the person [5]. The effects of coping can be evaluated by observing emotional reactions, motor activities or physiological symptoms. A person can assess the efficacy of the chosen coping strategy based on its "psychological cost" and secondary threats, with such an appraisal leading to a change in the coping strategy [3].

According to Lazarus and Folkman, problem-focused strategies are a type of coping strategies aimed at changing the stress-inducing situation and finding a solution to the problem. They include confrontational coping, self-control, seeking social support, acceptance of responsibility, as well as planning and solving the problem [2]. Efficient problem-focused coping requires good use of cognitive components such as rationality, flexibility or being oriented at long-term outcomes, with both realistic and accurate evaluation of the stressor and available resources being indispensable [6]. People applying problem-focused strategies undertake different actions to solve the problem or change the stressful situation using cognitive processes, thereby adapting to changing conditions. Such an individual, thanks to mobilisation and concentration of efforts, makes plans and relies on other people's advice, presence and knowledge [7]. Furthermore, Folkman and Lazarus claim that people show a tendency to use problem-focused strategies when the required solution needs to be concrete, innovative and positive. It is believed that problem-focused strategies are the most adaptive for individual human beings [1].

Another kind of coping strategies is emotion-focused strategies which consist in dealing with an emotional reaction to the occurring stressor [8]. The regulatory function of emotion-focused coping helps to control the emotional reaction to the stressor. In the coping process, problem-focused strategies are given greater prominence. Still, the role of emotions has been emphasised and it has been indicated that, regardless of signs, emotions perform an adaptive function. Emotion-focused coping may result in emotional arousal, which provides a powerful stimulus to act [9].

Emigration is correlated with an increased risk of mental disorders caused by severe stress, as well as adaptational difficulties. Research conducted in the late 1960s on Finnish economic migrants to Sweden showed that a significant percentage of subjects suffered from various mental disorders and diseases, including a sense of being harassed, various psychosomatic symptoms and alcoholism [10]. Experts stress that any type of migration, including voluntary migration, poses mental health risks. Indeed, Polish emigrants are particularly exposed to stress and other mental disorders due to high and often unrealistic expectations related to living in another country. After arriving in a new country, emigrants face the necessity to take up a less prestigious job for which they are overqualified, hence, they experience much frustration. Some people are not prepared for the difficulties related to the organisation of life abroad, such as the need to complete numerous formalities, find somewhere to live, as well as problems with communication - the language barrier [10].

Each trip abroad from the country of origin is a contact with a different culture, and all kinds of contacts with people from different cultural circles, whether resulting from relocation or working in multicultural teams or finally from emigration, are inherently associated with an increased level of stress. Emigration may also cause disturbances in the performance of family roles, mainly parental roles, or be one of the factors determining emigration, as tensions and conflicts in the family may act as a potential push factor [11].

Staying in a new country, intercultural interaction, trying to establish relationships and meeting everyday needs is also a confrontation with intercultural differences. As shown by the perspective of acculturation stress, experiencing cultural differences is one of the reasons for experiencing difficult emotions during a stay abroad. The dif-

ference, unlike similarity, often causes a negative assessment of a person or event [10].

Stress not only leads to the development of various disorders and diseases but also affects the person's behaviour and the treatment process. There is empirical evidence indicating that stressful situations, especially those critical to the person, deteriorate their health habits and, in turn, encourage unhealthy behaviours such as smoking or drinking and disturbed eating or sleeping habits. Such behaviours may have an addictive and autodestructive nature [12].

As regards unhealthy behaviours, coping involves, among other things, the use of psychoactive substances. The main function of intoxication is the regulation of emotions. In effect, the tension is being either reduced or induced in the sense that it makes the person feel powerful. The use of such substances is classified under avoidant coping strategies and intoxicants such as alcohol, sedatives, analgesics or narcotics distort the rational perception of reality. Their stress-reducing effects can be seen in their tranquillising properties, the elimination of fatigue or openness in social contacts, consequently, coping resources are reduced and permanently blocked. The willingness to engage in other remedial measures is lacking, hence, such coping strategies are autodestructive. Gambling, compulsive eating or spending too much time watching television are treated analogously as autodestructive [13].

Currently, the most common substances used to cope with stress are alcohol, nicotine and specific groups of sedatives or analgesics. There is also a whole range of drugs that are no less popular despite their varying legal status which have strong stress-reducing effects, including heroin, marihuana or cocaine. Both tension-reducing and tension-inducing, as well as empowering effects of intoxicants, are among the reasons why people use intoxicants, which may become a habit [12]. Apart from autodestructive coping strategies involving the use of intoxicants, there are other coping strategies with a similar psychological function and often similar impact, including compulsive eating, gambling, compulsive gaming or TV watching or sexual addiction [12].

Stress, adaptational difficulties and the feeling of loneliness may result in many health problems, most often including depression and psychosomatic symptoms such as hypertension, dizziness, gastrointestinal or hormonal disorders [10]. Also, there is a high incidence of suicides among emigrants. The causes are many and usually determined by different overlapping circumstances, however, maladaptation and uprooting are often repeated among the causes of suicide attempts. Maladaptation of emigrants may result from different factors, such as the never-ending spiral of failures described by Osipowicz as "lack of a job, the inability to get it or keep it, unemployment – these are the worst scenarios for any economic migrant." Such a person has to face their financial failure and becomes convinced of one's uselessness. The lack of money and the inability to pay for one's food, accommodation or clothes pose direct threats and the individual may become unable and unwilling to act. In extreme cases, unemployment may result in depression and frustration [11].

Social maladaptation may be accompanied by a sense of uprooting and is particularly characteristic of those emigrants who, on the one hand, find it difficult to integrate with the host community, but on the other, are faced with disturbed functioning while in the host community. It has been postulated that integrating with the community may have a protective effect on a person's health. However, the integration with the host community becomes increasingly difficult due to the changing public opinion of economic migrants from poorer countries of the European Union [14]. The role of an external source of coping, namely social support, has also been emphasised lately because of its potential for enhancing self-esteem [15].

Empirical findings prove that Polish economic migrants are usually lonely as they find themselves in a new environment and need to adapt to the existing rules and conditions. So, the life of an individual abroad has two dimensions. Firstly, they are far from home with spatially-limited contact with their family. Secondly, they must settle in a completely unfamiliar environment. They miss their families, which results in the feeling of loneliness and poses many threats, out of which getting lost in one's system of norms and values seems to be the most dangerous [16].

The research on social support shows that the received support reduces the perceived threat in stressful situations and the available social sup-

port directly influences the person's health and well-being regardless of situational factors. It also becomes a predictor of applied self-regulatory strategies such as planning of actions aimed at reducing difficulties [17].

Material and Methods

In the present study, 96 Polish emigrants living in the Netherlands were recruited from 12 July 2017 until 20 September 2017. They were clients of the Pomoc Nederland company and had lived abroad for 1 to 20 years. At the time of conducting the study, all subjects were of legal age and provided written informed consent to participate in the study. They were informed of its objective as well as of the fact that the obtained results were to be further used for research.

The main aim of the study was to establish if and what correlations there are between different styles of coping with stress, social support and psychological consequences resulting from emigration. For this, the following research tools were used: the Inventory to Measure Coping Strategies with Stress Mini-COPE, the Social Support Questionnaire, the Scale of Positive and Negative Experience (SPANE), the State-Trait Anxiety Inventory (STAI) and the Satisfaction with Life Scale (SWLS).

The COPE inventory is among the most commonly applied tools for the measurement of stress coping [9] and consists of 28 statements to measure 14 strategies of coping with a difficult situation. The strategies include active coping, planning, positive reinterpretation, acceptance, humour, turning to religion, seeking of emotional social support, seeking of instrumental social support, competing activities, denial, venting of emotions, psychoactive substance use, restraint coping, self-blaming. The answers are rated on a 4-point scale, where 0 means "I usually don't do this at all" and 3 means "I usually do this a lot". The score is given as a sum of answers for particular dimensions [18].

The Social Support Questionnaire is used to measure the received social support and includes 40 items, each with a 5-point response scale ranging from A (almost every day) to E (not at all). According to instructions, the help received over the last month should be taken into account. The questionnaire aims to determine if the evaluated person feels that other people help or try to make life better and how this person feels about it. Respondents evaluate their feelings in four dimensions related to material, emotional, instrumental and cognitive support. There is also an additional question that asks about whom the respondent relies upon in a difficult situation and where they seek help.

The SPANE is intended for the measurement of overall affect balance and consists of two subscales regarding positive (P) and negative (N) feelings. For the SPANE-P subscale, the answers are given on a five-point scale (1–5), then summed up for six positive feelings: positive, good, pleasant, joy, happy, contended. For the SPANE-N subscale, the answers are given on a five-point scale (1–5), then summed for six negative feelings: negative, bad, unpleasant, sad, afraid, angry. To obtain the overall affect balance, the SPANE-P score is subtracted from the SPANE-N score.

The STAI is used to measure anxiety understood as a relatively constant personality trait. It was developed by Spielberger, Gorsuch and Lushene and adapted to Polish conditions by Spielberger, Tysarczyk and Wrześniewski. This research tool is composed of two scales, each including 20 items. The X-1 scale assesses state anxiety and the X-2 scale assesses trait anxiety. Answers are marked with values ranging from 1 to 4 and respondents choose answers according to their feelings.

The SWLS evaluates the satisfaction with one's life, achievements and living conditions. The tool was designed by Diener et al. and adapted by Juczyński. Based on the SWLS, global satisfaction with one's life can be measured. It consists of 5 statements concerning the cognitive judgement of life as a whole. The first four statements are about the present, whereas the last statement encourages the evaluation of the past and summing-up of one's life so far.

Study group

The study group comprised 96 Polish emigrants living in the Netherlands, mainly women (63.5%). Subjects aged from 31 to 40 years (n=29) were the largest subgroup, followed by subjects aged from 25 to 30 years (n=21; 21.9%), up to 24 years of age (n=18; 18.8%) and aged from 41 to 50 years

(n=15; 15.6%). Subjects of over 50 years of age were the least numerous subgroup (13.5%). Most participants had lived abroad from 3 to 10 years (52.1%), followed by from 1 to 3 years (19.8%), 10 to 20 years (15.6%) and less than a year (11.5%). Only one person lived abroad for more than 20 years.

Among the respondents, most were in a relationship and shared a household with their partner (n=35; 36.5%), with 29 married respondents married (30.2%) and 32 single subjects (33.3%).

Regarding educational background, most respondents had secondary education (n=39; 40.6%), followed by post-secondary education (n=22; 22.9%), basic vocational education (n=18; 18.8%), higher education (n=14; 14.6%), and primary education (n=2; 2.1%), whereas one person had lower secondary education (1.0%).

Statistical analysis

The participants' responses were entered into the database, with data presented as means, standard deviations, min and max. The reliability of the analysed questionaires was assessed by Cronbach's Alpha coefficient. The Kendall Tau-b correlation was used to verify whether there was a relationship between the Material, Emotional, Instrumental and Cognitive Support and the psychological consequences of emigration stress.

Results

The results presented in the tables below show the minimum and maximum scores, means, standard deviations, Cronbach's Alpha reliability coefficients. The reliability of each of the applied scales was assessed as suitable for the scales to be used in further analysis (**Tables 2-4**). However, the reliability coefficient for the Active Coping variable in **Table 3**, the Acceptance and Humour variables in **Table 4** and the Competing Activities, Denial and Venting of Emotions variables in **Table 5** were moderate and close to alpha ≈ 0.50, hence not low enough to exclude the variables from further analysis.

After analysing all the variables and their distribution, Kendall's Tau-b correlation was used to test the null hypothesis. **Table 6** presents the results of coping strategy application concerning the psychological consequences of stress caused by emigration, indicating that Positive Feelings

Table 1. Statistical description of dependent variables – psychological consequences of emigration-related stress

Variable	Min	Max	M	SD	Cronbach's Alpha
Positive Feelings	8	30	22.75	4.81	0.90
Negative Feelings	6	26	13.99	5.44	0.88
Affect Balance	-24	18	-8.76	9.07	0.86
Anxiety as a state	20	75	37.76	12.51	0.95
Trait anxiety	21	76	40.42	12.30	0.93
Satisfaction with Life	5	34	22.15	6.64	0.82

Table 2. Statistical description of independent variables – social support

Variable	Min	Max	M	SD	Cronbach's Alpha
Material Support	16	40	34.73	4.75	0.70
Emotional Support	12	60	41.51	10.08	0.86
Instrumental Support	9	35	26.69	5.89	0.76
Cognitive Support	22	65	48.57	10.88	0.89

Table 3. Statistical description of independent variables – problem-focused coping in an emigration-related stressful situation

Variable	Min	Max	M	SD	Cronbach's Alpha
Problem-focused Coping	2	18	11.30	3.39	0.70
Active Coping	1	26	13.66	4.96	0.50
Planning	0	31	12.40	6.53	0.65
Seeking of Instrumental Social Support	0	6	4.19	1.42	0.71

Table 4. Statistical description of independent variables – emotion-focused coping in an emigration-related stressful situation

Variable	Min	Max	M	SD	Cronbach's Alpha
Emotion-focused Coping	0	6	4.11	1.54	0.71
Positive Reinterpretation	0	6	2.98	1.61	0.68
Acceptance	0	6	3.38	1.57	0.51
Humour	0	6	3.55	1.62	0.50
Turning to Religion	0	6	2.09	1.49	0.88
Seeking of Emotional Social Support	0	6	1.38	1.73	0.83

Table 5. Statistical description of independent variables – dysfunctional coping in an emigration-related stressful situation

Variable	Min	Max	M	SD	Cronbach's Alpha
Dysfunctional Coping	0	6	3.23	1.78	0.82
Competing Activities	0	6	3.43	1.65	0.52
Denial	0	6	1.71	1.62	0.52
Venting of Emotions	0	6	2.54	1.38	0.50
Psychoactive Substance Use	0	5	0.77	1.38	0.86
Restraint Coping	0	6	1.37	1.44	0.65
Self-blaming	0	6	2.56	1.92	0.85

Table 6. Coping strategies compared to the psychological consequences of emigration-related stress – Kendall's Tau-b correlation coefficients

	Positive Feelings	Negative Feelings	Affect Balance	State-Anxiety	Satisfaction with Life
Problem-focused Coping	0.132*	0.054	-0.049	-0.058	0.024
Active Coping	0.202**	-0.029	-0.127	-0.087	-0.010
Planning	0.074	0.076	-0.011	0.004	0.028
Seeking of Instrumental Social Support	0.012	0.106	0.034	-0.002	-0.016
Emotion-focused Coping	0.318**	-0.106	-0.241**	-0.159*	0.245**
Positive Reinterpretation	0.282**	-0.115	-0.235**	-0.164*	0.197**
Acceptance	0.200**	-0.116	-0.189**	0.144**	0.084
Humour	0.064	-0.084	-0.089	-0.117	0.159*
Turning to Religion	0.092	0.113	0.025	0.0097	0.015
Seeking of Emotional Social Support	0.283**	-0.099	-0.222**	0.218**	0.257**
Dysfunctional Coping	-0.173**	0.411**	0.328**	0.337**	-0.261**
Competing Activities	0.112	0.172*	0.040	0.092	-0.026
Denial	-0.149*	0.336**	0.259**	0.256**	-0.252**
Venting of Emotions	-0.164*	0.353**	0.298**	0.258**	-0.156*
Psychoactive Substance Use	-0.148*	0.174*	0.193**	0.197**	-0.239**
Restraint Coping	-0.185**	0.341**	0.295**	0.324**	-0.192**
Self-blaming	-0.209**	0.417**	0.352**	0.370**	-0.314**

* $p < 0.05$, ** $p < 0.01$. Source: authors' research

were significantly, weakly and positively correlated with Problem-focused Coping, Active Coping, Emotion-focused Coping, Positive Reinterpretation, Acceptance and Seeking of Emotional Social Support. Therefore the high values obtained for the Positive Feelings scale corresponded to high values for Problem-focused Coping, Active Coping, Emotion-focused Coping, Positive Reinterpretation, Acceptance and Seeking of Emotional Social Support. Positive Feelings were weakly and negatively correlated with Dysfunctional Coping, Denial, Venting of Emotions, Psychoactive Substance Use, Restraint Coping and Self-blaming. Therefore, the high values obtained for the Positive Feelings scale corresponded to low values for Dysfunctional Coping, Denial, Venting of Emotions, Psychoactive Substance Use, Restraint Coping and Self-blaming.

Negative Feelings were moderately and positively correlated with Dysfunctional Coping,

whereas weakly and positively with Competing Activities, Denial, Venting of Emotions, Psychoactive Substance Use, Restraint Coping and Self-blaming, that is, the high values obtained for the Negative Feelings scale corresponded to high values for Dysfunctional Coping, Competing Activities, Denial, Venting of Emotions, Psychoactive Substance Use, Restraint Coping and Self-blaming.

Affect Balance and State-Anxiety were weakly and negatively correlated with Emotion-focused Coping, Positive Reinterpretation, Acceptance and Seeking of Emotional Social Support. They were also weakly but positively correlated with Denial, Venting of Emotions, Psychoactive Substance Use, Restraint Coping and Self-blaming. This means that high values obtained for Affect Balance and State-Anxiety were associated with low values for Emotion-focused Coping, Positive Reinterpretation, Acceptance and Seeking of Emotional Social Support, as well as with high values obtained for Denial, Venting of Emotions, Psychoactive Substance Use, Restraint Coping and Self-blaming.

Satisfaction with Life was weakly and positively correlated with Emotion-focused Coping, Positive Reinterpretation and Seeking of Emotional Social Support, as well as weakly and negatively correlated with Denial, Venting of Emotions, Psychoactive Substance Use, Restraint Coping and Self-blaming. This indicates that high values in the SWLS corresponded to high values for Emotion-focused Coping, Positive Reinterpretation and Seeking of Emotional Social Support but to low values obtained for Denial, Venting of Emotions, Psychoactive Substance Use, Restraint Coping and Self-blaming.

These findings indicate that the more positive feelings a person has, the more satisfied they are with their life, the better they cope with stress and the more likely they are to choose problem-focused and emotion-focused coping strategies. Moreover, more negative feelings and anxiety a person experiences, the worse they cope with stress and are more likely to choose dysfunctional coping strategies.

To check if there was a correlation between Material, Emotional, Instrumental, Cognitive Support and psychological consequences of stress resulting from emigration, Kendall's Tau-b correlation coefficient was calculated for given pairs of variables (**Table 7**), revealing that Emotional Support was weakly and negatively correlated with Positive Feelings, as well as weakly and positively correlated with Affect Balance. This means that high values obtained for Emotional Support corresponded to low values obtained for the Positive Feelings scale and high values obtained for the Affect Balance scale. It was observed that the more emotional support a person receives, the fewer positive feelings the y show.

