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Research

"The Culture palette"- a randomized intervention study for women with burnout symptoms in Sweden.

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Abstract

Burnout is common among women in Sweden. Cultural activities, i.e. arts, have benefitted different patient populations and may have potential for treating this group as well.

Aim: To evaluate possible health effects of regular cultural activities for women with burnout symptoms with focus on exhaustion level.

Methods: 48 women (mean age 54) were randomly assigned either to a cultural activity group (intervention group) or to a control group. Four health care centers were the settings for a "Culture Palette" comprised of six different cultural activity packages: interactive theater, movie, vocal improvisation and drawing, dance, mindfulness training and musical show. The activity packages were offered once a week over a period of three months. Standardized questionnaires; the Karolinska Exhaustion Disorder Scale (KEDS), Sense of Coherence (SOC), Toronto Alexithymia Scale (TAS) and Self-rated health were used at baseline, in month three and at follow-up in month six. Qualitative interviews with patients, cultural producers and health care staff were conducted at month three and month six.

Results: Burnout symptoms/exhaustion (P< .001) and alexithymia (P=0.007) as well as self-rated health (P<0.001) improved more in the intervention group than in the control group with clinically relevant effect variances. There was no statistical evidence of any difference in the development of SOC between the intervention and the control group. The healthcare staff were also positively affected although they did not participate in the cultural activities.

Conclusion: Regular cultural activities affected this group of women beneficially with enhanced health and decreased levels of exhaustion.

Keywords: arts, burnout, cultural activities, exhaustion symptoms, health care centers, self-rated health, women.

Introduction

Population studies in Norway are showing that taking part of (creative) or receiving (receptive) cultural activities, i.e. arts, is associated with good health and good satisfaction with life among other things,[1]. Cultural activities have the potential to affect individuals beneficially: physiologically, biologically and emotionally, and several studies show that cultural activities can stimulate emotions and behaviors that make life easier, [2–5]. Cultural activities can enrich and enhance our memory, stimulate connections among brain networks and enable us to accelerate learning and differentiate feelings of meaning and context,[6,7] Cultural activities have also improved both physical health, social function and vitality among health care staff,[8].

In an analysis of data from a large longitudinal cohort-study of a working population (called the SLOSH study = Swedish longitudinal occupational survey of health), some interesting associations were revealed between access to cultural activities in the workplace and health. Participants reporting many cultural activities at work had a more favorable improvement of emotional exhaustion during a follow-up period of two years than those whose workplaces did not offer these amenities,[9]. Other studies in which cultural activities have been offered to patients on long-term sick leave confirm that cultural activities have beneficial effects on both self-confidence and pain,[10,11].

In a new approach, an artistic leadership program, called "Shibboleth", affects not only managers included in the study, but also their employees (who did not participate in the artistic program). This one year art-based program showed statistically significantly more improvement of mental health, covert coping and performance-based self-esteem than the comparison group (who participated in an ordinary leadership program). They also experienced less winter/fall deterioration in the serum concentration of DHEA-S (dehydroepiandrostereone-sulfate), a regenerative/anabolic hormone,[12].

Studies on singers, both amateur and professional singers and choir singers, show positive effects on different biological markers such as oxytocin and testosterone,[13–15]. On the basis of results from another Swedish project, "Prescribed Culture", which aimed to evaluate the effects of prescribed cultural experiences in the treatment of patients on long term sick leave, it was claimed that cultural experiences have their best effects when used in health promotion and prevention , rather than when the individual is already sick,[16]. Multimodal stimulation seems to have particularly strong effects. For instance, concomitant visual and auditory stimulation gives rise to stronger activation of "visual" and "auditory" parts of the brain than separate visual and auditory stimulation,[17].

A mixture of different cultural activities seems to optimize influence on the limbic system since a broader emotional perception is activated,[7]. Cultural activities offered to participants that would not have chosen them spontaneously, could enhance already existing pathways in the brain enabling deeper cognitive behavioral change,[17–20].

Despite this knowledge regarding the potential benefit of cultural activities in different contexts on both individuals and groups there is still a missing accessible practical functioning link between producers of culture and different groups of practitioners within health-care.