These findings may point to the fact that the higher the person's emotional support, the higher the person's Affect Balance, which means that negative feelings exceed positive feelings for such a person.

Table 7. Social support compared to the psychological consequences of emigration-related stress – Kendall's Tau-b correlation coefficients

	Positive Feelings	Negative Feelings	Affect Balance	State-Anxiety	Satisfaction with Life
Material Support	-0.043	-0.052	0.006	0.050	-0.011
Emotional Support	-0.179**	0.011	0.128*	0.078	-0.052
Instrumental Support	-0.071	-0.091	0.001	0.013	-0.036
Cognitive Support	-0.096	-0.071	0.036	-0.013	0.010

* $p < 0.05$, ** $p < 0.01$. Source: authors' research

Table 8. Emotional support, cognitive support, life satisfaction and gender

Variable	Women N=61 M (SD)	Men N=35 M (SD)	t	df	p
Satisfaction with Life	21.95 (6.59)	22.49 (6.79)	-0.38	94	0.70
Emotional Support	51.93 (5.36)	55.63 (5.15)	-0.75	94	0.45
Cognitive Support	53.60 (4.08)	54.20 (5.61)	-0.23	94	0.82

Then, the gender differences in the analysed variables were determined. The distribution of variables: Positive Feelings, Negative Feelings, Affective Balance, Anxiety-State were not consistent with a normal distribution. The Satisfaction with Life variable was normally distributed. Material support and Instrumental support do not follow the normal distribution, whereas Emotional support and Cognitive support are normally distributed. Moreover, all styles of coping with stress do not follow a normal distribution. When determining the differences between the sexes, the student's t-test (normal distribution) or the Mann-Whitney test (not normally distributed) were used (**Tables 8, 9**).

Significant gender differences were found in the coping style focused on turning to religion ($Z = 2.44$; $p = 0.01$; $p < 0.05$) and dealing with something else ($Z = 2.39$; $p = 0.02$; $p < 0.05$), with more women turning to religion to cope with stress.

In the last step of considering the relationship between marital status and the analysed variables, the ANOVA test (normal distribution) or Kruskal-Wallis test (not normally distributed) were applied (**Tables 10, 11**). Marital status significantly differentiated the level of Satisfaction with Life ($F = 3.31$; $p = 0.04$; $p < 0.05$), with married people characterised by the highest level of life satisfaction, while people in a partnership relationship were characterised by the lowest level of life satisfaction. Also, marital status differentiated the intensity of using a coping style focused on a sense of humour ($H = 6.21$; $p = 0.04$; $p < 0.05$), with singles using a humour-centred style more often than those in a relationship. Moreover, marital status was differentiated by the intensity of using the discharge-focused coping style ($H = 6.18$; $p = 0.04$; $p < 0.05$), with married people more likely to use the discharge-focused style compared to singles.

Table 9. Social support, anxiety as a state, positive and negative feelings, styles of coping with stress and gender

Variable	Women Sum. rang	Men Sum. rang	U	Z	p
State-Anxiety	3154.00	1502.00	872.00	1.48	0.14
Positive Feelings	3009.50	1646.50	1016.50	0.38	0.70
Negative Feelings	3212.00	1444.00	814.00	1.93	0.09
Affect Balance	3086.50	1569.50	939.50	0.97	0.33
Active Coping	3134.50	1521.50	891.50	1.34	0.18
Planning	3014.00	1642.00	1012.00	0.42	0.68
Positive Reinterpretation	3048.50	1607.50	977.50	0.68	0.49
Acceptance	2902.50	1753.50	1011.50	-0.42	0.67
Humour	2707.50	1948.50	816.50	-1.91	0.09
Turning to Religion	3279.00	1377.00	747.00	2.44	0.01*
Cognitive Support	3209.00	1447.00	817.00	1.90	0.09
Seeking of Emotional Social Support	3148.00	1508.00	878.00	1.44	0.15
Seeking of Instrumental Social Support	3272.50	1383.50	753.50	2.39	0.02*
Competing Activities	3140.50	1515.50	885.50	1.38	0.17
Denial	3175.50	1480.50	850.50	1.65	0.10
Venting of Emotions	2805.50	1850.50	914.50	-1.16	0.25
Psychoactive Substance Use	2989.50	1666.50	1036.50	0.23	0.82
Restraint Coping	3084.50	1571.50	941.50	0.96	0.34
Self-blaming	3154.00	1502.00	872.00	1.48	0.14

* $p < 0.05$, ** $p < 0.01$. Source: authors' research

Table 10. Emotional support, cognitive support, life satisfaction and marital status

Variable	SS	df	MS	F	p
Satisfaction with Life	278.33	2	139.17	3.31	0.04*
Emotional Support	0.86	2	0.43	0.15	0.86
Cognitive Support	19.28	2	9.64	1.58	0.21

* $p < 0.05$, ** $p < 0.01$. Source: authors' research

Table 11. Social support, anxiety as a state, positive and negative feelings, styles of coping with stress and marital status

Variable	H (2, N = 96)	p
State-Anxiety	0.27	0.87
Positive Feelings	0.73	0.69
Negative Feelings	0.56	0.76
Affect Balance	0.31	0.86
Active Coping	1.59	0.45
Planning	0.64	0.73
Positive Reinterpretation	2.12	0.35
Acceptance	2.39	0.30
Humour	6.21	0.04*
Turning to Religion	1.26	0.53
Cognitive Support	1.17	0.56
Seeking of Emotional Social Support	0.10	0.95
Seeking of Instrumental Social Support	0.72	0.70
Competing Activities	0.61	0.74
Denial	0.20	0.91
Venting of Emotions	6.18	0.04*
Psychoactive Substance Use	1.46	0.48
Restraint Coping	2.13	0.34
Self-blaming	0.57	0.75

* **p** < 0.05, ** p < 0.01. Source: authors' research

Discussion

The main aim of the study was to establish if and what correlations there are between different styles of coping with stress, social support and psychological consequences resulting from emigration. It was assumed that there is a correlation between stress coping strategies and psychological consequences of emigration-related stress: Positive Feelings, Negative Feelings, Affect Balance, State-Anxiety, Satisfaction with Life. Moreover, an assumption was made that Material, Emotional, Instrumental and Cognitive Support is correlated with psychological consequences of stress resulting from emigration: Positive Feelings, Negative Feelings, Affect Balance, State-Anxiety, Satisfaction with Life.

The obtained results show that the more positive feelings a person has and the more satisfied they are with their life, the better they cope with stress and the more likely they are to choose problem-focused and emotion-focused coping strategies. In contrast, the more negative feelings and anxiety a person experiences, the worse they cope with stress and the more likely they are to choose dysfunctional coping strategies. Thus, among the Polish emigrants sampled in the Netherlands, those who were not anxious about nor afraid of living in a foreign country showed more positive feelings and were satisfied with their lives. Additionally, these subjects did not experience any negative consequences of stress resulting from living abroad, far away from their families. The bigger problems a person has to face while staying abroad, the more negative feelings and anxiety they experience, consequently, they are less satisfied with their life and have fewer positive feelings.

The studies on emigration-related stress have shown that economic migrants face increased health-associated risks, which is caused among other factors by the nature of the undertaken job. Most studies on the health of migrants put a greater emphasis on mental health problems such as stress, depression, adaptational difficulties or culture shock. Experts have highlighted that any kind of migration is associated with mental health risks. Polish emigrants are particularly vulnerable to stress and other mental disorders due to high and frequently unrealistic expectations associated with their emigration. Additionally, some emigrants are not prepared for the many difficulties of living abroad, including formal requirements, finding somewhere to live or the language barrier [9].

Our findings also show that there are significant, negative, moderate correlations between Material, Emotional, Instrumental, Cognitive Support and psychological consequences of emigration-related stress: Positive Feelings, Negative Feelings, Affect Balance, State-Anxiety, Satisfaction with Life. This suggests that the more emotional support a person receives, the fewer positive feelings the person shows. Moreover, the higher the person's emotional support, the higher their Affect Balance, which means that negative feelings exceed positive feelings for such a person.

However, the study findings do not allow to explicitly state whether emotional social support is beneficial to those living abroad. The research conducted so far has proven that greater social support makes people plan and seek a solution to a problem, as well as positively reinterpret and actively seek support. When social support is scarce, positive reinterpretation is a dominating strategy but wishful thinking and blaming oneself for what has happened play an increasing role [18]. It is worth mentioning that the stress experienced by an emigrant depends greatly on their environment and the degree of integration with their countrymen or ethnic group. Insufficient social support is believed to be one of the causes of mental disorders among emigrants [9]. During social interaction, emotions, information, as well as physical goods are delivered and received, perceived, assessed or used in various ways. Very complex mechanisms and correlations between the characteristics of a difficult situation, the person under stress or in crisis and different helping groups determine the effect of social support [19]. Support "may function as a resource, a desire caused by one's assessment of a situation or as an element of a coping strategy, a moderator or mediator in the dynamics of coping with stress" [20].

The results obtained in the study may be used by academic teachers and psychologists engaged in therapeutic workshops or training aimed at preventing emigration-related stress and negative emotions. Moreover, they can be applied by any professional helping emigrants adapt to living in a foreign country. The present article may be useful to those who study stress and its consequences. However, the limitation of this study is the fact that only emigration was controlled and no other stressful events.

Conclusions

- Positive feelings experienced by an individual and their satisfaction with living abroad lead to better management of stress, especially by applying problem-focused and emotion-focused coping strategies.
- Negative feelings and stress-related anxiety decrease the efficacy of coping strategies in the sense that dysfunctional coping is mainly applied.
- The high values obtained by emigrants for Emotional Support correspond to high values obtained for the Affect Balance scale. The higher the person's emotional support, the higher the person's Affect Balance, which means that negative feelings exceed positive feelings for such a person.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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ORIGINAL PAPER

JMS Journal of Medical Science

Allergic Manifestation in Paediatric Patients with Primary Immunodeficiency Diseases

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DOI: https://doi.org/10.20883/medical.e442

Keywords: immunodeficiencies, allergy, asthma, atopy, allergic manifestation

Published: 2020-10-29

How to cite: Pawłowska J, Sobocińska A, Kałuzińska-Parzyszek I, Jerzyńska J, Brzozowska A. Allergic Manifestation in Paediatric Patients with Primary Immunodeficiency Diseases. JMS [Internet]. 2020 Oct 29;89(4):e442. doi:10.20883/medical.e442

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ABSTRACT

Introduction. Primary immunodeficiency diseases (PID) are a diverse group of rare genetic disorders that affect the development and/or function of the immune system. Affected individuals are predisposed to an increased rate and severity of infections, allergy, autoimmunity and malignancy. Primary immunodeficiency diseases are considered rare; physicians and general practitioners have little knowledge about the clinical presentation, diagnostic approach and health impact of PID. Many PID patients have a clinical history in favour of allergic diseases. Nevertheless, in these patients, the importance and prevalence of atopic disorders have not been completely explained.

Aim. The aim of this study was to evaluate atopic presentations, including atopic dermatitis, allergic rhinitis and asthma in a group of PID patients under the care of our clinic.

Material and Methods. Fifty-seven pediatric patients with PID primary immunodeficiency diseases were enrolled from March 2018 to April 2019. Serum IgE levels were measured. Information regarding the patient's history of allergic diseases, including asthma, allergic rhinitis and atopic dermatitis were analysed.

Results and Conclusions. Confirmed allergy/asthma was found in 40 patients (70%). Thirty-eight patients (66.7%) had a diagnosis of asthma, 7 patients (12.3%) of allergic rhinitis and 13 (22.8%) of atopic dermatitis. Serum IgE total level was elevated in 12 patients (21%).

Introduction

Immunodeficiency diseases (ID) involve a quantitative and/or functional disorder in the immune system [1] that can result in a greater susceptibility to infections, immunological disruption, autoimmunological dysregulation, inflammation and malignancy. If the origin is genetic, it is classified

as primary immunodeficiency disorder (PID) and as secondary immunodeficiency disorder (SID) if acquired. To date, about 300 separate primary immunodeficiency disorders have been defined [2], in most cases they are antibody disorders (56.7%), other well defined PIDs (13.9%), phagocytic disorders (8.7%), T-cell deficiencies (7.5%) and complement deficiencies (4.9%) [3]. An incidence of PID is estimated as 41–83/100.000 population, according to most studies [4].

There are reports about a probable correlation between some PID and allergic diseases, due to their common atopic presentations. A lot of patients affected by PID manifest a clinical history which may suggest an allergic asthma, allergic rhinitis or atopic dermatitis [5–8].

There is some data indicating that immunodeficiencies, for example, hyper-IgE syndrome and Wiskott–Aldrich syndrome, may have an atopic component. In other PID, mainly those considering antibody deficiencies, atopy is more prevalent than in normal population, however its role has not been fully revealed [9]. Since patients with PID and allergic disease first present to a specialist with alike complaints, these two disease groups regularly take the same place in their differential diagnosis.

Aim

The aim of this study was to evaluate atopic presentations, including atopic dermatitis, allergic rhinitis and asthma in a group of PID patients.

Material and Methods

Study Design and Subjects

The study was conducted in the Department of Pediatrics and Allergy, Medical University of Lodz, Poland, from March 2018 to April 2019. Fifty-seven patients (38 males and 19 females) aged 4–18 years, with a diagnosis of primary immunodeficiencies who attended our department at that time, were enrolled in the study.

The diagnosis was established previously and the patients were evaluated due to the clinical and laboratory criteria of PID, according to the International Union of Immunological Societies (IUIS) Primary Immunodeficiency Diseases Classification Committee [6,9].

Data including age, history of asthma, allergic rhinitis and atopic dermatitis were collected from all patients by analysis of medical documentation and medical interviews. Total serum IgE levels and specific IgE level (against *Dermatophagoides pteronyssinus, Dermatophagoides farinae, Cladosporium, Alternaria*, cat and dog dander, *Aspergillus,* grass mix and tree mix) were measured (by using ImmunoCAP method) in all patients. Allergic rhinitis, atopic dermatitis and asthma diagnosis were defined according to international guidelines [10–12]. Diagnosis was confirmed by a specialist and documented.

Results

Fifty-seven eligible patients (66% males and 33% females) were enrolled into the analysis. Within the study group, 20 patients (35%) suffered from hypogammaglobulinaemia, 31 patients (54%) had IgG subclass deficiency, 3 patients (5%) had common variable immunodeficiency, and 3 (5%) patients were diagnosed with agammaglobulinaemia (**Figure 1**).

Confirmed allergy/asthma was found in 40 patients (70%). The allergic evaluation revealed that 38 patients (66.7%) had a diagnosis of asthma, 13 patients (22.8%) had a clinical history of atopic dermatitis and 7 patients (12.3%) suffered from allergic rhinitis (**Figure 2**). Fifteen patients (26.3%) manifested at least two diseases amongst asthma, atopic dermatitis and allergic rhinitis, while 14 patients from the study group (24.6%) were diagnosed with three of diseases.

.The IgE total level was elevated in 12 patients (21%) and specific IgE level was detected also in

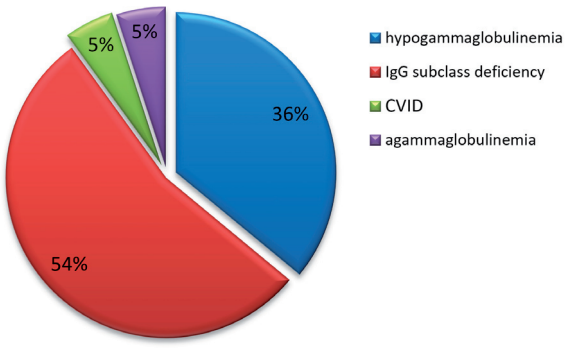

Figure 1. Characteristics of primary immunodeficiency in the study group

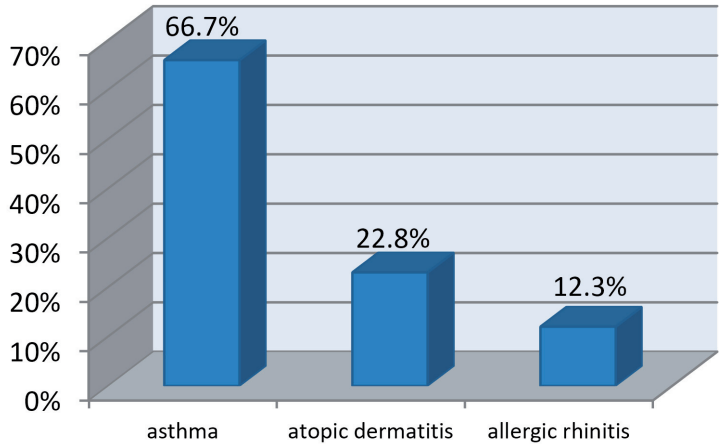

Figure 2. Patients with a positive history of allergic diseases in the study group

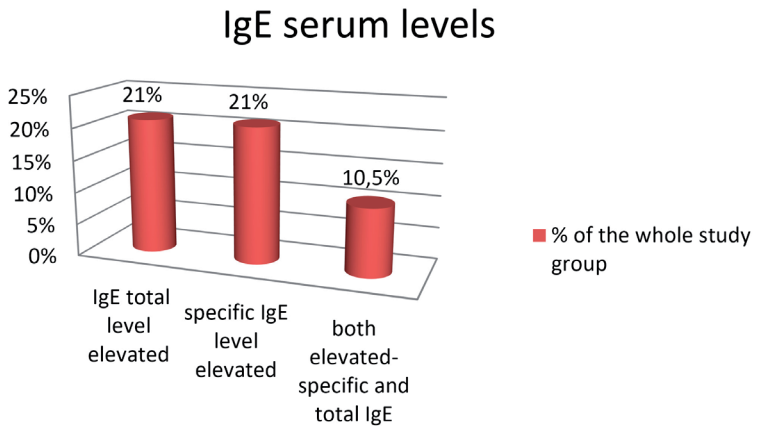

Figure 3. The percentage of patients with an elevated IgE in the study patients

12 patients (21%), while the presence of specific IgE level accompanied by elevated IgE total level was observed in 6 patients (10.5%) (**Figure 3**).

In this study, asthma was the most common (66.7%) atopic manifestation in PID patients; allergic rhinitis and atopic dermatitis were 12.3% and 22.8% respectively.

Discussion

This study was carried out to extend our knowledge about atopies in children diagnosed with PID. Several studies have reported that the frequency of atopy and allergic disease may be higher in patients with PID [9] than the general population.

Allergic disorders and primary immunodeficiency may appear simultaneously. The large surface area of the respiratory, genitourinary, gastrointestinal system enable the potential invasion of pathogens. It is known that secretory IgA (its production may be insufficient in PID patients) acts an important role in the protection of the body through particular immune receptors and modulators. Secretory IgA also acts as a relevant antibody supervising allergic symptoms and limiting allergens to lamina propria, thus reducing the inflammatory response [13]. Remittent infections may not only be with regard to immunodeficiency but also an allergic background has a significant role in clinical presentation [14,15]. In our population, 70% of patients with PID had allergic/asthma diseases.