Burnout is characterized by emotional exhaustion, detachment from work and decreased effectiveness at work. This can develop in situations with excessive workload and insufficient resources as well as lack of control and support,[21]. If the process of burnout is a reaction to long-term stress, without enough recovery, this can lead to the more severe exhaustion syndrome,[22]. Symptoms include fatigue, impaired emotional regulation, cognitive problems and sleeping disorders. Most of these patients have an increased sensitivity for stress even after recovery,[22]. In recent years, Swedish rates of sick leave due to minor psychiatric morbidity , and burnout symptoms, have increased dramatically,[23-24] . Complaints usually include physical, emotional and cognitive exhaustion, which in most cases appear to be related to chronic stress without restitution,[25–28]. Today many women in Sweden have stress related symptoms, and some are diagnosed with exhaustion syndrome. If these women are detected at an early stage, the prognosis is good,[22].

Alexithymia, (the difficulty to differentiate your own and others feelings), can be a silent but severe problem for persons suffering from this personality trait. Grabe et al.,[29] conducted a study in which the questionnaire TAS-20 was used for the assessment of alexithymia. Medical examination was also performed. In this study alexithymia was related to hypertension and arteriosclerotic plaques. Alexithymic personality traits may increase the risk for CVD (cardio vascular disease).

The rationale behind choosing symptoms of exhaustion, SOC and alexithymia as main outcome variables was the intention to examine whether cultural activities in this form can change pattern of thought, feelings and behavior in participants with burnout symptoms. If cultural activities prove effective for this participant group, they could have considerable benefits both financially in terms of reducing sick leave and health care consumption and of reduced individual suffering.

Aim

The aim of the study was to assess to what extent symptoms of exhaustion, sense of coherence, alexithymia and self-rated health among women with burnout symptoms can be beneficially influenced by cultural activities organized in health care centers.

Method

Participants

Four health care centers in Stockholm County hosted the cultural activities. Medical doctors and social workers distributed information about the study to women diagnosed with exhaustion disorder or exhaustion symptoms. Women, native and foreign born, with burnout/exhaustion symptoms (fatigue syndrome or stress-related fatigue) who were curious about new clinical approaches were asked by the doctor to participate in the study and screened for inclusion and exclusion criteria. Participants (women age > 18) with burnout / exhaustion symptoms such as strong fatigue, cognitive problems, and sleep disturbances were enrolled. There was an inclusion criterion with a score above 2 on the KEDS scale. The diagnosis was made by the doctor.

Exclusion criteria: Participants with difficulty in speaking and understanding Swedish, participants with alcohol or drug abuse problems, or/and participants with severe depression or psychiatric borderline. Also excluded were participants with severe somatic diseases (such as serious angina pectoris or participants who had had a stroke). Randomization was done using a 3:1 allocation to intervention or control groups.

The randomization was done using a stratified randomization by center. Randomization was done by the statistician. The group allocations were sent in individual envelopes which were distributed to centers and blinded to the site staff. Envelopes were further drawn in a consecutive order with regard to recruitment of subjects at each of the four health care centers. Thirty-six participants were allocated to the intervention group (nine patients in each group) and twelve participants to the control group. The standard care that each participant received included physiotherapy such as relaxation and physical light training.

All randomized participants gave their written consent to participation in the study. Data were collected over a period of 6 months. The project includes evaluation of six different culture activities. In the selection of the health care centers socio- economic diversity and employment status were considered. We used regularly occurring structured cultural activities in cooperation with culture producers, i.e. actors, musicians, dance teachers. The Regional Research Ethics Committee of Uppsala has approved the study (Dnr. 2012/359).

The culture palette: six different cultural packages

The following cultural activities were included in the study; five of them have previously been presented in the literature with good evidence on other groups of patients. One package (the musical show), which has not been presented previously on groups of patients, was chosen as it represents a combination of different modalities of activities at the same time. The active mechanism of all six cultural activities was to stimulate different modalities of the senses such as the visual, motor, verbal, auditory, emotional and sensational, according to Downing's levels of perception, [30]. All participants were offered six cultural packages:

1. Interactive theater: An experienced actor introduced poetical lyrics and poems and then initiated and participated in discussions with the participants regarding thoughts, emotions, and experiences evoked by the texts.

2. Movie: After showing a movie, a film expert initiated discussions among the participants about experiences and thoughts evoked by the movie.

3. Vocal improvisation and drawing: After participating in a vocal improvisation session with an experienced performance artist and pianist, the participants painted a picture representing emotions, thoughts and pictures evoked during the improvisation

4. Exploring Dance: The participants improvised dance movements under the guidance of a dance movement pedagogue/music teacher. The dance movements were staged according to the situation in the room and with focus on bodily awareness. Afterwards the group discussed their experiences during the dance session.