Further studies have shown evidence linking antibody deficiency with asthma, which may indicate a higher prevalence of asthma in patients with PID than the normal population [16]. Importantly the United States Immunodeficiency Network (USIDNET) imply that asthma,

not bronchiectasis, is the most prevalent respiratory disorder among CVID patients [16]. There are also data insinuating that some asthma affected patients may also suffer from underlying PID which might not be diagnosed [17]. An impaired immune defence leading to remittent infections can cause a chronic inflammatory response, resulting in airway hyperreactivity, remodelling, and ultimately to fixed obstruction.

At the beginning of the infectious-inflammatory process, convertible changes might be clinically assessed as asthma [18]. There are opinions that remittent sinopulmonary infections with regard to PID, which might be underdiagnosed, could be the cause of chronic inflammation, resulting in hyperreactivity, damages and remodelling [16]. Identification of the role of PID as a participant in remittent infections and airway damage should refine the treatment of those potentially preventable forms of COPD.

There are reports of severe asthma in patients affected with high IgG subclass deficiency [9]. In our population, asthma was confirmed in 66.7% of patients. Furthermore, a positive role of antibiotic usage in early childhood in the development of asthma and allergic diseases is discussed. The risk of asthma development may be increased in children who undergo more than four antibiotic therapies during their first year of life [19]. From this perspective, many patients affected with PID could be at higher risk of developing asthma and allergy due to recurrent infections and frequent antibiotic courses during early childhood [15].

Allergic rhinitis is diagnosed on the basis of the patient's symptoms and specific IgE detection. Taking in consideration the abnormalities in the production of immunoglobulin and especially that the majority of CVID affected individuals do not produce IgE [5], it is noticeable that the detection of specific IgE to aeroallergens, as a diagnostic standard for allergic rhinitis, might not be manageable. For that reason, CVID patients suspected of allergic rhinitis may require additional testing, for example, by nasal provocation with the most prevalent allergens [6]. In our population, AR was diagnosed in 12.3% cases. A feasible illumination for the low detection of serum specific IgE in individuals affected CVID and allergic rhinitis can be their defective efficiency in producing immunoglobulins on a larger scale with continually present local specific IgE production to aeroallergens. According to some studies, the specific IgE local production in patients affected asthma or rhinitis was evaluated by detecting the transcription and mRNA expression of IgE in the local mucosa [20].

Approximately 50% of patients with PID show cutaneous manifestations. Skin infections are triggered frequently by *Staphylococcus aureus* and eczemas are the two most common ones. Eczematous dermatitis is one of the noninfectious skin manifestations in PID patients but is also commonly reported in the general population [21]. Thus, it is significant to be aware that the single presence of particular skin lesions does not always indicate immunological disorders. On the other hand, there are also some reports indicating that dermal alterations predated and were the grounds for clinical immunological diagnosis [22]. That is why the identification of precise skin symptoms in association with another clinical condition which may suggest immunity impairment and should point towards suspicion of underlying PID and consequently facilitate early recognition [23].

The frequent occurrence of allergies and asthma noticed in PID individuals may be considered as a result of an unstable equilibrium of the cellular and humoral immune system. The inclusion of reported atopic presentations in our study group may result in an over-estimation of its prevalence, but on the other hand, the overlapping of allergic disorders and immunodeficiency can be the reason for delayed recognition. The fact that pediatric patients with atopic disorders can present higher frequency and severity courses of infectious diseases is probable due to persistent inflammation in the airways and skin. Thus, manifestations descending from an impaired immune system may be recognised as part of the atopic disorder and vice versa [24].

Evaluation of atopy in PID patients is a challenge. Respiratory symptoms might be both a presentation of infectious complications or an allergic reaction of the respiratory tract. Moreover, PID, particularly CIVD, are often diagnosed belatedly [15,25]. A considerable cause of this situation might be the insufficient knowledge of PID amongst paediatricians, besides those in specialised centres. Contrarily, the high prevalence of remittent minor infections in children with an unaffected immune system and the significance of clinical overlapping with atopic disorders make

it extremely difficult to establish a proper diagnosis. Paediatric patients who manifest atopic or autoimmune diseases and remittent infections should have at least their immunoglobulin levels evaluated to ensure exact treatment as quickly as possible. On a final note, it will minimalise the risk related to severe infection and improve the quality of life patients with chronic infectious diseases [24]. In summary, Atopic manifestations, including asthma, allergic rhinitis and eczema should be evaluated in patients with PID.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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ORIGINAL PAPER

JMS Journal of Medical Science

What are Polish women afraid of in vaginal birth? – A Cross-Sectional Study

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DOI: https://doi.org/10.20883/medical.e489

Keywords: vaginal delivery, cesarean section, fear of childbirth

Published: 2020-12-29

How to cite: Walasik I, Kosińska-Kaczyńska K, Kwiatkowska K, Roman N, Wysińska J, Szymusik I. What are Polish women afraid of in vaginal birth? – A Cross-Sectional Study. JMS [Internet]. 2020 Dec 29;89(4):e489. doi:10.20883/medical.e489

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ABSTRACT

Introduction. Fear of childbirth is a specific feeling related to approaching birth that ranges from negligible to very intense. Women's choices and doubts regarding the way of birth may be related to a lack of knowledge about the benefits and advantages of VB or a fear of this method of childbearing.
Aim. The aim of the study was to assess knowledge regarding labour, its possible complications and ways to prepare for vaginal delivery among Polish women
Material and Methods. A cross-sectional study was performed among 4721 women who were pregnant or who had had at least one delivery. A self-composed questionnaire was distributed via the internet in 2018.
Results. It seems that 13.9% of the respondents were pregnant, 49.2% women gave birth vaginally and 30.8% had a caesarean delivery. Most of the respondents were afraid of the pain associated with the labour (75% pregnant women, 63.4% women after vaginal birth, 59.1% women after caesarean section), and 57.8% of respondents would like to avoid episiotomy, but only 27,5% of them used any methods of perineal protection for vaginal delivery. Also, 43.4 % of respondents believe that vaginal delivery may have a negative impact on satisfaction in their sexual life, 26% of respondents think that a caesarean section scar has no impact on subsequent pregnancies, and 41% claim that women who had a caesarean delivery feel discriminated against as a cesarean section is considered to be a labour failure in society.
Conclusions. Women's knowledge on the advantages and risks related to the methods of labour is insufficient, which may affect their preferences regarding vaginal or cesarean birth.

Introduction

Fear of childbirth is a specific feeling related to approaching birth that ranges from negligible to very intense. According to Ryding et al., women reporting severe fear are more likely to give birth by caesarean section (CS) (OR 1.66; 95% CI 1.05–2.61). They are also at higher risk of emergency CS and more likely to have an elective CS, mostly due to non-obstetric indications (OR 1.87; 95% CI 1.30–2.69) [1]. While nowadays CS is a safe and life-saving operation, it still carries a 2 to 7-times higher risk of maternal morbidity and mortality than vaginal birth (VB) [2, 3]. Despite those risks, women often request CS without any medical indications, mostly because of the fear of VB. Quinlivan et al. conducted a 2-year audit in a teaching hospital in Australia and found maternal choice to be the most common indication for an elective CS [4]. According to Pevzner at al., 6–15% of women would prefer their baby to be borne by CS [5]. Many authors have concluded that the increasing rate of CS is being largely attributed to maternal request [6–9]. There is no legal option for CS on maternal request in Poland and the Polish Society of Obstetricians and Gynaecologists advises against performing such operations. However, the real rate of CS "on demand" is not reported and not known. Women's choices and doubts regarding the way of birth may be related to a lack of knowledge about the benefits and advantages of VB or the fear of this method of childbearing.

Aim

The aim of the study is to investigate what Polish women are afraid of in VB and to assess their knowledge regarding the benefits and complications related to this way of birth.

Materials and Methods

A cross-sectional survey was performed. A self-composed questionnaire, composed of 29 questions in the Polish language, was distributed via the internet between November and December 2018, posted on internet forums and Facebook groups for mothers. The participants had to log in before fulfilling the survey, and it was automatically blocked after the last question to minimise the risk of multiple answers from one person. The first part of the questionnaire included sociodemographic data and information on the current or last pregnancy and birth. The second part consisted of questions regarding the knowledge and attitude towards childbirth. Primigravid women who were currently pregnant or those who previously gave birth at least once, but not later than 5 years before, were included in the study. Only completely fulfilled questionnaires were taken into analysis. The reported answers were double-checked by the researchers, and there were no identical records.

The study protocol obtained the approval of the Ethics Committee of the Medical University of Warsaw (no AKBE/126/2018). The committee waived the obligation to gain written or verbal consent to participate in the study as fulfilling the questionnaire was tantamount to giving consent.

Statistical analysis

Data was expressed as absolute numbers and percentages. Statistical analyses were performed using R version 3.2.5 (R Foundation for Statistical Computing, Vienna, Austria), and the $\chi 2$ or Fisher exact tests were used to compare categorical variables. All tests were two tailed and $p<0.05$ was considered significant.

Results

Characteristics of the study group

It can be seen that 4721 women fulfilled the questionnaire completely: 13.9% of all the respondents were pregnant at the time of survey (656), 49.2% had experienced VB before (2322), 30.8% underwent CS (1454) and 6.1% had previously delivered both vaginally and via CS (289). Also, 2669 women gave birth once and 1396 at least twice. The maternal characteristics of the study group are presented in **Table 1**.

Fear for delivery

The respondents were asked about issues they were concerned about the most regarding vaginal childbirth. Their answers are presented in **Table 2**.

Most of women pointed to pain as the most frightening aspect of vaginal birth (63.4% of them

Table 1. Maternal characteristics of the study group (study group N=4721)

	N (%)			
age (years)	≤ 20 250 (5.3)	21–30 3135 (66.4)	31–40 1256 (26.6)	≥ 41 80 (1.7)
education	basic 156 (3.3)	secondary 1657 (35.1)	vocational 278 (5.9)	university education 2630 (55.7)
inhabitancy	countryside 1109 (23.5)	cities < 100.000 inhabitants 1582 (33.5)	cities > 100.000 inhabitants 2030 (43)	

Table 2. Causes of fear for vaginal delivery among Polish women

Cause of fear	All N=4721	Pregnant N=656	After VB N=2322	After CS N=1454	After VB and CS N=289	p
	N (%)	N (%)	N (%)	N (%)	N (%)	
Pain	2993 (63.4)	492 (75)	1472 (63.4)	859 (59.1)	170 (58.8)	1 vs. 2* 1 vs. 3* 1 vs. 4* 2 vs. 3*
VB ending in CS	2068 (43.8)	337 (51.3)	918 (39.6)	691 (47.5)	122 (42.2)	1 vs. 2* 1 vs. 4* 2 vs. 3*
Defecation	1441 (30.5)	259 (39.5)	768 (33.1)	346 (23.8)	68 (23.5)	1 vs. 2* 1 vs. 3* 1 vs. 4* 2 vs. 3* 2 vs. 4*
Episiotomy	1767 (37.4)	375 (57.1)	779 (33.6)	536 (36.9)	77 (26.6)	1 vs. 2* 1 vs. 3* 1 vs. 4* 3 vs. 4* 2 vs. 3** 2 vs. 4***
Newborn's complications	2774 (58.8)	418 (63.7)	1300 (56)	908 (62.4)	148 (51.2)	1 vs. 2* 1 vs. 4* 2 vs. 3* 2 vs. 4* 3 vs. 4*

*- p<0.01; **- p=0.04; ***- p=0.02; VB – vaginal birth; CS – caesarean section

responded "yes" or "rather yes" to the question concerning the fear of this aspect). Moreover, pain was the most frightening issue for pregnant respondents, while women who previously gave birth pointed to it significantly less often (75% vs. 63.4% of women after childbirth; p<0.01). The method of the previous birth affected the fear of pain – significantly more women after VB than after CS reported being scared of it (63.4% vs. 59.1%; p<0.01). The women who were afraid of pain less often lived in big cities (42% vs. 44.6%; p=0.01), while their age or education was not related to the answers. Interestingly, childbirth schools' attendance also had no impact on the fear of pain during vaginal birth – 66.9% of women who attended and 68.8% of women who did not attend childbirth schools were mostly afraid of pain (p=0.1). Interestingly, women who experienced vaginal delivery were afraid less often of pain, infant's complications or episiotomy than women who had cesarean sections or were pregnant (p<0.05).

Labour pain manegement

As the pain was such an important issue for the respondents, they were asked which methods of pain relief they would prefer to use during VB. The answers are presented in **Table 3**.

It can be seen that 55.5% respondents claimed that VB is more likely to cause neonatal hypoxia than CS. Significantly more women who had a previous CS believed that it is a safer way of birth for a newborn (66% vs. 49% of pregnant women and 51.2% of women after VB; p<0.01).

Table 3. Methods of pain relief during vaginal delivery

	Respondents N=4721 N (%)	Pregnant N=656 N (%)	After VB N=2322 N (%)	After CS N=1454 N (%)	After VB and CS N=289 N (%)	p
Partner's support	3099 (65.6)	441 (67.2)	1593 (68.6)	897 (61.7)	168 (58.1)	1 vs. 4* 2 vs. 3* 2 vs. 4* 1 vs. 3**
Spine massage	1737 (36.8)	314 (47.9)	752 (32.4)	562 (38.7)	109 (37.7)	1 vs. 2* 1 vs. 3* 1 vs. 4* 2 vs. 3*
Breathing techniques	2711 (57.4)	429 (65.5)	1361 (58.6)	758 (52.1)	163 (56.4)	1 vs. 2* 1 vs. 3* 2 vs. 3* 2 vs. 4***
Music	617 (13.1)	118 (18)	246 (10.6)	220 (15.1)	33 (11.4)	1 vs. 2* 2 vs. 3* 1 vs. 4***
Screaming	906 (19.2)	94 (14.3)	497 (21.4)	244 (16.8)	71 (24.6)	1 vs. 2* 1 vs. 4* 2 vs. 3* 3 vs. 4*
Comfortable position	2393 (50.7)	314 (4.9)	1195 (51.5)	706 (48.6)	178 (61.6)	1 vs. 4* 2 vs. 4* 3 vs. 4*
Labour in water	1536 (32.6)	302 (46)	620 (26.7)	514 (35.4)	100 (34.6)	1 vs. 2* 1 vs. 3* 1 vs. 4* 2 vs. 3*
Epidural analgesia	2519 (53.4)	416 (63.5)	993 (42.8)	961 (66)	149 (51.6)	1 vs. 2* 2 vs. 3* 1 vs. 4* 3 vs. 4*
Other****	363 (7.7)	34 (5.2)	192 (8.2)	106 (7.3)	31 (10.7)	1 vs. 2* 1 vs. 4*

* – p<0.01, ** – p=0.015, *** – p=0.01, **** – acupuncture, aromatherapy, TENS electrostimulation, nitrous oxide analgesia, VB – vaginal birth, CS – caesarean section

Episiotomy

It was found that 37.4% of the respondents were afraid of episiotomy during VB (table 2) and 59% of all women would rather to avoid it. Maternal age, education or inhabitance did not influence any kind of decision. Women who attended childbirth schools wanted to avoid episiotomy significantly more often (41.8% of childbirth schools participants and 31.1% of women who did not attend childbirth schools wanted to avoid episiotomy; p<0.01). Regardless of preferences, 74.4% of women who had previously delivered vaginally experienced episiotomy before. However, only 27.6% of respondents who wanted to avoid episiotomy used any kind of techniques of perineal preparation for vaginal birth, while 25.5% massaged the perineal tissue during pregnancy and 2.1% used any medical devices for perineum preparation.

Sexual function after labour

Women were asked if they were afraid of delivery via VB because of its possible consequences in their further sexual lives. Similar rates of respondents believed that it can or cannot have a negative impact on sexual satisfaction (42.4% and 42.9% respectively; p=0.2). Education, place of residence or childbirth schools' attendance did not influence respondents' opinions. Pregnant women believed that vaginal delivery can influence future sexual life (Yes - 42.29% vs No - 37.10%), but respondents who experienced vaginal labour had different opinions, mostly not noticing a difference (Yes - 40.24% vs. No - 52.56%).

Cesarean section scar

Assuming that women choose CS because of fear of VB, they were asked if they believed that

the uterine scar after a previous CS could have an impact on subsequent pregnancies. Only 26% of them believed it did not. Also, 7.3% of women thought that one could not have a VB after a previous single CS. Pregnant respondents more often claimed that it was an absolute contraindication for subsequent VB (15%) than women who had already delivered vaginally (11%; p<0.01)) and women who previously had a CS (5.1%; p=0.01).

Sources of knowlegde

Concerning the above answers, respondents were asked about the sources of their knowledge regarding labour. Only two thirds of them claimed to gain information from obstetricians during antenatal counselling (65.3%), 54% of respondents were based on their families' or friends' opinions, and almost half of them searched for information regarding birth on internet forums or blogs (48.9% and 48.4% respectively). Also, 43.5% of women learned about pregnancy and birth from books, 37.5% participated in childbirth schools and 38.3% declared that they would do so in a few weeks. However, only 32.5% of women pointed to childbirth classes as their main source of knowledge regarding birth.

Social attitude

An interesting aspect of the study was to investigate if, in women's opinion, society supports choosing CS as a way of delivering a child. Surprisingly, 41% of the respondents claimed that CS is considered to be a failure by society, and women who had a cesarean section might feel discriminated against. The results indicate that 59% of women who had a previous CS, 33% after a previous VB and 28% of pregnant respondents shared that point of view.

Discussion

Almost two thirds of the respondents in the above study indicated pain as the most fearful element of childbirth. Pain during VB was the most frightening for pregnant women; however, more than half of the respondents who already gave birth were also afraid of it. The finding of the above study is in accordance with previously published results. Sioma-Markowska et al. conducted a prospective research among pregnant women and found a very high level of anxiety related to labour in 6.7% of them. In 85% the anxiety was caused by the fear of pain during VB [10]. According to Eriksson et al., the fear of pain was the most common reason for women to choose an elective CS [11]. In countries with a high rate of CS, the studies indicated the fear of labour pain to be the primary reason for requesting an elective CS [12–16]. According to Yıldız et al., women choose CS as it is considered to be "comfortable and easy" [17]. Dehghani et al. confirmed that fear of labour pain was an independent predictor of choosing an elective CS [18].

As the fear of pain during VB is such an important issue, the analysis of methods of relieving pain chosen by the respondents was conducted. The most important method to manage pain turned out to be the partner's support during birth. Slightly over 50% of women chose breathing techniques, adopting a comfortable position during childbirth or epidural analgesia. As pain is the most frightening aspect of VB for women, it seems essential to propagate knowledge regarding the available methods of managing it. It is possible that broader knowledge of analgesia could decrease the fear of pain among women, especially pregnant ones, and therefore decrease the fear of VB itself. This hypothesis was confirmed by Alakeely et al. in a cross-sectional study among primigravid women. The health education regarding epidural analgesia during antenatal care was an important factor in favour of increasing women's desire to request it during labour [19]

According to the results of the above research, more than half of women were anxious about possible neonatal complications during VB and claimed that CS was a safer option for the newborn. Similar parturients' opinions were reported by several authors. Serçekuş et al. found that "not putting a baby at risk" was the main reason for choosing CS among Turkish pregnant women [14]. Among Iranian primigravidae who requested an elective CS without any medical indications, the fear of infant injury during VB was one of the most frequent reasons [20]. Other researches also indicated that women chose an elective CS because they believed that it was safer for their infants [8,12,14,15, 21–23].

The level of knowledge regarding benefits and risks related to the way of birth among Polish

women is insufficient. Women's knowledge on implications of delivering via CS for subsequent pregnancies and deliveries was investigated in the presented study. Every fourth respondent in the survey believed that a CS uterine scar had no impact on subsequent pregnancies. Although 7.1% of women claimed that having one CS is associated with a necessity for all subsequent deliveries to be cesarean as well, another study also found that one third of women after a previous CS did not agree to a VB trial following gestation [24]. Most women would like to avoid episiotomy during VB, but only one in four used any techniques for perineal preparation during the procedure. All those examples indicate a low level of knowledge regarding natural birth and CS. This may be a consequence of the sources of information on labour chosen by participants of the survey. The most reliable sources, medical staff and childbirth schools, were claimed by 65.3% and 32.5% women respectively. Other women gained information from magazines, relatives, friends and internet forums or blogs. The knowledge gained from unreliable sources leading to wrong conclusions may intensify the fear of VB and influence the rate of CS on demand. According to the presented results, the issues that women are mostly afraid of in VB are generally modifiable. The health education among pregnant women regarding the methods of managing labour pain, increasing the chances of avoiding episiotomy, or the real data on the consequences of having vaginal or cesarean birth could decrease the level of fear of VB.

In our study group, more than a half of respondents had higher education. We assume it is due to the method of recruitment for the study via the internet. Obviously it is not representative of the whole Polish population of women at a reproductive age. According to the Central Statistical Office in 2018, 32.6% of women aged 15–64 had higher education [25].

The strength of the study is its uniquely large group of respondents of childbearing age. The anonymity and distribution of the questionnaire via the internet may promote honesty in the answers. To our knowledge, no other research in such a large group of pregnant woman in Poland has been conducted and published to date. This unique analysis of causes of fear of VB in a Polish population of women identifies key point, in which spreading reliable information may have a crucial impact on women's choices regarding vaginal or cesarean birth. However, there are some limitations to the study. The analysed data is derived from a self-composed questionnaire, which could be the cause of an inherent bias. It was distributed online; therefore, the sample may be biased, as only those who could respond to an online survey could participate. The question of the reliability of the results is a valid concern.

Conclusions

In conclusion, women's knowledge regarding the advantages and risks related to methods of labour is insufficient, which may affect their preferences regarding vaginal or cesarean birth. Most of the fearful issues of vaginal birth can be managed by medical staff throughout sharing knowledge on parturition. The presented study emphasises the need for raising awareness regarding birth among Polish women.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Data availability statement
The data that support the findings of this study is available from the corresponding author upon reasonable request.

Funding sources
There are no sources of funding to declare.

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REVIEW PAPER

JMS Journal of Medical Science

The utility of cerebral oxygenation monitoring in premature neonates

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DOI: https://doi.org/10.20883/medical.e485

Keywords: NIRS, near-infrared spectroscopy, preterm, neonate, neonatology, cerebral oxygenation

Published: 2020-12-30

How to cite: Nesargi S, Nitsch A, Wolf M. The utility of cerebral oxygenation monitoring in premature neonates. JMS [Internet]. 2020 Dec 30;89(4):e485. doi:10.20883/medical.e485

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ABSTRACT

Near-infrared spectroscopy allows the measurement of cerebral oxygenation in preterm infants. This study aimed to demonstrate several highly relevant clinical situations in preterm infants in which the standard set of monitoring parameters without near-infrared spectroscopy is not sufficient to detect possible adverse situations, possibly resulting in severe complications, i.e. adverse neurological outcomes. The examples include situations of low blood pressure, persistent open ductus arteriosus, malfunctioning autoregulation of the brain oxygenation, and periods of irregular breathing. Without near-infrared spectroscopy, it is impossible to determine whether such a situation imposes any risk for the brain, whereas the measurement of cerebral oxygenation as an additional source of information enables the clinician to recognise these conditions and modify treatment or use countermeasures to protect the patient from brain damage and ensuing lifelong disabilities.

Introduction

Tissue oximetry using near-infrared spectroscopy (NIRS) is a well-established technology. Its most prominent field of application is pulse oximetry, commonly known as the "finger clips" which are fixed to hospitalised patients in many conditions, and procedures to measure oxygen in the arterial circulation. This technology is attractive to clinicians and patients because it is non-invasive and harmless, simply using low-power light sources to obtain vital clinical information from light travelling through human tissue.

NIRS oximetry uses a similar principle, focusing on the *local* oxygenation of the tissue underneath the sensor. Pulse oximetry assesses the arterial oxygenation, which reflects adequate ventilation, whereas NIRS oximetry provides the tissue oxygen saturation, which reflects the balance of oxygen supply and consumption at the measurement location and is crucial to determine whether an organ is adequately oxygenated. It is used to monitor specific high-risk body parts and organs, such as the brains of preterm children. These patients have taken their first steps into life with underdeveloped lungs and an extreme-

ly fragile overall condition, hence, early death or long-term complications for survivors are a considerable threat. The brain is of particular concern because it is highly sensitive to a lack (or even an *excess*) of oxygen. When lesions occur, the brain does not heal well, consequently, lifelong disabilities occur constituting the most severe complication for preterm infants.

This paper summarises some of the key benefits of the additional use of cerebral oximetry for newborn preterms compared to their regular treatment.

Materials and Methods

For this Review Article, findings from two influential publications on the effects of NIRS in the care of preterm neonates were used. First, the regular treatment which is typically applied on neonatal units is outlined, then, four typical clinical scenarios are investigated, each of them without and with cerebral oxygenation information available to the medical staff.

Results & Discussion

In all four investigated scenarios, it was shown that the availability of cerebral oxygenation as an additional measurement parameter is advantageous for medical staff, as dangerous clinical situations can be avoided and treatment errors reduced.

Regular treatment

Commonly, patients on neonatal intensive care units (NICUs) are monitored using the following methods and tools:

- Heart rate measurement
- Temperature measurement
- Transcutaneous oxygen (O_2) / carbon dioxide (CO_2) measurement
- Arterial oxygenation measurement (pulse oximetry) (SpO_2 or SaO_2)
- On-demand blood gas analyses

These vital signs monitoring enables the application of the necessary treatment to keep the infant alive. Please note that the brain, although being the most sensitive organ to hypoxia, is not considered by these methods. In the next sections, various clinical scenarios will be illustrated, with comparisons between clinical assessment without and with brain oxygenation monitoring being used.

Scenario 1: Low blood pressure

In preterm neonates, as a rule of thumb, a minimum blood pressure of 30 mmHg is considered acceptable [3]. However, low blood pressure occurs frequently and raises the question of whether to treat it (**Figure 1**).

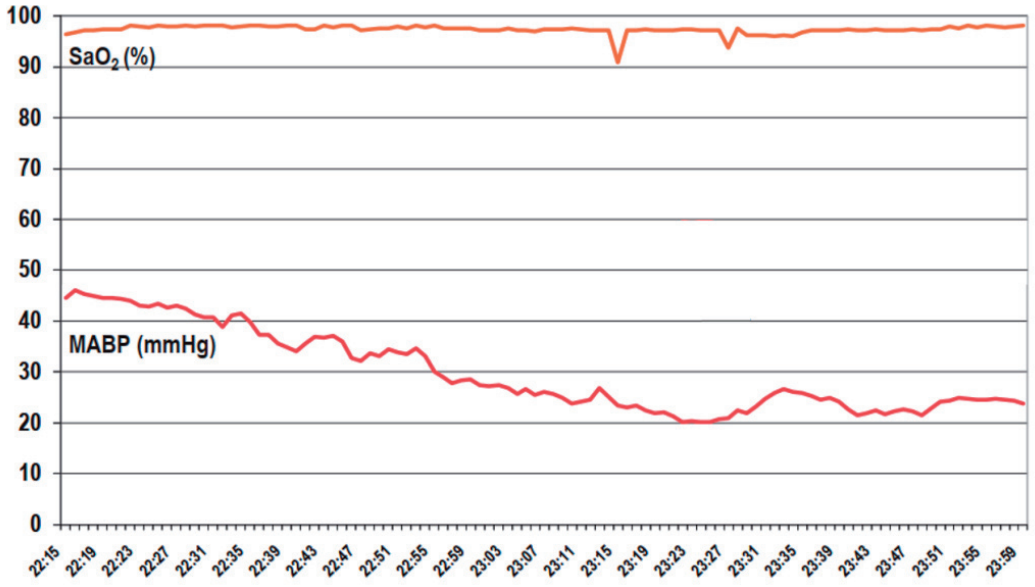

Figure 1. MABP, cerebral oxygenation (StO_2) curve removed for illustrative purposes. Original chart: Wolf, Naulaers, van Bel, Kleiser, Greisen. JNIRS 20, 43–55 (2012) open access.

The arterial oxygenation (SaO_2 measured by the pulse oximeter) does not react to the blood pressure (MABP) dropping below 30 mmHg. The downward spikes in SaO_2 around 23:15 and 23:27 are most likely movement artefacts. For the clinician, it is very difficult to assess the situation and decide on treatment, as the consequence of the low blood pressure is not visible in any of the available parameters (**Figure 2**).

In contrast, cerebral oxygenation (StO_2 measured by the NIRS monitor) *is* affected by the dropping blood pressure. A StO_2 level below 55% is considered dangerous [4], indicating to the clinician that due to the low blood pressure, the oxygen supply to the brain is dangerously low and not adequate for the brain's oxygen consumption, hence, treatment for low blood pressure is required. Several well-known treatment

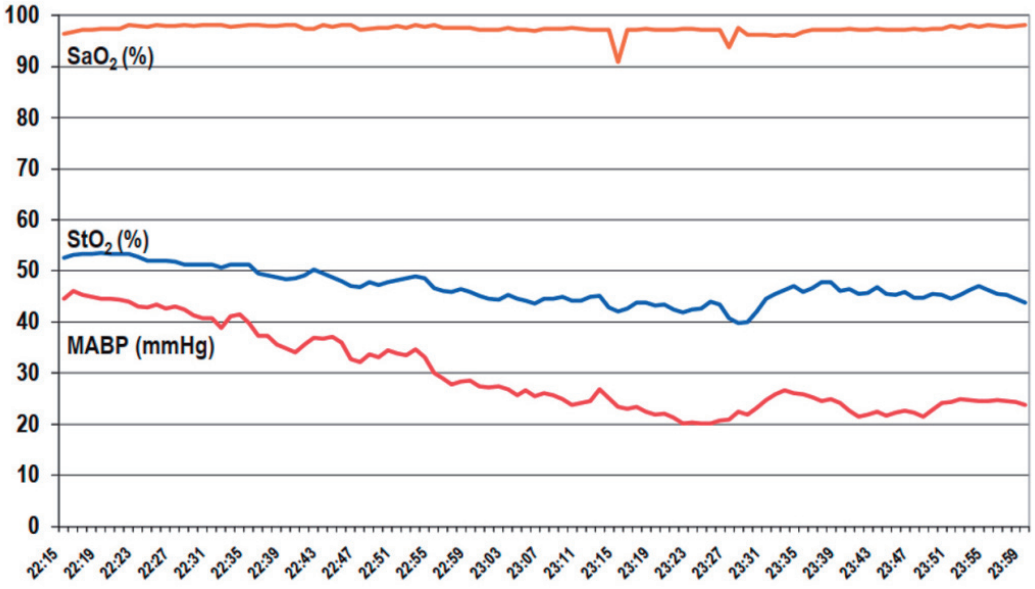

Figure 2. MABP including cerebral oxygenation (StO_2) curve. Chart: Wolf, Naulaers, van Bel, Kleiser, Greisen. JNIRS 20, 43-55 (2012) open access

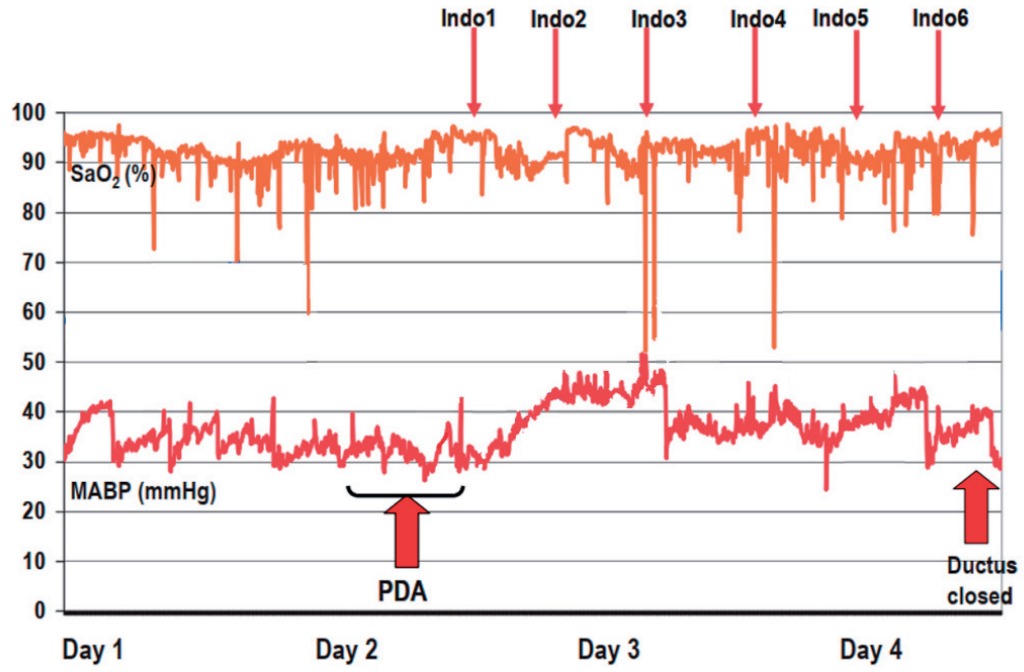

Figure 3. Treatment of a ductus arteriosus, cerebral oxygenation (StO_2) curve removed for illustrative purposes. Original chart: Wolf, Naulaers, van Bel, Kleiser, Greisen. JNIRS 20, 43–55 (2012) open access.

options are available for this, therefore, by using StO_2, the decreasing brain oxygen levels can be recognised and treated before brain damage occurs.

Scenario 2: Ductus arteriosus

A persistent open ductus arteriosus (PDA) allows venous blood with low oxygenation to enter the arteries, thus hampers the oxygen supply to the body. When a PDA occurs, clinicians often use drugs, such as Indometacin, to constrict and close the ductus without having to perform surgery (**Figure 3)**.

In this baby, six doses of Indometacin ("Indo1" to "Indo6") were administered after the occurrence of the PDA. Blood pressure (MABP, consistently over 30 mmHg) and arterial oxygenation (SaO_2, consistently around or above 90%, with occasional movement artefacts) were of no concern (**Figure 4)**.

The addition of cerebral oxygenation measurement (StO2) shows that several oxygen undersupply situations occur due to the PDA and during its treatment, thus the clinician can recognise that this situation is dangerous for the brain and apply countermeasures earlier.

Scenario 3: Impeded autoregulation

Autoregulation is the capability of the human brain to self-adjust to changing blood pressure to maintain stable oxygenation, however, often preterm neonates cannot autoregulate well (**Figure 5)**.

The above chart shows that the blood pressure (MABP) fluctuates in two patients, one with impeded autoregulation (top) and one with working autoregulation (bottom) but arterial oxygenation (SaO_2) levels remain in the desired range, hence, there is no cause for concern. However, assessing the cerebral autoregulation without cerebral oxygenation measurement is impossible only from the changes in blood pressure and arterial oxygenation (SaO_2) (**Figure 6)**.