5. Mindfulness and contemplation: The participants contemplated and practiced mindfulness together with an experienced mindfulness instructor. Attention was on breathing and body awareness. Thoughts, feelings, images and sensations were in focus and experiences were reflected in the group after the contemplation.

6. Musical show: after a musical show including music, song and dance focusing on bodily awareness, the participants discussed thoughts regarding the body with the actor.

Every session in each one of the six different cultural packages lasted for 90 minutes.

Evaluations

Three different standardized scales, and also self-rated health and self-figure drawing, were used.

KEDS - Karolinska Exhaustion Disorder Scale,[31]. Questions about concentration, memory, physical fatigue, endurance, recovery, sleep, hypersensitivity to sensory input, experience requirements and irritation and anger. Higher scores indicate worse disease activity/performance.

SOC - Sense of coherence,[32]. A key factor in being able to feel well-being and health. This factor has been shown to be crucial to helping individuals mobilize their self-healing systems. Higher scores indicate better performance.

TAS - Toronto Alexithymia Scale,[33]. Estimation of ability to recognize and interpret feelings in oneself and others. TAS contains three subscales; the inability to handle emotions due to emotions being poorly recognized (difficulty recognizing), the inability to describe feelings (difficulty describing), and mismatch between coping behavioral emotions (externally oriented thinking). This study used the full scale score, i.e. the summary of the three sub scores. Higher scores indicate worse performance.

Self-rated health (SRH) consists of a single item measure.

Procedures/implementation

The four different health care centers presented each activity on two consecutive occasions. After two weeks of one program, there was a new program on two consecutive occasions etc. Each participant has thus been offered 12 cultural packages during a three-month period, i.e. once a week. During the monitoring period between month 3 and month 6, there was no culture activity offered. The control group was monitored in parallel during the entire period monthly at 0, 3 and 6 months.

The participants evaluated the project individually with questionnaires prior to the sessions, after completion of the intervention at month 3, and at follow-up after 3 months i.e. month 6 (both intervention and control group). In-depth interviews with both participants and producers of culture, i.e. representatives for the various cultural activities and health care staff were conducted during the monitoring period (this data is not presented in this article).

Data analysis

The primary outcome efficacy end point/measure was mean change from baseline to three and six months in the KEDS summary score. The secondary outcome measures were mean change from baseline in the SOC summary score, the TAS summary score and the self-rated health, from baseline to three to six months.

All data were presented using descriptive statistics, i.e. mean and standard deviation for continuous variables and frequency and percentage for categorical variables. For all main outcome variables, data were further analyzed using the Linear Mixed Models, including group (intervention and control) and time (baseline, 3 month and 6 months) as fixed factors. Results were presented as marginal means, the estimated mean value adjusted for the factors included in the analyses model. The difference between intervention and control group with regard to the estimated and adjusted means are defined as the effect size, i.e. the mean difference between the intervention groups for each of the primary and secondary outcomes measures divided by the standard deviation. All tests were two-tailed and $p<0.05$ was regarded as statistically significant.

IBM SPSS version 22 was used for statistical calculations. In the presentation of the results from the statistical analyses, the measured effect size was used and derived as the absolute difference between active intervention and controls with regard to each of the outcome variables/endpoints used,[34].

Results

There were 55 participants screened in this study, however seven participants who met the exclusion criteria of too serious/severe depression was not included into the study. In total, there were 48 participants randomized into the study, age between 41 and 70 years, mean 53.8 (SD= 8.15).

The results showed that for KEDS (exhaustion) there was a statistically significant two-way interaction (P<0.001) with a decreased mean from baseline to three and six month respectively in the intervention group whereas in the control group there was no change. The mean treatment effect size, i.e. the mean difference between groups, in favor of the intervention group was 9.9 (SE=3.0) at 6 months. See table 1 and figure 1a.

There was no difference in mean SOC - Sense of Coherence – scores between the groups. See figure 1b. Further, the results revealed a statistically significantly more pronounced decrease in the intervention group compared to the control group in the alexithymia items of total score, (P=0.007, mean treatment effect size=5.4 (SE=2.2) at 6 months in favor of the intervention group), difficulty describing (P=0.004, 2.4 (0.9)), difficulty identifying (P=0.051, 2.6 (1.3)) but not for external orientation (P=0.334 0.5 (0.8)). See table 1 and figure 1c. There was also a statistically significant difference between the groups with regard to self-rated health (P<0.001) where mean scores increased over time in the intervention group but decreased in the control group. See figure 1d.