In the upper chart, the blood pressure changes directly lead to brain oxygenation changes, indicating impaired autoregulation, thus a higher risk for cerebral lesions. This patient suffers from several periods of brain oxygen undersupply (hypoxia), whereas the patient in the lower chart shows no effect of the substantial blood pressure changes on the brain oxygenation ($rScO_2$). This is a sign of intact autoregulation and this infant is much less at risk for brain lesions. By measur-

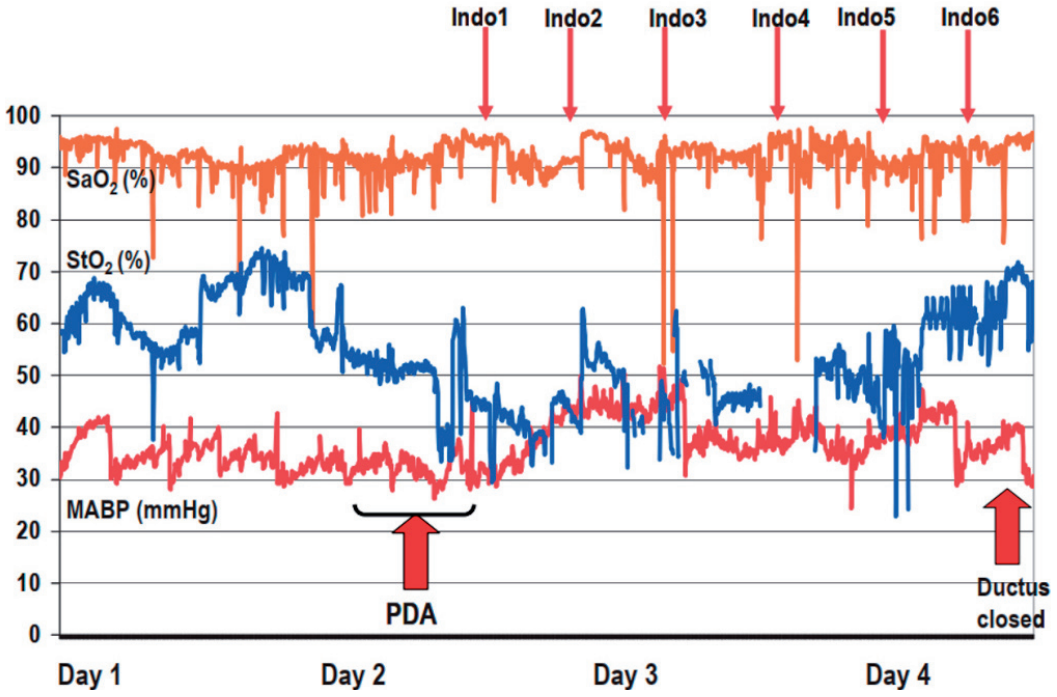

Figure 4. Treatment of a ductus arteriosus including cerebral oxygenation (StO_2) curve. Chart: Wolf, Naulaers, van Bel, Kleiser, Greisen. JNIRS 20, 43–55 (2012) open access

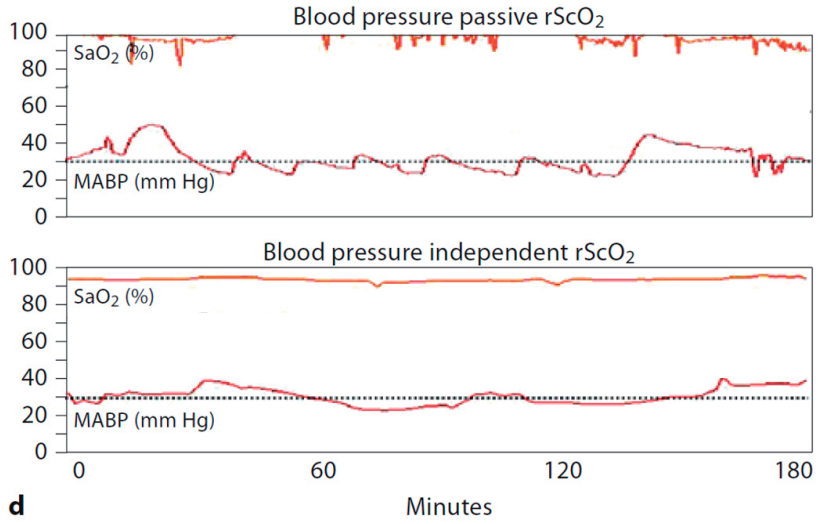

Figure 5. Impeded autoregulation, cerebral oxygenation ($rScO_2$) curve removed for illustrative purposes. Original chart: van Bel, Lemmers, Naulaers, Neonatology 2008;94:237–244

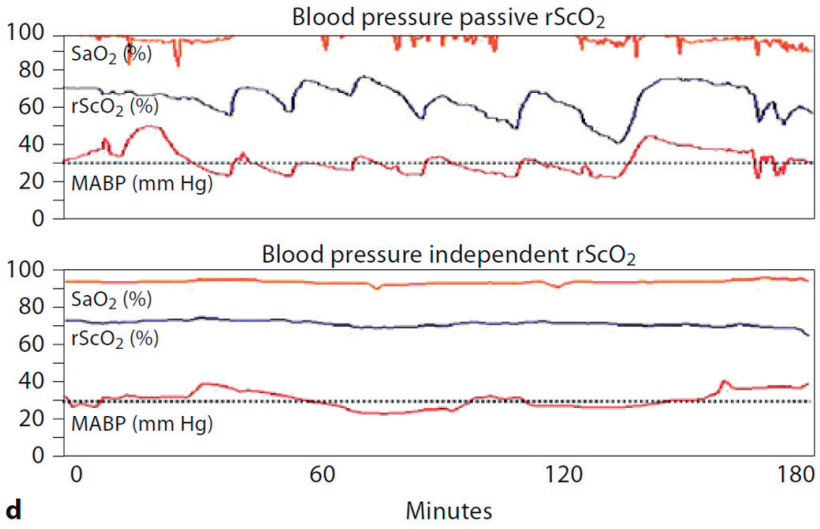

Figure 6. Impeded autoregulation including cerebral oxygenation ($rScO_2$) curve. Chart: van Bel, Lemmers, Naulaers, Neonatology 2008;94:237–244

ing cerebral oxygenation, the clinician becomes aware of these situations and can take measures to prevent brain lesions.

Scenario 4: O_2 administration during apnoea

Preterms often suffer from apnoea, that is, their breathing stops for a certain period, with no oxygen is supplied to the body during that time (**Figure 7)**.

Here, the arterial oxygenation (SaO_2) shows the phases of apnoea and this condition was treated by administering additional oxygen. Therefore, this condition was detectable using standard SaO_2 measurement (**Figure 8)**.

At points 1, 2, 3, and 4, additional oxygen is administered to the patient, i.e. the inspired oxygen fraction (FiO_2) is increased, with the SaO_2 returning to normal levels at each time point. However, adding the measurement of cerebral oxygenation ($rScO_2$ here) reveals that the brain oxygenation is *too high* >85% after this FiO_2 is increased (points 2, 3, and 4). This means that too much oxygen was given, resulting in over-oxygenation (hyperoxia) which can cause blindness, a constriction of the brain blood vessels and other adverse events. This threat would remain hidden to the clinicians without cerebral oximetry.

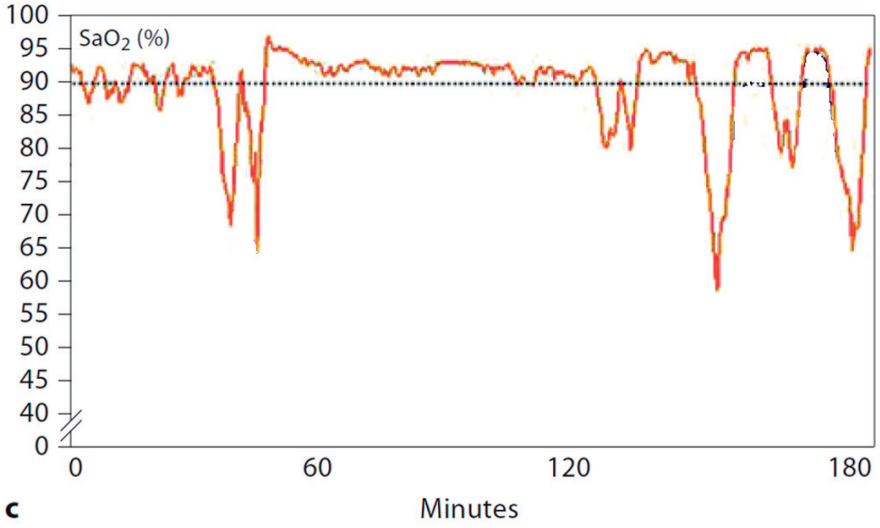

Figure 7. O_2 administration during apnoea, cerebral oxygenation ($rScO_2$) curve removed for illustrative purposes. Original chart: van Bel, Lemmers, Naulaers, Neonatology 2008;94:237–244

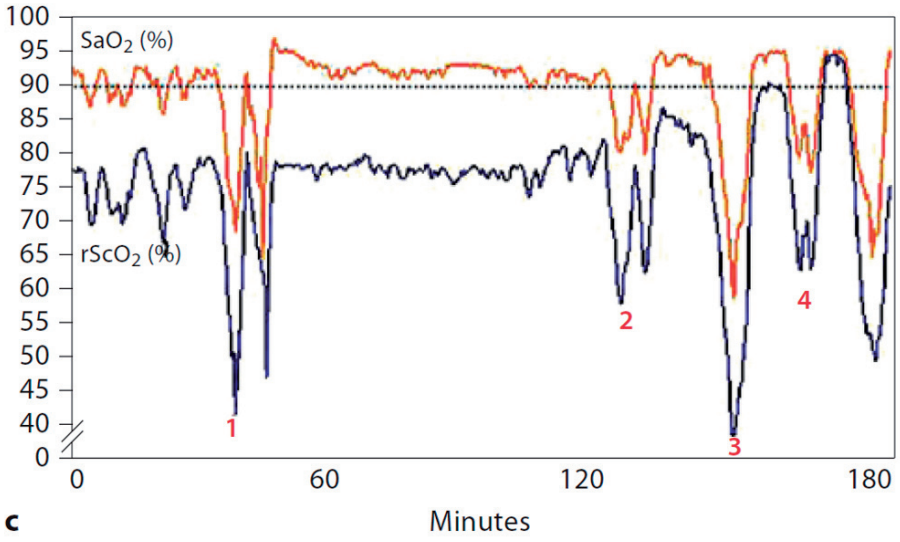

Figure 8. O_2 administration during apnoea including cerebral oxygenation ($rScO_2$) curve. Chart: van Bel, Lemmers, Naulaers, Neonatology 2008;94:237–244

Conclusion

NIRS oximetry provides useful and potentially life-saving additional information to medical professionals.

This review presented four examples of common medical conditions in neonatal care: *Low blood pressure* (Scenario 1), *persistent ductus arteriosus* (Scenario 2), *impeded autoregulation* (Scenario 3), and *apnoea* (Scenario 4).

Using only standard clinical parameters in these conditions, the clinician incurs the risk of at least one of the following two unwanted effects 1) dangerous situations may remain undetected and 2) treatment errors may occur. This may lead to potentially severe adverse outcomes, such as premature death as well as brain damage leading to lifelong disabilities, paralysis, cerebral palsy and/or learning/developmental impairments. Therefore, it is vital to further improve the quality of care for these high-risk patients wherever possible.

Adding NIRS oximetry to the routine set of monitoring parameters in neonatal care is an effective option: For every one of the four pre-

sented medical conditions, the usefulness of continuous cerebral oxygenation monitoring was demonstrated, hence, cerebral oxygenation monitoring is an important step towards improved clinical care for preterm infants. This enables not just a higher survival rate but also a better neurological outcome, therefore creating long-term benefits for the patients, their families, as well as public and private health systems.

Acknowledgements

Conflict of interest statement
Saudamini NESARGI: No conflicts of interest.

Alexander NITSCH: CEO of OxyPrem AG, a Swiss company active in the field of developing novel NIRS monitoring equipment for clinical use.

Martin WOLF: Chairman of the Board of OxyPrem AG, a Swiss company active in the field of developing novel NIRS monitoring equipment for clinical use..

Funding sources
There are no sources of funding to declare.

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REVIEW PAPER

JMS Journal of Medical Science

Subacute Thyroiditis – literature overview and COVID-19

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DOI: https://doi.org/10.20883/medical.e472

Keywords: subacute thyroiditis, de quervain thyroiditis, COVIS-19, SARS-CoV-2

Published: 2020-12-29

How to cite: Domin R, Szczepanek-Parulska E, Dadej D, Ruchała M. Subacute Thyroiditis – literature overview and COVID-19. JMS [Internet]. 2020 Dec 29;89(4):e472. doi:10.20883/medical.e472

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ABSTRACT

Subacute thyroiditis (SAT), also known as de Quervain's thyroiditis, is a rare thyroid gland disorder, although it is the most common type of painful thyroiditis. The incidence of this disorder is relatively low but likely to be underestimated. Epidemiological studies vary, estimating a prevalence of 12/100,000/year and patients with SAT constitute less than 5% of all patient consultations due to thyroid disease. For the reason, that SAT can present with a variety of symptoms to different specialists. This review summarises current knowledge of SAT with an emphasis on reports related to SARS-CoV-2.

Introduction

De Quervain's subacute thyroiditis (SAT) is a rare thyroid gland disorder first described in 1895 by *Mygind* and later characterised by *de Quervain* in 1904 [1]. Among thyroid disorders, it is the most common type of painful thyroiditis [2]. It should be highlighted that "de Quervain's thyroiditis" is not synonymous with "de Quervain's disease", a type of tenosynovitis affecting tendons in the first dorsal compartment of the wrist [3]. The incidence of SAT is relatively low, however likely to be underestimated. Due to its diverse and non-specific symptoms, patients are often diagnosed by family doctors, otolaryngologists, oncologists and other specialists before they eventually consult an endocrinologist. This review summarises the current knowledge of SAT and potential etiological factors (including severe acute respiratory syndrome coronavirus 2, SARS-CoV-2), clinical presentation, along with present diagnostic and therapeutic options.

Materials and Methods

The PubMed search engine was searched for the phrases "subacute thyroiditis", "subacute thyroiditis differential diagnosis", "subacute thyroiditis case report", "thyroiditis differentiation" and "SARS-CoV-2" to identify articles focused on the clinical presentation (including atypical cases), data on etiological factors, novel diagnostic methods and treatment recommendations of SAT.

Subacute thyroiditis

Epidemiology

Results of epidemiological studies vary but most indicate that SAT occurs mostly in females, with a peak incidence between 40 and 50 years of age [4]. Its estimated prevalence is equal to 12/100000/year, while subjects with SAT constitute less than 5% of all patients consultations due to thyroid disease. It was also observed that it occurs more frequently among first-degree relatives and twins.

Aetiology

The aetiology of SAT is unknown but predisposing factors include previous viral infection (i.e. adenoviruses, EBV, Dengue, hepatitis, influenza), immunomodulating treatment or genetic predisposition related to human leukocyte antigens (HLA) (B*35, B*18:01, DRB1*01 and -C*04:01) [5–9]. HLA-B*35 is the first and the most studied SAT susceptibility gene but its precise role in SAT occurrence is unclear. However, as SAT is related to viral infection, there may be a direct link considering HLA-B*35-restricted viral antigen presentation. There are a few hypotheses on the mechanism. One is molecular mimicry resulting in the cross-reactive immune response – specific viral amino acids may be similar to autologous thyroid peptides, thereby generating autoreactive T-cells that promote an autoimmune response against the thyroid. The second hypothesis is that as a result of infection, changes in tissue components occur through the release of viral products or the presentation of virus antigens by host cells. Then, along with the HLA-B*35 antigen, the thyroid cells are recognised as foreign and destroyed by the immune system [10].

Immunisation-related induction

COVID-19

SARS-CoV-2 originated in the Chinese city, Wuhan, in December 2019 and has since become a global pandemic. In most cases, the symptoms are mild, mainly a fever, cough or fatigue but in some people, especially the elderly with comorbidities, it can lead to pneumonia, causing acute respiratory distress syndrome (ARDS) and multiorgan dysfunction (MODS) [11].

The literature search revealed a total of eight patients/cases descriptions (7 women and 1 man). Six women aged 18–46 y.o. developed SAT soon after (from a few days up to 6 weeks) recovery from SARS-CoV-2 infection, with typical clinical presentation (i.e anterior neck pain, fever, cough) accompanied by markers of thyrotoxicosis. Only one patient had a previous medical history of thyroid disease (small diffuse non-toxic goitre). Response to treatment with prednisone in five and ibuprofen in one patient was good. On a follow-up visit, the parameters of thyroid function were back to reference ranges in four patients and two patients presented subclinical hypothyroidism [12–14].

Two patients were diagnosed with SAT in the course of SARS-CoV-2 infection. One report concerned a 69-year-old female with a previous history of non-toxic nodular goitre with a dominant benign nodule in the right lobe and repeatedly documented euthyroidism. During recovery after back surgery in hospital, she experienced cough, fever and dyspnoea. A swab confirmed SARS-CoV-2 infection and computed tomography of the chest revealed typical changes related to Coronavirus Disease 19 (COVID-19). On the fifth day of hydroxychloroquine and lopinavir treatment, the patient complained of palpitations, insomnia, and agitation. Thyroid laboratory findings revealed thyrotoxicosis. A thyroid scan using Tc-99 detected no uptake and bedside ultrasonography showed enlarged hypoechogenic goitre with a previously documented nodule in the right lobe. Based on clinical presentation and examination, the patient was diagnosed with SAT, possibly triggered by SARS-CoV-2. Biochemical thyrotoxicosis decreased after treatment with methimazole, intravenous methylprednisolone and oral continuation with prednisolone. Non-steroid anti-inflammatory drugs (NSAIDs) were

not implemented because of patients' hypersensitivity. Interestingly, the patient was still positive for SARS-CoV-2 after two months, although the patient was completely asymptomatic [15].

The second report described a 34-year old male primarily diagnosed with COVID-19, who presented new symptoms on the 9th day of illness. He complained of anterior neck pain refractory to paracetamol and dequalinium lozenges and developed tachycardia ranging from 90 to 120 beats/min. No other symptoms were present. Laboratory and ultrasound investigations revealed typical SAT features. After prednisolone and propranolol treatment, his symptoms and thyroid function normalised [16].

Post-vaccine

The presence of SAT was also documented following vaccines. *Passah et al.* reported a case of a young female with symptomatic thyrotoxicosis and neck pain of about one-month duration, with no past medical history of infection or sore throat. Eight weeks before symptoms, she was vaccinated with a live influenza virus vaccine. Previously, a few other cases of SAT after vaccination were reported, including the hepatitis B vaccine [17].

Paraplegia, sensory loss, SAT and Dengue fever

A 65-year old man was admitted to the Hospital of Guangzhou Medical University (Guangzhou, China) because of acute paraplegia and sensory loss. Almost a week before, he experienced an episode of fever which resolved a few days before admission, with sequential development of neurological symptoms. After laboratory tests and imaging diagnostics, the patient was diagnosed with acute transverse myelitis complicated with SAT as a result of a Dengue viral infection [18].

Clostridium difficile

SAT is associated with common viral infections. However, a recently published report suggests its induction after bacterial infection. A 24-year-old male soldier admitted for clinical evaluation prior to the military programme, reported mild anterior neck pain, fatigue, night chills and sometimes palpitations persisting for one month. A few months earlier, he was initially treated for *Clostridium difficile* infection with vancomycin. However, in further investigation, his diarrhoeal problems were still present. Biochemical tests revealed a decreased level of thyroid-stimulating hormone (TSH) and slightly increased T3 and C-reactive protein (CRP), with other thyroid parameters within their reference ranges. Ultrasound examination detected no abnormalities. After evaluation, he was treated with fidaxomicin for 10 days for *C. difficile* infection. He fully recovered and his thyroid parameters went back to reference ranges 8 weeks after the first evaluation [19]. However, in this particular case, in the differential diagnosis, we should consider autoimmune background, as bacterial induction of SAT seems controversial.

Immunomodulating drugs

The cases presented below document that drugs used as immunomodulatory agents in autoimmune diseases, such as anti-TNF-α inhibitors, can also play a role in the development of SAT [20].

Infliximab

A 56-year old male suffering from Leśniowski-Crohn Disease started treatment with infliximab to reduce diarrhoea. Four weeks later, he presented with neck pain and swelling with tenderness in the thyroid area. Laboratory tests revealed features of thyrotoxicosis, ultrasound examination demonstrated hypoechogenic goitre and a fine needle biopsy showed amyloid deposition. His symptoms resolved and thyroid function returned to normal after treatment with prednisolone, however, goitre did not. Previously, there were few cases of anti-TNF-α induced SAT but never with accompanying amyloid deposition [21].

Adalimumab

A 26-year old female suffering from psoriasis and psoriatic arthritis was prescribed adalimumab because of disease progression causing joint degeneration. Seven months later, she started to cough so treatment was discontinued for three weeks, then the patient developed symptoms like fever, sore throat, anterior neck tenderness, lymphadenopathy, hand tremors and palpitations. In laboratory tests, there were features of thyrotoxicosis and hypoechogenic heterogeneous lesions in ultrasound examination. The symptoms resolved, and thyroid function resumed after

treatment with prednisolone. Due to the increased risk of thyroid diseases in patients receiving anti-TNF-α therapy, the authors recommend regular thyroid gland examination before and during treatment with anti-TNF-α inhibitors [22].