Table 1: KEDS (Karolinska Exhaustion Disorder Scale) and TAS (Toronto Alexithymia Scale) and SRH (self-rated health) at baseline, month 3 and month 6.

	Control Group (n=12)			**Intervention Group (n=36)**		
	Count	**Mean**	**Standard Deviation**	**Count**	**Mean**	**Standard Deviation**
KEDS						
Baseline	12	32.7	8.2	35	31.7	8.4
Month 3	12	34.9	9.2	34	23.6	8.6
Month 6	12	33.9	8.7	33	23.7	10.1
Sense of Coherence						
Baseline	12	117.2	29.9	33	118.0	28.0
Month 3	12	112.8	30.3	33	121.1	30.5
Month 6	12	115.1	24.2	34	123.9	28.2
Difficulty Describing						
Baseline	12	14.8	4.3	34	14.2	4.6
Month 3	12	15.3	3.6	31	12.7	4.6
Month 6	12	15.2	4.1	34	11.8	3.9
Difficulty Identifying						
Baseline	12	20.0	6.0	34	20.3	6.3
Month 3	12	20.6	6.5	31	19.0	6.9
Month 6	12	20.0	6.1	34	17.4	5.0
Externally Oriented						
Baseline	12	14.9	4.2	34	13.8	4.4
Month 3	12	15.4	4.3	31	13.9	3.9
Month 6	12	14.6	4.8	34	13.2	3.5
TAS						
Baseline	12	49.7	13.1	34	48.3	13.4
Month 3	12	51.3	13.3	31	45.6	13.9
Month 6	12	49.8	13.9	34	42.4	10.8
Self-rated Health						
Baseline	12	5.2	1.5	36	4.8	1.9
Month 3	12	4.6	1.9	36	6.0	1.9
Month 6	12	3.6	1.6	35	6.4	1.9

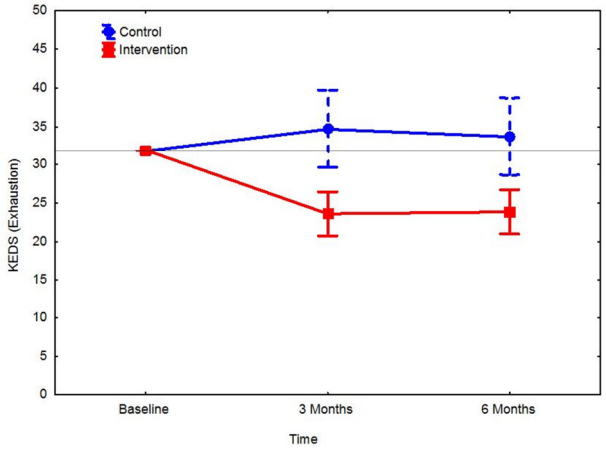

Figure 1a: Marginal means and 95 % confidence intervals for the KEDS (exhaustion) scale by group and time. Results were based on the linear mixed models analysis adjusted for baseline.

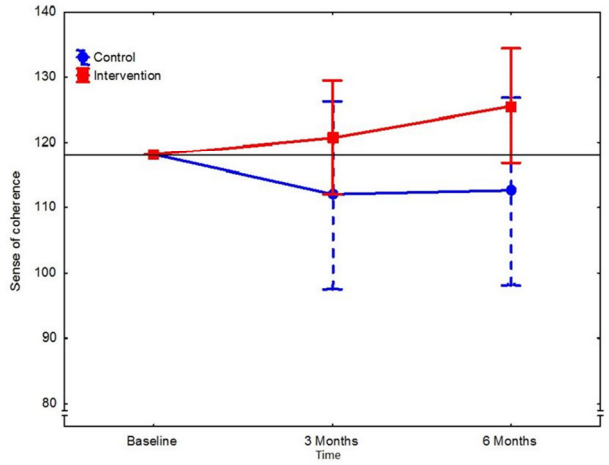

Figure 1b: Marginal means and 95 % confidence intervals for the sense of coherence (SOC) scale by group and time. Results were based on the linear mixed models analysis adjusted for baseline.

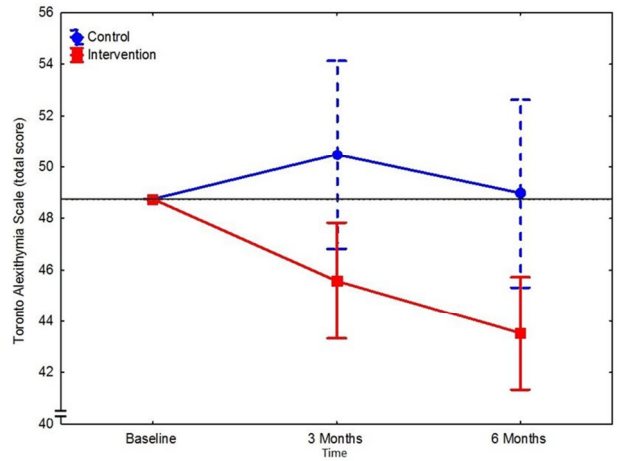

Figure 1c: Marginal means and 95 % confidence intervals for the Toronto Alexithymia Scale (TAS) by group and time. Results were based on the linear mixed models analysis adjusted for baseline.

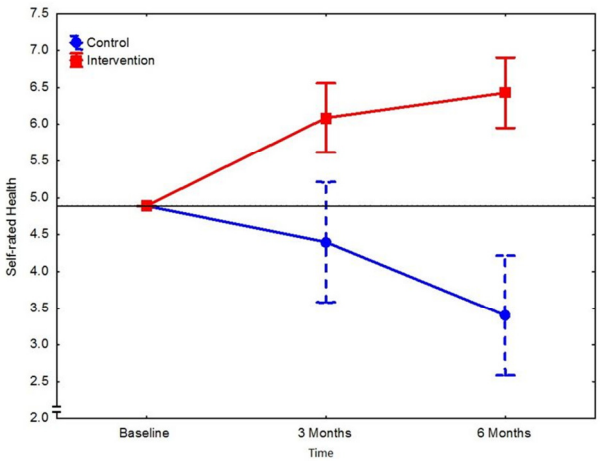

Figure 1d: Marginal means and 95 % confidence intervals for the self-rated health scale (SRH) by group and time. Results were based on the linear mixed models analysis adjusted for baseline.

Discussion

The results show that the different exhaustion factors measured by means of KEDS (Karolinska Exhaustion Disorder Scale) decreased in the intervention group compared to the control group. With regard to the total score of TAS (Toronto Alexithymic Scale) there was a statistically significant decrease in the intervention group compared to the controls, i.e. the participants started to improve their differentiation of feelings and emotions after three months with cultural activities. The same pattern was seen with regard to self-rated health, which improved in the intervention group. However, there was no significant difference between the groups with regard to the development of sense of coherence.

It seems that the different cultural activities have helped the participants become more aware of their feelings and sensations; to describe and to identify feelings. It is not easy to explain the positive results based on one clear paradigm. It is likely a mixture of psychological, neurological and social factors or changes that interact in a complex manner.

Previous studies have discussed the theory of the emotional brain - cultural modalities can “surprise” the cognitive brain unconsciously. LeDoux,[20] discusses the upper/slower and the lower/faster pathway in the brain. Emotionally loaded visual and auditory stimuli are transmitted on both types of pathways. Music impulses are for example evoking activities in the emotional brain much more rapidly than in the cognitive brain. However, impulses spread secondarily from the emotional to the cognitive brain. This can trigger the participants awareness of different emotions and may start a process of differentiation, possibly initiating a change of life course. By using different cultural activities, that the participants normally would not try, the differentiation process may be amplified. This suggests that cultural activities can surpass automated thinking and create new "pathways '' with changes in behavior and increased well-being.

In other studies we have observed that a mixture of different cultural activities can increase the amount of stimuli affecting a broader network of emotional correlates, [14,16,18] . A very interesting long-term decrease in alexithymia, [35] was associated with lowered blood pressure and a decrease in sick leave. By allowing the participants to try new cultural stimuli we may have helped the participants change old habits. A hypothesis is that this may also have contributed to the observed decrease in exhaustion.

Why did we not see any increase in the sense of coherence in the intervention group? It is very difficult to change patterns of thought and behavior although we can argue that the participants in the control group also found a new sense of coherence just by being invited to answer questions about themselves and being focused upon. Many of the participants did not go out spontaneously because of their fear of socializing. Some of them described their situation as black or white, not wanting to change routines that made them feel less safe,[36].