Clinical presentation

Typical

Inflammation and thyreometabolic dysregulation underlying SAT result in various symptoms, including goitre, pain in the neck area, palpable thyroid nodule or lymphadenopathy. However, other local symptoms like migratory thyroiditis, hard goitre and pain radiation to jaw, ears or chest are also possible. Systemic symptoms are flu-like (fever, myalgia, weakness) with acute onset and related to the stage of the disease and thyroid hormones levels range from clinically overt hyper- to hypothyroidism [4, 23–26].

SAT usually comprises consecutive phases of hyper-, hypo- and euthyroid state independently of the initiating factor. The inflammatory process leads to thyroid gland destruction and thyroglobulin (Tg) proteolysis, which results in the release of thyroxine (T4) and triiodothyronine (T3) into the bloodstream. Secondary to that, pituitary-thyroid axis regulation is disrupted by the suppression of TSH. With decreasing inflammation, the thyroid regenerates and hormonal homeostasis is restored. Each phase lasts for two to eight weeks [27].

Laboratory findings

Standard biochemical parameters should be measured including TSH, free thyroid hormones (fT3, fT4), anti-thyroid peroxidase antibodies (aTPO), anti-thyroglobulin antibodies (aTG) and anti-TSH receptor antibodies (TRAb), CRP and erythrocyte sedimentation rate (ESR). In the first phase of SAT, when most diagnoses are made, we should expect biochemical thyrotoxicosis, elevated CRP, elevated ESR and negative thyroid antibodies [28]. However, in some cases, the presence of elevated antibodies (aTPO, aTG, TRAb) may also occur [29].

Hernik et al. investigated the possible use of hepcidin levels in SAT. Hepcidin is a reactive inflammatory protein regulating ferrum homeostasis and is increased during SAT. Promising results show that with a cut-off value, diagnosis is more likely. Additionally, it could be used as a monitoring tool, due to its decreasing manner during effective treatment [28].

An important note is that the diagnosis of SAT cannot be excluded if biochemical parameters are normal. In the study by *Tachibana et al.*, the mean interval between symptoms and abnormal laboratory findings was 6.3 weeks and the longest interval was 11 weeks [30].

Imaging

Typical imaging diagnostics include ultrasound and scintigraphy, with the use of radioactive iodine and Tc99m. The most common features of ultrasound examination are heterogeneous hypoechoic areas of the affected tissue with a lack of flow on colour Doppler. Most changes are bilateral with characteristic features like "lava flow" [31], in turn, decreasing the uptake of radioactive iodine and Tc99m [32, 33]. Another valuable diagnostic parameter is strain ratio (SR) acquired during real-time sonoelastography of the thyroid gland, which is high in SAT compared to hyperthyroidism and Hashimoto's thyroiditis [34]. Recently, a novel diagnostic tool, a fusion scan of images from ultrasound and 124I-PET was reported, which might be useful when a scintigraphy scan does not match the ultrasound examination findings [35].

Fluorodeoxyglucose Whole-Body Positron-Emission Tomography/CT (18F-FDG PET/CT) is another tool. During SAT, there is a possibility of increased FDG uptake, so this condition should be included in the differential diagnosis when assessing lesions with an increased maximum standardised uptake value (SUVmax) [36].

Fine needle aspiration cytology (FNAC)

The diagnosis of SAT does not require obligatory FNAC examination, though it might be helpful, especially in the exclusion of co-existing thyroid pathologies (i.e. thyroid nodules) and differential diagnosis in cases of uncertainty [37].

Thyroid puzzle - case reports

Fever of unknown origin

In 1961, *Petersdorf and Beeson* characterised fever of unknown origin (FUO) as a body tem-

perature equal or higher than 38.3°C with a duration of three weeks without a diagnosis after one-week intensive inpatient investigation [38]. Currently, due to diagnostic technology development, the one-week inpatient investigation is no longer required but experts suggest certain initial tests to establish the diagnosis of FUO [39]. As SAT can present by fever only, with no other typical clinical signs of thyrotoxicosis, it should be taken into consideration during the evaluation of FUO [2, 40–42].

Acute myocardial infarction and sustained ventricular tachycardia

The most common cause of acute myocardial infarction (AMI) is the rupture of atherosclerotic plaques leading to thrombosis in coronary arteries, which instantly decreases blood flow, that is, the oxygen demand of the myocardium is greater than the oxygen supply. More aetiologies of MI include trauma, vasculitis, drug use, coronary artery anomalies, coronary artery embolism or aortic dissection. Excess demand on the heart, which can be the result of hyperthyroidism, is also listed [43].

Hyperthyroidism/thyrotoxicosis is the first clinical stage of SAT. AMI seems an unlikely presentation of SAT, yet *Guerrero et al.* reported a case of a 32-year-old female presenting with chest pain and biochemical markers of MI and thyrotoxicosis with changes in their ECG. There were no disturbances in coronarography and echocardiography. Five days earlier, she was diagnosed with SAT based on neck pain, goitre and fever. The final diagnosis was a thyrotoxic crisis in the course of early relapse of SAT. After treatment with prednisolone and propranolol symptoms, biochemical and ECG changes resolved [44].

Another extremely rare presentation was the case of a 38-year-old woman with no previous medical history, complaining of fatigue and palpitations. Physical examination revealed tender goitre. The ECG showed bigeminy and premature ventricular contractions (PVCs) with a ventricular rate of about 140 bpm. During the examination, the monitor displayed an episode of sustained ventricular tachycardia, 278bpm, which was stopped by an infusion of landiolol. Cardiac biochemical parameters were within reference ranges and features of thyrotoxicosis [45].

Encephalopathy

Encephalopathy is a symptom of brain dysfunction, recognised by an altered mental state and other neurological dysfunctions. Hashimoto encephalitis is also known as "steroid-responsive encephalopathy associated with autoimmune thyroiditis" (SREAT) or "non-vasculitic autoimmune meningoencephalitis" (NAIM) [46]. *Chung et al.* presented a case of a 49-year-old female admitted to the hospital because of neurological symptoms. Physical examination revealed somnolence, memory impairment, dysarthria, right-hand weakness, gait disturbance and tender goitre. There were no major deviations in laboratory findings besides thyrotoxicosis and brain magnetic resonance imaging was normal. By contrast, imaging of the thyroid presented an acute phase of SAT. After initial treatment with steroids, her mental status improved significantly but two months later, she experienced a relapse in neurological deterioration accompanied by hypothyroidism. Her symptoms resolved after treatment with pulses of methylprednisolone and levothyroxine substitution [47].

Psychosis

According to the American Psychiatric Association and the World Health Organization, "psychosis" is defined as a state of impaired reality testing with the presence of hallucinations, delusions or both [48]. It can be induced by thyrotoxicosis or hyperthyroidism but generally, psychosis is not the main feature of these conditions. An 18-year-old male presented to the emergency department due to features of psychomotor arousal and paranoid mental state for three days. There was no medical history of previous drug use or psychiatric disorders in the family. Physical examination revealed tachycardia, moist skin, and elevated body temperature, and the thyroid gland was hard and tender on palpation. Laboratory tests revealed biochemical thyrotoxicosis. Due to his mental state, the patient was admitted to the psychiatric department and initially treated with prednisolone and antipsychotic drugs with good effect. On a follow-up visit, the patient remained asymptomatic and was attending school again [49].

Differential diagnosis

Before setting the diagnosis of the classic variant of SAT, we should take into consideration

a few differential diagnoses like suppurative thyroiditis [50], Riedel's thyroiditis or haemorrhage to the thyroid nodule. There is also the possibility of a painful variant of Hashimoto's thyroiditis, however, only a dozen cases have been described over the last few decades [51]. Other differential diagnoses should include disorders causing thyrotoxicoses like Graves's disease or intoxication with thyroid hormones medications.

Treatment

Once the diagnosis is established, treatment should be initiated, however, there is no consensus regarding the scheme of steroid administration. In our department, the following scheme is administered: 40 mg of prednisolone daily in a tapered manner with dose reduction every week for 6–8 weeks. In less severe cases or subjects with contraindications to steroid therapy, the use of NSAIDs like ibuprofen or naproxen can be beneficial, however, is not obligatory. Regarding the study by *Sato et al.*, the effect of stand-alone steroids treatment is superior to NSAIDs [52]. As an additive treatment, in the hyperthyroidism stage, we recommend propranolol and in hypothyroidism levothyroxine but only when the patient is symptomatic.

A novel therapeutic approach was investigated and reported in a study by *Shao-Gang et al.,* intra-thyroid injections of lidocaine and dexamethasone saline solution every other day for one week. The results were compared to typical treatment with oral prednisolone and the injection group was characterised by a more rapid reduction of pain and a shorter duration of treatment [53].

Unfortunately, some patients will need surgical treatment, especially when a malignancy is suspected by FNAC examination or when the patient is unresponsive to pharmacological treatment and symptoms (tender goitre, dysphagia) persist [54, 55].

Outcome and recurrence

Most patients will recover with no long-term complications, though some may experience a relapse or persistent/chronic hypothyroidism. The recurrence rate is 20–30%, yet the reason for this is still unknown and factors determining the risk of recurrence are lacking. In a recent study by *Stasiak et al.* focused on haplotypes, the co-presence of HLA-B*18:01 and HLA-B*35 was associated with a higher risk of recurrence, suggesting that high-risk patients should be initially treated with higher doses of steroids with slower dose reduction [56]. Long-lasting hypothyroidism demanding substitution of levothyroxine will occur in 0.5-15% of patients but predictive factors are still unknown [4].

Final word

The diagnosis of SAT, also known as de Quervain's thyroiditis, can be challenging due to the diversity in severity and presentation of symptoms. The described inducing factors and various clinical presentations of SAT confirm that this condition is indeed a disease of "thousand faces". Even if recognised as a typical endocrine disorder, due to its insidious nature, ill patients can visit physicians of various specialities, so clinicians should be aware of its symptoms and potential triggering factors.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Contribution
R.D. overviewed the literature, prepared draft and did the final editing. E. S-P. is the originator of the paper, collected literature and made major corrections. D.D. proofread the manuscript. M.R. is the senior author. All authors of this paper have read and approved the final version.

Funding sources
There are no sources of funding to declare.

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JMS Journal of Medical Science

Thyroid sonography as an extension of the bedside examination in hyperthyroidism

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DOI: https://doi.org/10.20883/medical.e482

Keywords: hyperthyroidism, graves, sonography, ultrasound, point-of-care

Published: 2020-12-29

How to cite: Kyriacou A, Economides PA, Syed AA. Thyroid sonography as an extension of the bedside examination in hyperthyroidism. JMS [Internet]. 2020 Dec 29;89(4):e482. doi:10.20883/medical.e482

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ABSTRACT

In this mini-review, we discuss the role of thyroid sonography as a 'point-of-care' tool for assessing and managing patients with (suspected) hyperthyroidism who present to the endocrine outpatient clinic. A thyroid ultrasound may aid in distinguishing between hyperthyroidism and destructive thyroiditis. The presence of intense vascularity ('thyroid inferno') on the power Doppler has a very high positive predictive value in identifying hyperthyroidism. It may also allow for the sub-classification of hyperthyroidism into autoimmune and nodular hyperthyroidism. It is important to identify the presence of thyroid nodules at an early stage, as this may influence management. Toxic nodules requires definitive treatment, as well as the presence of nodules in Graves' disease because of increased risk of malignancy. Current guidelines on hyperthyroidism do not clearly state thyroid sonography as a first line investigation, although recent authoritative reviews point in that direction. Given the aforementioned benefits of thyroid sonography, alongside the reduced costs and widespread availability of high-resolution (including portable) ultrasound devices, there is an argument for thyroid sonography to be applied as a first line investigation for all patients with hyperthyroidism. Endocrinologists trained in thyroid sonography could perform this as an extension of their clinical examination when patients first present with hyperthyroidism at the endocrine clinic.

Thyroid ultrasound scanning (USS) is the most sensitive imaging modality for assessing the morphology of the thyroid. It is also the most commonly accepted imaging modality for assessing thyroid nodules, including its application in guiding fine needle aspirations, and in the long-term monitoring of patients who were treated for thyroid cancer (alongside tumour markers).

However, thyroid USS is infrequently utilised in the investigation of patients presenting primarily with thyrotoxicosis. The differential diagnosis of thyrotoxicosis is wide [1], and includes conditions that cause increased thyroid hormone production and secretion (hyperthyroidism; e.g. Graves' disease (GD), toxic multi-nodular goitre and solitary toxic nodule) and conditions that do not (e.g.

thyroiditis and factitious thyrotoxicosis). Thyroid USS can often help differentiate hyperthyroidism from destructive thyroiditis and other thyrotoxicosis-causing conditions, such as factitious thyrotoxicosis and struma ovarii, which are associated with a morphologically-normal thyroid gland. Similarly, thyroid USS can promptly differentiate between autoimmune and nodular causes of hyperthyroidism. Whilst thyroid function tests (TFTs) are readily available when a patient first presents to the endocrinologist, in this narrative review we discuss the inclusion of thyroid USS as another first line bedside investigation in thyrotoxicosis.

Given the increasing availability and affordability of high-resolution (including portable) USS devices, there is a de facto inclusion of thyroid sonography as an extension of the bedside examination at many endocrine centres around the globe. Notwithstanding, this is not a universal policy and not all endocrinologists believe that thyroid USS has a role in the diagnosis and management of GD. Indeed, it must be noted that the bedside thyroid USS is not a practice that is as yet endorsed by international guidelines.

The sonographic signature characteristics of GD include a diffuse reduction in echogenicity, linear echogenic inclusions, and increased gland volume, usually with a symmetrical enlargement of the entire gland with consequent displacement of the vascular bundles of the neck laterally and/or dorsally [2]. However, it is the intense vascularity ('thyroid inferno') on the power Doppler that appears pathognomonic of GD with a positive predictive value of 95% [3]. Nevertheless, in mild, and treated, GD, the vascularity may be mildly increased or even normal and, conversely, hashitoxicosis may give a markedly increased vascularity [4]. Various techniques do exist to quantify the vascularity using colour Doppler imaging: thyroid blood flow area (TBFA), superior, or inferior, thyroid artery mean peak systolic velocity, and dedicated software calculating thyroid blood flow area [5-8]. In clinical practice, this means that in many cases the diagnosis can be instantly confirmed long before TSH receptor antibody (TRAb) results – which have high sensitivity and specificity for GD [9] – become available. Even in TRAb-positive patients, the co-existence of GD and toxic nodules (or the presence of nodular GD) is of interest, as it may guide the management towards definitive treatment. Similarly, it is useful to recognise the co-existence of parathyroid adenomas as this may also influence the management [10]. In a surgical series of 96 patients who underwent thyroidectomy for hyperthyroidism, 13 (13.5%) were found to have concomitant primary hyperparathyroidism (11 with a parathyroid adenoma and two with hyperplasia) [11]. Another single-centre series reported 21 cases of concomitant GD and primary hyperparathyroidism diagnosed based on clinical, intraoperative parathyroid hormone monitoring and histology criteria [12]. Regardless of the likely selection bias in this single-centre series, the point should be made that the co-existence of these two pathologies is not infrequent and that mild hypercalcaemia in patients with hyperthyroidism should not be assumed to be due to the hyperthyroidism per se.

Furthermore, suspicious and malignant cytology (Bethesda classifications 5 and 6, respectively) is significantly more common in nodules aspirated in patients with GD (20% of fine-needle aspirations vs. 7% in patients without GD) [13]. Indeed, in a systematic review and meta-analysis, which included a total of seven retrospective studies and 2,582 patients with GD, 297 (11.5%) were found to have thyroid cancer [14]. Thyroid nodules were identified in 968 (37.5%) patients and were correlated with a fivefold increased risk of thyroid carcinoma vs. those with GD and no nodules on the thyroid USS [14]. Nevertheless, it is worth noting the high study heterogeneity, the retrospective nature and the possible selection bias of the included studies, which enrolled only participants who underwent surgery. Moreover, these studies did not report on ultrasound stratification systems ((e.g. the ATA [15], TIRADS [16], ACR-TIRADS [17] or EU-TIRADS [18]) and, perhaps more importantly, did not report on the percentage of papillary microcarcinomas (micro-PTC). This was addressed in a retrospective surgical series of 526 patients who underwent thyroidectomy for GD. The above-mentioned study again showed high prevalence of thyroid nodules (177/526, 34%), a significant prevalence of thyroid cancer (42/526, 8%), and a significantly increased risk of thyroid cancer in the presence of a nodule [19]. It also provided information regarding the nature of thyroid cancer; all 42 patients had papillary thyroid carcinoma (PTC), 33 (79%) had micro-PTC, three (7%) had lymph node infiltra-

tion and 37 (88%) were deemed to have Stage I disease [19]. During a seven-year follow-up, recurrence was observed in three (7%) patients, including one with micro-PTC, and no mortality was seen [19]. On the other hand, some studies reported a higher incidence of aggressive variants of papillary thyroid carcinoma and lymph node metastases [20,21]. Pathophysiologically, the increased incidence and aggressiveness of thyroid carcinoma in the context of hyperthyroidism may relate to the stimulatory effect of TRAb on the differentiated thyroid carcinoma cells which retain their TRAb receptors [22,23]. Based on the above evidence, an over-diagnosis of papillary micro-carcinomas is a concern when it comes to the widespread application of thyroid sonography. This concern can be ameliorated if the sonography is performed by experienced and formally-accredited sonographers who adhere to international guidelines on the management of thyroid nodules and cancer [15,17].

Moreover, it is worth briefly mentioning the utility of thyroid sonography in the diagnostic work-up of medication-induced thyrotoxicosis. With amiodarone [24], interferon [25] and the newer immune-complex inhibitors [24-26], the distinction is usually between a destructive thyroiditis and hyperthyroidism. Thyroiditis is, more often than not, associated with reduced vascularity and echogenicity on USS and little or no diffuse thyroid enlargement. Conversely, medication-induced hyperthyroidism is more commonly associated with increased vascularity, diffuse thyroid enlargement or a multi-nodular goitre. With the aforementioned medications, along with denileukin diftitox (IL-2 fused to diphtheria toxin), a destructive thyroiditis is the more frequent cause of the thyrotoxicosis, whereas with alemtuzumab [27] Graves' disease, hyperthyroidism appears to be more common, although regarding these latter two medications not a lot of evidence exists in relation to their sonographic signature.

The American Thyroid Association 2016 guidelines on hyperthyroidism state that, if the diagnosis is not apparent clinically and biochemically, then, depending on expertise and resources, measurement of TRAb or radioiodine uptake scintigraphy or measurement of thyroid blood flow on USS can be performed, with preference for scintigraphy when the clinical presentation suggests a toxic adenoma or multi-nodular goitre [10]. However, the reliance on palpation for the identification of thyroid nodules is problematic, with low sensitivity and specificity. For example, in a study of 135 patients with hyperthyroidism, 60 (45%) were found to have thyroid nodules, of which a third were not felt on palpation [28]. Moreover, considering the aforementioned high incidence of thyroid malignancy in patients who present with hyperthyroidism and thyroid nodules [13], and the delay in performing scintigraphy, the higher costs and the radiation involved with it, it may seem logical for thyroid sonography to be carried out first in all patients. Consequently, scintigraphy can be reserved in a minority of cases, as clinically indicated. Indeed, thyroid sonography appears to be the preferred method of investigation employed by endocrinologists in the modern era. This is reflected in the results of two surveys that examined how endocrinologists manage hyperthyroidism. The first, from France, included 992 patients managed by 263 endocrinologists; thyroid USS was performed in 94% of the cases (vs. 40% and 58% who had scintigraphy and TRAb, respectively) [29]. The second survey, from Italy, included 947 endocrinologists; 92% reported that they would request a thyroid USS for hyperthyroidism (vs. 25% for scintigraphy) and, overwhelmingly, chose thyroid sonography in conjunction with TRAb as their preferred diagnostic modalities [30]. Our practice preference in Cyprus is also to perform both thyroid sonography and TRAb, in that sequence, invariably in all patients presenting with hyperthyroidism. It is worth mentioning the better diagnostic performance of TRAb vs. the clinical assessment of hyperthyroidism, as well as the fact that a negative TRAb does not distinguish among other aetiologies and may, on occasion, be seen in very mild GD [1,10,31].

In a recent authoritative review on Graves' disease [32], the utilisation of thyroid sonography was upgraded to a first line investigation, even in patients with clinically suspected hyperthyroidism whose TFTs were not available. The authors highlighted that thyroid USS can allow for the immediate distinction between GD and multi-nodular goitre, which can be achieved on a patient's first presentation and without the need for radiological imaging [32]. TRAb has been recommended as a subsequent investigation tool in all patients for the definitive diagnosis of GD and for aiding management, whereas radioiodine uptake scan

is considered unnecessary if the patient is TRAb positive [1,32]. These recommendations are congruent with our own practice and the conclusions drawn from this literature review.

Case study

A 26-year-old female presented to the endocrine clinic with malaise, tremor, restlessness and palpitations for a month. Physical examination revealed resting tachycardia at 100 beats per minute, tremors and a non-tender goitre, but no pathognomonic features of Graves' disease, such as ophthalmopathy, pretibial myxoedema or acropachy. Blood tests (performed prior to the consultation by her general practitioner) showed a free tetraiodothyronine (T4) of 59.9 (reference range, 10.00 – 19.78) pmol/L and a supressed TSH at <0.005 (0.25 – 5.00) mIU/L. Thus, the patient's clinical features and blood tests were consistent with thyrotoxicosis. In the absence of a clinically evident cause, the differential diagnosis included Graves' disease, thyroiditis and nodular disease. A thyroid ultrasound scan performed as an extension of the physical exami-

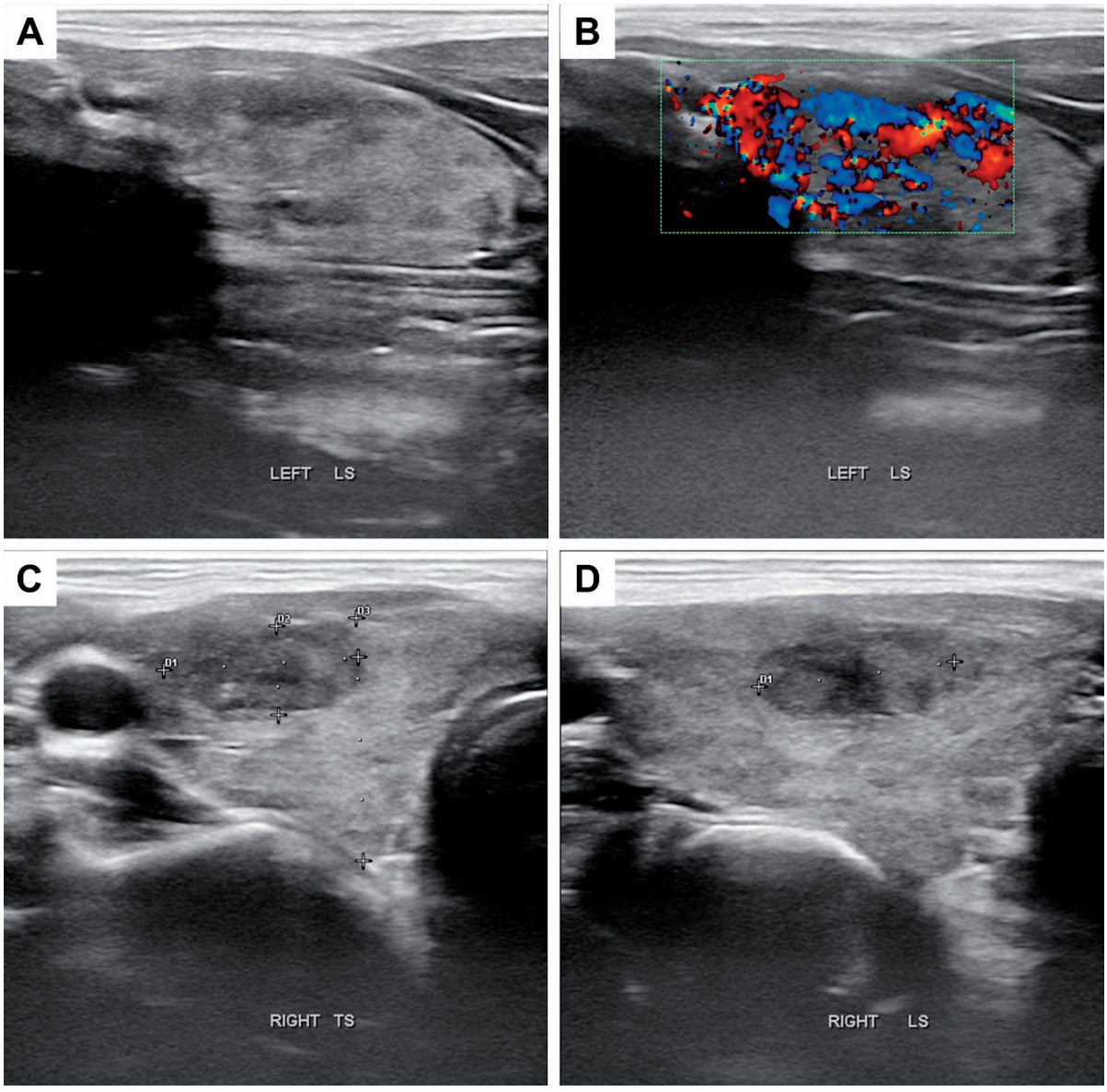

Figure 1. Bedside thyroid ultrasound scan showing an enlarged thyroid with diffuse and marked heterogeneity (A), along with an intensely increased vascularity on power Doppler, indicative of 'thyroid inferno' (B). A thyroid nodule was also visible on the right lobe (C); this measured 16.1x7.3x16.3mm and was hypoechoic with irregular borders, subcapsular and in contact, but not clearly infiltrating, the anterior capsule (D) and stratified as a 'high risk' nodule

nation 'on the spot' revealed an enlarged thyroid with diffuse and marked heterogeneity along with an intensely increased vascularity on the power Doppler, indicative of 'thyroid inferno' (**Figure 1**). However, a thyroid nodule was also identified in the right lobe; this was hypoechoic with irregular borders, subcapsular and in contact with, but not clearly infiltrating, the anterior thyroid capsule; it was stratified as a 'high risk' nodule as per American Thyroid Association 2015 guidelines on the management of thyroid nodules and cancer [15]. By the end of her first visit to the endocrinologist, a dual diagnosis of Graves' disease and possible thyroid carcinoma was given. She was started on anti-thyroid drugs and counselled that surgery may be required. Subsequently, her TSH receptor antibody (TRAb) titres came back significantly raised, confirming Graves' disease. A radioiodine uptake scan showed reduced uptake in the right-sided nodule region and an ultrasound-guided fine-needle aspiration test showed cytological appearances of papillary thyroid carcinoma (PTC) (Thy 5 or Bethesda 6). A total thyroidectomy with therapeutic central compartment lymph node dissection was successfully performed within six weeks of presentation. Histopathologically, a 15 mm right-sided PTC was evident with no extrathyroidal extension and no capsular or vascular invasion, with an incidental finding of left-sided 2 mm and 3 mm PTC foci. Six out of 17 lymph nodes were also positive for PTC (max. diameter was 4 mm). Overall, tumour grading was pT1b(m)N1aM0R0; stage 1. Radioactive iodine ablation (30mCi) was administered three months post-operatively. The patient has since been well-controlled on levothyroxine and remains euthyroid to this date (two and a half years after her presentation) with an undetectable thyroglobulin, negative thyroglobulin antibodies and a normal post-thyroidectomy thyroid ultrasound scan, hence no evidence of thyroid cancer recurrence.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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JMS Journal of Medical Science

Pharmaceutical Care in Ontario

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DOI: https://doi.org/10.20883/medical.e458

Keywords: pharmacist, expanded scope of practice, services, medication management, prescribing, injections

Published: 2020-12-29

How to cite: Dzionek J. Pharmaceutical Care in Ontario. JMS [Internet]. 2020 Dec 29;89(4):e458. doi:10.20883/medical.e458

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ABSTRACT

Pharmaceutical care is an integral part of global healthcare. Indeed, pharmacists are recognised as a primary point of care, providing many services to optimise the patient's healthcare. The article provides insight on how expanding the scope of pharmacists' practice can facilitate collaboration between healthcare providers, relieve the workload of the physicians, also providing patients with optimal healthcare service globally. This article focuses specifically on the expanded scope of pharmacists in Ontario, Canada and the services that pharmacists can provide in the pharmacy for all patients.

Over the years, pharmaceutical care as pharmacists has grown worldwide. Indeed, the industry for pharmacists has expanded, whether working in pharmaceutical companies, academia, hospital pharmacies, or community pharmacies [1]. In Canada, there are over 45,000 licensed pharmacists, with over 11,000 pharmacies providing healthcare to all Canadians [2]. Traditionally, pharmacists would dispense medications but over the years, the scope of practice has expanded and pharmacists can deliver more innovative services to benefit public health. These services not only provide the most appropriate medication management for the patient but allow pharmacists to collaborate with their healthcare providers to optimise their healthcare [3]. Depending on the province or territory the pharmacist is in, the scope of practice/authority may differ slightly, but the main services such as medication reviews, chronic disease management, immunisation services and wellness checks are available country-wide [4,5]. This article will focus on the province of Ontario and the services pharmacists can provide to improve healthcare for all patients. The types of services are listed in **Figure 1**.

Prescriptive authority for smoking/tobacco cessation

Pharmacists are available to enrol patients who are covered under the provincial health insurance programme (OHIP) into the Smoke Free Ontario Strategy programme [6], providing support to patients who are willing to quit smoking, as well as access to appropriate medications to help in cessation [6]. This facilitates the appropriate therapy since pharmacists are familiar with the medications as well as patient adherence, which is a key element in the smoking cessation programme.

Figure 1. Types of services provided by pharmacists in Ontario, Canada [4,5]

Renew/extend prescriptions for continuity of care

Pharmacists can renew and extend prescriptions under certain rules and regulations [4,5]. When adapting a prescription, the pharmacist has the right to alter the dose, the form of medication and route of administration to benefit the patient's needs or circumstances [7]. The adaptation does not include changing the medication or active ingredient. When renewing a prescription, the pharmacist may renew for the total quantity that was originally prescribed by the prescriber, including refills, or a six-month supply of that prescription [7]. However, to do so, the guidelines state that the pharmacist must be in possession and/or have access to the original prescription to be renewed or adapted. The pharmacist must also assess the patient to determine if the therapy is safe and outweighs the benefits over risk, seek consent from the patient or their authorised agent and provide proper documentation and notification to the prescriber (within a reasonable time after the mentioned above) to ensure continuity of care [7]. It is important to note, pharmacists do not have the right to renew or adapt any controlled substance whether it be narcotics, controlled and targeted substances or any medication that is monitored under the Narcotic Safety and Awareness Act [7].

Injection (SC or IM) of vaccines, including influenza vaccine

For a pharmacist to administer an injection, they are required to have completed training approved by the OCP (Ontario College of Pharmacists) and register their training and maintain an active certification in CPR and First Aid [5,8,9]. Pharmacists can administer injections for the following circumstances [8,9]:

- The patient is 5 years of age or older and consent has been obtained from the patient (or their authorised agent)
- The injections are administered in an environment that is safe and clean following all appropriate infection control procedures
- The patient has been prescribed an injection that they can self-administer but they (or their

authorised agent) prefer to have the injection dispensed and administered by the pharmacist for education and demonstration of how to administer the injection

- Patients prescribed Schedule I vaccine specified in regulations
- Patients requiring a Schedule II vaccine specified in regulations
- Administering the influenza vaccine under the Universal Influenza Immunisation Programme
- Substances that are not listed in any of the schedules may be administered in a medical directive context
- List of vaccinations that can be administered by pharmacists can be found in **Figure 2**.

After receiving an administered injection, the pharmacist must have all proper documentation as well as informed their PCP (primary care provider) of the administered injection [8,9]. Pharmacists can monetarily charge administering injections for patients who meet the criteria for publicly funded vaccines but they must inform the patient that they can receive the vaccine administered by their PCP at no cost to the patient [9].

Medication reviews and chronic disease management

Medication reviews are an opportunity for pharmacists to meet and educate their patients on the medications they are taking to optimise their healthcare. In 2007, the MedsCheck programme was initiated for patients in Ontario taking a minimum of three medications for a chronic condition [11]. Over the years, the programme has expanded and is now available to patients who are residents of long-term care homes, patients with diabetes and home-bound patients who are unable to visit the pharmacy [11]. The MedsCheck programme helps pharmacists to understand their patients and identify problems as well as help resolve medication issues for the most beneficial usage of the medication. During this review, pharmacists will consult the patient one-on-one and answer any questions that they have about their medications whether prescribed and/or over the counter, help patients understand their medications and what they do, inform and/or identify adverse effects the patient can expect but most

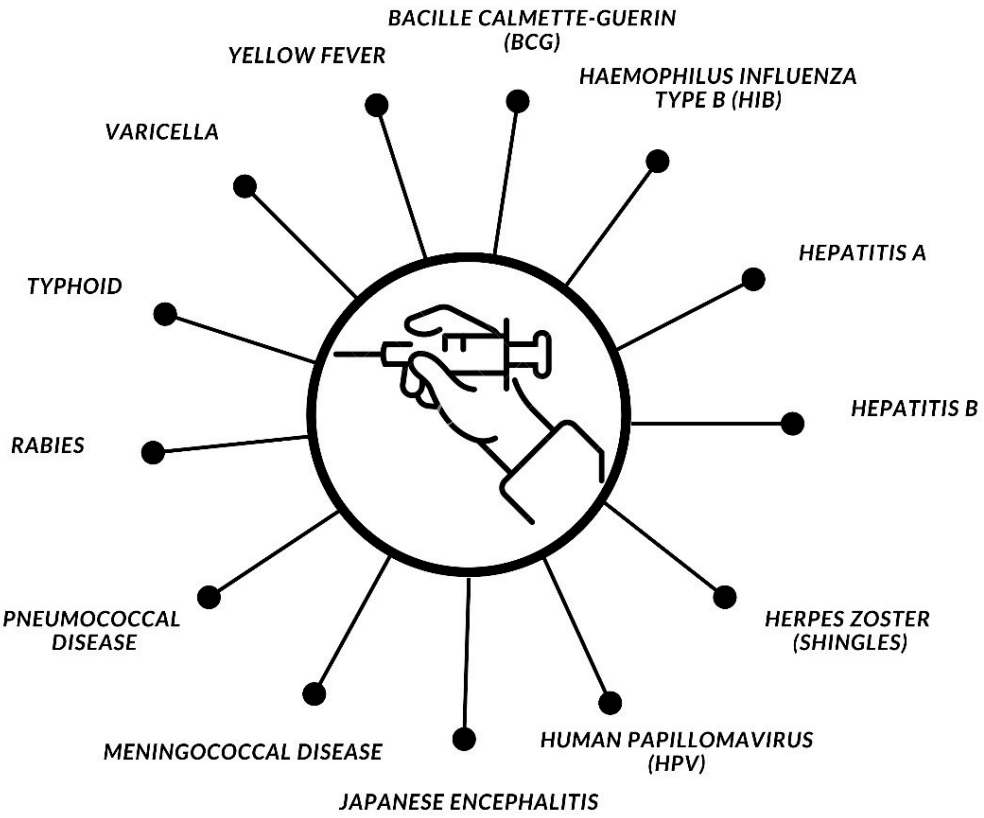

Figure 2. Types of vaccinations that pharmacists can administer in Ontario [10]

importantly, the pharmacist now has a complete and accurate medication list for the patient, which can be shared with their PCP to support collaboration to optimise the patient's healthcare [11].

Discussion

The scope of practice for Ontario pharmacists is continuing to grow, with pharmacists becoming experts on medication management and providing advice and suggestions to the health care team. With over 15,000 licensed pharmacists, the increased scope of practice of renewing medication, being able to provide injections, and safer medication management provides easier access to healthcare, as well as helping to ease the amount of work for the patient's PCP, thereby providing patients with the most optimal healthcare. This is not only seen and proven in Ontario but in other provinces in Canada and countries who have expanded the scope of practice for pharmacists. In provinces such as Alberta, Saskatchewan, Manitoba and New Brunswick, pharmacists can initiate a prescription for chronic diseases under certain restrictions [12]. In Quebec, pharmacists cannot initiate a new prescription but are allowed to adjust doses to meet a therapeutic target as well as prescribe a new dose to meet that target [12]. In America, pharmacists are also allowed to administer injections [13]. It has been shown that due to the pharmacists' ability to provide medication management therapy, they could create an "inferred diagnosis" from medication reviews and identify the need for a vaccine [14]. It also facilitates the administration of the vaccine because most PCPs do not stock the vaccine in their offices and the pharmacist can dispense and administer the vaccine [14]. This helps the PCP because it reduces the workload and it is not necessary for the patient to return to the clinic. Around the world, many countries such as the United Kingdom, Ireland, Portugal and Australia have expanded the scope to allow pharmacists to administer injections [15,16]. Pharmacists in England, Scotland and Wales can prescribe, supply and administer medicines and medical devices using their knowledge of medications to ensure their prescribing services are provided safely and effectively [17]. The United Kingdom has also introduced the 'New Medicine Service' that provides patients with extra support from pharmacists when starting a new medical treatment for certain chronic conditions [18,19]. The New Medicine Services provides a series of three appointments with a scheme for patients to follow while taking their new medication for the first time, all while being closely monitored by the pharmacist to ensure proper adherence and understanding of the treatment [20]. Nevertheless, there are countries, such as Poland, who have not expanded the scope of practice for pharmacists that would greatly benefit from such an expansion. With an expansion to their practice, like in Ontario, there is potential for pharmacists in Poland to provide better medication management, open the doors for communication between patients and their PCPs and improve pharmaceutical care [21].

Conclusion

With an expanded scope of practice, pharmacists are positioned to play an integral role in the healthcare system. The expanded services that pharmacists can provide may increase accessibility to a healthcare professional for patients, shorten wait times at a physician's clinic as well as reduce the physician's workload by administering injections or providing extended prescriptions. For the continued and future expansion of services to optimise global healthcare, it is important to educate patients, as well as physicians, about the services pharmacists can provide.

Acknowledgements

I would like to sincerely thank Mikołaj Seostianin MD 6th year student at PUMS for all his hard work in designing the graphics.

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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JMS Journal of Medical Science

Rationale, design and methods planned in a prospective study concerning the circadian rhythm of heart rate asymmetry in healthy subjects

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DOI: https://doi.org/10.20883/medical.e492

Keywords: ageing, cardiovascular time series, circadian rhythm, heart rate asymmetry, heart rate variability, physical activity, sex differences

Published: 2020-12-29

How to cite: Sibrecht G, Krauze T, Dobkowska R, Wykrętowicz A, Piskorski J, Guzik P. Rationale, design and methods planned in a prospective study concerning the circadian rhythm of heart rate asymmetry in healthy subjects. JMS [Internet]. 2020 Dec 29;89(4):e492. doi:10.20883/medical.e492

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ABSTRACT

Heart rate asymmetry (HRA) is a physiological phenomenon caused by an unequal (asymmetric) contribution of heart rate decelerations and accelerations to the variability (variance) and microstructure of the heart rhythm of sinus origin. HRA has been studied in healthy people and patients with heart failure, diabetes, obstructive sleep apnoea, ischaemic heart disease, and survivors of myocardial infarction. HRA is a particular form of the heart rate variability (HRV) phenomenon related to the changes in the duration of cardiac cycles of sinus origin. HRV is influenced by physical activity, age, gender or time of day. It has been reported that HRA expression differs between day and night. However, its circadian rhythm has not been analysed so far. Moreover, the differences in HRA expression related to gender, level of physical activity or age have not been investigated either. With this study, we aim to explore the circadian rhythm of the HRA features, as well as the relation of the HRA expression to gender, physical activity, sleep pattern and body composition in a group of at least 100 healthy adults of both sexes aged between 19 and 60. This study might provide reference values for HRA as well as confirming or dismissing the existence of circadian rhythm of this physiological phenomenon.

Basic concept and hypotheses

Heart rate asymmetry (HRA) is a phenomenon caused by the different behaviour of heart rate (HR) accelerations and decelerations, which have unequal input to the short-, long-term and total heart rate variability (HRV) as well as the HR complexity and microstructure [1-5]. HRA was first discovered and described in the short-term HRV in 2006 by Guzik and Piskorski [1]. In the following years, these authors also reported asymmetric features of [1] the long-term and total HRV; [2] HR microstructure composed of monotonic runs of consecutive decelerations and accelerations; and [3] HR complexity measured by entropy derived separately from decelerations and accelerations [2,3].

In more detail, HR decelerations make a significantly higher contribution than accelerations to the short-term variance of RR intervals but a lower contribution to the long-term and total HRV in healthy people [1,4]. The analysis of the HRA microstructure has revealed that the number of deceleration runs is significantly lower than that of acceleration runs, and the longest monotonic runs are usually composed of accelerations but not decelerations [2,5]. Consequently, the heart rate entropy (a measure of complexity) derived from decelerations is lower than that from accelerations [2].

Since the first papers on HRA, there has been a growing interest in this phenomenon. HRA has been studied both in physiological and clinical studies. The HRA expression is reduced in patients with type 1 diabetes [4], heart failure [5], sleep apnoea [6,7], septic new-borns or people with emotional stress [8-10].

Many physiological phenomena are oscillatory, and some present a diurnal variation or circadian rhythm [11,12]. Our daily routines related to eating, working, leisure time and lifestyle behaviour have a specific repeated pattern and present typical features of diurnal variation [13]. The autonomic nervous system also shows the circadian activity [14,15]. The system's sympathetic part is usually more active during the day, whereas parasympathetic tone increases at night. Both the heart rate and respiratory rate go down at night and increase during the day [16]. Blood pressure usually increases when someone is awake and drops during sleep [17,18].

Studies in animals showed that the activity of potassium channels Kv1.5 and 4.2 is linked with circadian rhythm. A similar phenomenon occurs with the regulation of intracellular calcium concentration via the ryanodine receptor and multiple T-type calcium channels. In the sinus node of rats, the HCN4 protein and HCN4 mRNA concentrations change with the circadian rhythm. Remodelling of the ion channels leads to their different expression on the cells' membranes. Circulating fatty acids influence the activity of fatty acid dehydrogenase through transcriptional, translational and post-translational mechanisms [19]. Impairment of the natural clock or the function of clock genes such as CLOCK, BMAL1, Per, and Cry may cause hypertension, obesity, heart attacks, ischaemic strokes, and mood and mental disorders. Changes in the phosphorylation of eNOS during the day and night cycle lead to endothelial dysfunction [20-22].

It is assumed that our human physiological reactions have adapted to environmental stimuli which change during a day [23]. As already mentioned, HR and HRV are typical examples of the cardiovascular circadian rhythm (**Figure 1**) [24,25]. The HRA phenomenon is a specific part of HRV and as such should have similar behaviour, e.g. diurnal variation. However, HRA circadian rhythm has not yet been studied.

For this study, we hypothesise that some HRA features have a circadian pattern and thus should change their expression during day and night. Porta et al. partially showed that short-term HRA differs between day and night in patients with heart failure [26]. However, they have studied it neither in healthy people nor for all HRA features, nor with the methods dedicated to the circadian rhythm analysis.

Many natural oscillations are quite frequent, e.g. breathing occurs 12 to 18 times a minute (0.2-0.3 Hz), and spontaneous increases of arterial pulse pressure known as Mayer waves appear every 10 seconds (0.1 Hz) [28]. Some other oscillations are rarer and can be spotted once every 24 hours [27]. It is relatively easy to observe oscillations appearing twice or more times during 24 hours, but oscillations present once a day may be inappropriately identified with the 24-hour ECG recordings. According to the Nyquist theorem, when it comes to studying slow oscillations present once a day (0.000012 Hz), the recording should last at least

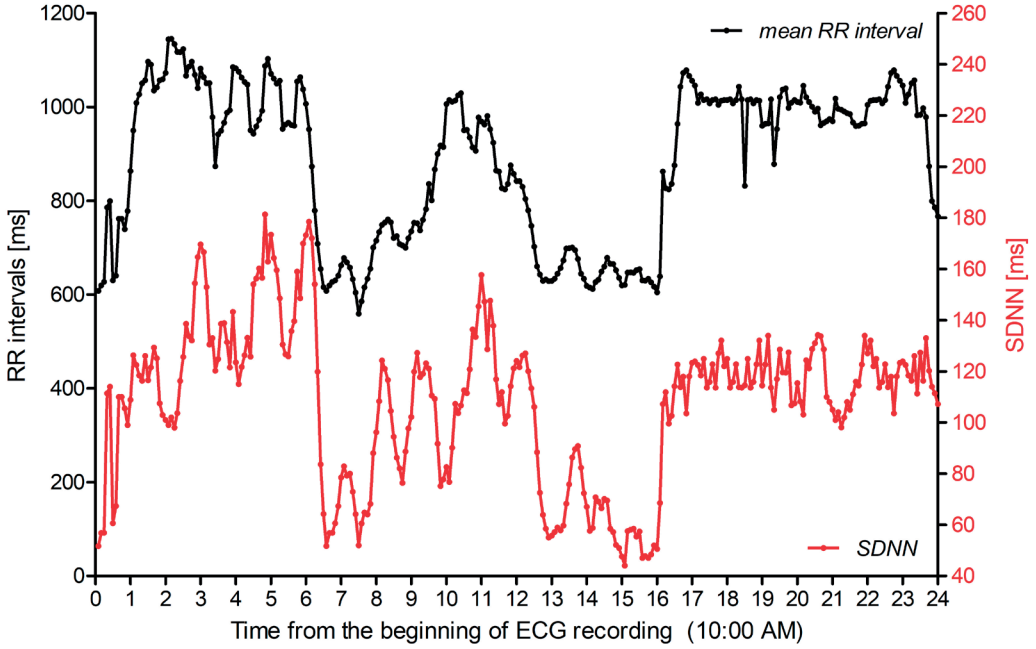

Figure 1. Oscillations of 5-minute means of RR intervals and values of the standard deviation of normal-to-normal RR intervals (SDNN) in a 24-hour ECG recording acquired from a healthy 20-year-old male

48 hours [29]. For HRA, some very long acceleration and deceleration runs appear only once a day or even less frequently. Runs composed of 16 consecutive decelerations or 20 consecutive accelerations are just two examples [2]. Whether more prolonged deceleration and acceleration runs may occur in the 48-hour ECGs is uncertain.

There is a known effect of ageing on HRV – most of the variance-based parameters become reduced with advancing age [30,31]. Further, sex differences in HRV have also been reported [32]. However, neither effect of age nor sex on HRA have been studied so far. We hypothesise that both factors might contribute to the expression of the HRA phenomenon. Usually, HRV is reduced in overweight and obese people, but it increases in individuals who are more active and sleep longer [33-36]. Yet, the relationships between HRA and body composition, level of physical activity, and sleep duration and quality have never been investigated.

The analysis of the asymmetric properties of the HR microstructure has shown that the number of acceleration runs is usually higher than that of deceleration runs [13]. Additionally, the longest runs in the same people come from accelerations rather than decelerations. Previous studies on the HRA microstructure used a lower sampling frequency of 200 Hz for the 24-h Holter ECGs, which translates into a precision of RR intervals of 5 ms [2]. There was a substantial number of so-called neutral runs (up to 6-7% of all beats), i.e. such consecutive RR intervals which have identical duration. For instance, the neutral run of three is composed of four consecutive RR intervals, with the first as the reference for the 2nd, the 2nd for the 3rd, and the 3rd for the 4th RR interval. RR intervals before the 1st and the 4th RR intervals must be different. In total, however, the number of comparisons showing no change for this particular neutral run equals three. The following time series of RR intervals is more explanatory: 1,000 ms (1st RR interval), 1,000 ms (2nd RR interval), 1,000 ms (3rd RR interval), and 1,000 ms (4th RR interval). For more details on the HRA microstructure please refer to references 2 and 5.

As discussed in the previous study [2], the neutral runs seem to be an artificial effect of low sampling frequency rather than a genuine physiological phenomenon. Therefore, studying the distribution of acceleration and deceleration runs in Holter ECGs recorded at a much higher frequency of at least 4,000 Hz (precision of 0.25 ms), i.e. over 20 times higher than in the original paper, should result in a lower number of, or even no, neutral runs, and more precise description of the asymmetric features of the heart rate microstructure.

Study aims

Based on the above reasoning, we have proposed several study aims, which are summarised in **Table 1**. The whole study is designed as a prospective piece of work, in a group of healthy people with a wide age range who will undergo the 48-hour Holter ECG recording.

Research plan, material and methods

Our methodological aim is to collect at least 100 good-quality 48-hour Holter ECG recordings from men and women of a wide age range. We intend to achieve equal gender distribution; therefore, the same number of men and women will be recruited. Additionally, to preserve an equal contribution of age to our results, we intend to collect at least 20 ECG recordings of the 48-hour duration from men and women in each of the following age groups:

- 19-29 years;
- 30-39 years;
- 40-49 years; and
- 50-60 years.

The quality of Holter ECG recordings is unpredictable, and correcting technical artefacts is sometimes impossible. To avoid methodological problems related to an insufficient statistical power secondary to poor quality of recorded ECGs, we plan to examine up to 200 healthy people. In this way, we will increase the likelihood of collecting 100 good-quality 48-hour ECGs.

Each participant will go through a standard clinical interview and examination, body composition analysis, the 48-hour Holter ECG, transthoracic echocardiography, and estimation of daily activity performed with a sports watch. All gathered data will be stored in digitised form and later used for mathematical and statistical analyses. **Table 2** shows the inclusion criteria for all participants.

The study was approved (708/18) by the Bioethics Committee at Poznan University of Medical Sciences, Poznan, Poland.

Body composition analysis

The body composition will be measured using the total body impedance with the TANITA MC180-MA medical device (Tanita, Japan); four different electrical current frequencies will be employed. This test makes it possible to determine body mass, body fat percentage, lean and water mass, and basal metabolic rate [37].

48-hour Holter ECG recording

To acquire the 48-hour ECG with at least 4,000 Hz sampling frequency, it is necessary to employ the Medilog® DARWIN 2 Enterprise system with the 3-lead ECG recorder Medilog AR12plus (Schiller, Switzerland). Such ECG recordings will be col-

Table 1. The study aims of this project

	We intend to explore:
1	the circadian rhythm of different features of HRA;
2	the gender differences in the HRA expression;
3	the relationship between the HRA expression and body composition;
4	the association between the HRA expression and daily activity;
5	the link between the HRA expression and duration and quality of sleep;
6	the distribution of acceleration and deceleration runs in recordings of at least 4,000 Hz sampling frequency.

Table 2. Inclusion criteria for individuals enrolled in this study

The following inclusion criteria will be required from each study participant:
Voluntary participation;
Accepting all study conditions and signing informed consent;
Feeling healthy;
No known chronic diseases or any acute illness in the past three months;
No history of myocardial infarction, cerebral stroke, neoplasm, atrial fibrillation or flutter, pulmonary embolism;
Not taking medications (except for hormonal contraception, nutrients and typical supplements such as vitamins and minerals);
No past surgeries or interventions related to the cardiovascular, respiratory or nervous system;
Normal findings in physical examination, resting 12-lead ECG and transthoracic echocardiography.

lected from all healthy participants with normal results for their resting ECG, blood pressure measurement and transthoracic echocardiography. In addition to standard Holter ECG analysis such as arrhythmia, ST-segment and QT analysis, the reconstructed respiratory curve will be analysed so as to identify potential episodes of apnoea and hypopnea. For this purpose, the ECG-Derived Respiration monitoring (EDR) index will be employed, i.e. a parameter derived from the analysis of the R wave amplitude variation. An EDR value above 20 is considered as a severe risk of apnoeas in the subjects [38-41].

Each Holter recording will first be automatically analysed and then reviewed manually to correct, if necessary, inappropriately-identified RR intervals. Finally, the duration of each RR interval and information about its origin, i.e. from the sinus node, atria or atrioventricular junction, or ventricles, or labelled as a technical artefact, will be exported to ASCII files for further analysis of HRV and HRA.

Daily activity, duration, and quality of sleep

The daily activity, duration, and quality of sleep of each participant will be monitored and recorded using the M430 POLAR Running Watch (Polar Electro, Finland). This sports watch will be placed on the wrist of each individual and programmed with personal details such as age, gender, and current body weight. After 48 hours, the data recorded by each sports watch will be uploaded to the PolarFlow service to retrieve the following information:

These data will be used for further analysis.

Heart rate variability analysis

For the HRV and HRA analysis, we will use the set of parameters defined in a specific HRV guideline [42,43] or papers on HRA published by our team.

The list of HRV and HRA methods applied for the measurement of many possible parameters is shown in Table 3 [1,2,44-46].

Data collection

All data will be, after coding, placed and stored in a specialised electronic data capture form prepared with the use of the REDCap environment. The REDCAP project is available for scientific research at Poznan University of Medical Sciences at redcap.ump.edu.pl.

Statistical analysis

Data distribution will be analysed using the Shapiro-Wilk test. A summary of the data will be presented, with the mean, standard deviation, median, and 25th-75th percentiles.

For the analysis of associations between different HRV and HRA features and the remaining parameters, nonparametric Spearman, parametric Pearson, and linear regression models will be used.

The binomial tests will be applied to study whether or not specific asymmetric features are present.

For the analysis of the circadian rhythm of HRA and HRV we intend to use the time series analysis methods for correlated series to avoid variation, inflation, and loss of statistical significance.

Measurable effects and expected results

We plan to gather for our database at least 100 good-quality ECGs of 48-hour duration with a sampling frequency of at least 4,000 Hz. These recordings will be equally distributed between men and women and across consecutive age decades between 19 and 60 years old. We intend to use such a database not only for HRA and HRV measurements, but also for other newer and emerging methods related to the RR interval analysis.

As we have developed several different methods for the quantitative and qualitative analysis of HRA, we believe that, with this database, it will be possible to establish reference values for various measures of HRA. One of our primary goals is to study the circadian pattern of HRA – we hope to explore this issue and find specific answers. Additionally, we will be able to compare the HRA expression between men and women, so as to investigate any association between age, body composition, quality of sleep, real daily activity, and HRV and HRA. With our results, we should also be able to answer the question regarding the value of high sampling frequency for the HRV and HRA analysis, and define reference values for such sampling. Most of these aspects have never been studied for HRA, and, in many cases, neither for HRV.

Based on our previous experience and the available literature, we expect that:

- 19-29 years;
- 30-39 years;
- 40-49 years; and
- 50-60 years.
- number of steps a day;
- total distance walked;
- duration and quality of sleep;
- number of burned calories.
- the circadian rhythm of HRA exists;
- women have a weaker expression of HRA than men;
- HRA expression attenuates with ageing;
- more active people have higher values of HRV and stronger HRA expression;
- HRA expression and HRV values are related to the duration of sleep, and potential episodes of sleep apnoea;
- higher sampling frequency will reduce the number of so-called neutral runs and improve the differentiation between heart rate accelerations and decelerations.

Acknowledgements

Ethical Committee permission number: Bioethical Committee of Poznan University of Medical Sciences no 708/18 signed on 14.06.2018.

Conflict of interest statement
GS, TK and JP are beneficiaries of the "Diamond Grant" programme (0184/DIA/2018/47) which provided funds for this research project.

Funding sources
This scientific work is financed by the budget for science of The Polish Ministry of Science and Higher Education as a research project of the programme "Diamond Grant".
Funding source and grant number: This study is financed by The Polish Ministry of Science and Higher Education within the programme "Diamond Grant" (0184/DIA/2018/47). Principal investigator: Greta Sibrecht.

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Books

Personal author(s)

1. Rang HP, Dale MM, Ritter JM, Moore PK. Pharmacology. 5th ed. Edinburgh: Churchill Livingstone; 2003.

Editor(s) or compiler(s) as authors

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