Despite the fact that the health care staff did not participate in the culture palette, they were also affected by the cultural activities [36]. This may be a mirroring effect, or emotional contagiousness on health care staff, which may also play a role between the participants and their staff. The passive cultural activation phenomenon has previously been presented in the literature,[37] and there seem to be possible well-being effects of just watching dance or visiting a theatre, [6,10] which may explain the positive health care staff response to the culture palette. The results of this study underscore the importance of regarding the health care system as a whole, where patients, health care staff and visiting relatives affect each other. Empathic behaviors contaminate in all directions and we need to be aware of how we project ourselves when working in a caring context.

Modified "culture palettes" and "train the trainer" programs and workshops are now in use in Sweden, inspiring cultural producers to further develop the health care system and a cultural health box - a box with six different books about cultural activities and the research behind this - have been distributed to all health care centers in Sweden, [38].

Developing and adapting cultural programs to fit other kind of groups of participants could cross-fertilize health care thru culture production.

Limitations

This study was limited to women with exhaustion symptoms and therefore further research on implementation of cultural activities within different groups of participants and sexes is needed before we can generalize the results to other groups of participants. Another limitation is that we did not control for outside activities, such as doing walks in nature. In this study we only presented indoor cultural activities.

Conclusion

The cultural activities in this study made exhausted women understand what makes them vital, confirmed, curious, healthy and creative. The study also illustrated that there could be synergistic effects when bringing cultural activities into the health care system[36].

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Review Article

Phytochemicals in cancer prevention and management?

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Abstract
Phytochemicals are compounds found in plants, which are responsible for the colour, taste and aroma of foods. Over and above these pleasant attributes, they protect us from environmental and ingested carcinogens by arming our antioxidant enzymes, enhancing DNA repair pathways and have direct effects on the fundamental hallmarks of cancer progression and metastasis. It is not a surprise then that analysis from the World Cancer Research Fund and other academic bodies, report that individuals eating phytochemical-rich foods have a lower risk of cancer or relapse after treatments. The debate lies in whether concentrating these foods, or elements of these foods, into nutritional supplements may boost their health attributes. One notable randomised controlled trial (RCT) has demonstrated benefits for men with prostate cancer, but other trials of extracted chemicals have shown no benefit or even an increased cancer risk. This article provides a clinical overview, for medical practitioners, of the major classes of phytochemicals with examples of their common food sources. It reviews the international evidence for their anti-cancer mechanisms of action and their clinical benefits, as well as discussing the pros and cons of concentrating them into nutritional supplements.
Keywords: Cancer, diet, phytochemicals, polyphenols

Introduction

Phytochemicals, are not regarded as essential nutrients in humans although an increasing number of well-conducted studies are linking higher intake with a lower risk of developing cancer, as well as lower relapse after initial treatment completion [1,2,3]. There is a wide range of dietary phytochemicals, but one of the largest and well-known groups being the polyphenols [Table.1]. The average total dietary intake of polyphenols is reported to be over 1g per day, which is up to ten times higher than that of all other classes of phytochemicals and known dietary antioxidants[4]. The health benefits of phytochemical rich foods or concentrated nutritional supplements are often being highlighted in the medical and popular media and hence they are an increasing topic of conversation between medical practitioners and their patients especially those with cancer who have a particular interest in over the counter self help strategies [5,6]. This article provides an overview of the major classes of phytochemicals with examples of their common food sources. It highlights the international evidence for their anti-cancer mechanisms of action, their clinical benefits, as well as discuss the pros and cons of concentrating them and, into nutritional supplements in an attempt to harness and boost their health benefits. Hopefully this review will provide some useful learning points to aid communication between patients and clinicians [Table. 2].

Classification

There are three major groups of phytochemicals: the polyphenols which can be subcategorized as the flavonoids, phenolic acids and other non-flavonoid polyphenols; the terpenoids, which can be subcategorized as the carotenoids and non-carotenoid terpenoids; and the thiols, which includes the glucosinolates, allylic sulfides and non-sulphur containing indoles (Table. 1). There are other phytochemical group, which although have some properties within these groups, have been classified within a miscellaneous category and examples of these include the betaines, chlorophylls and capsaicin.

Table.1 Classification of phytochemicals with notable food rich sources

Polyphenols
1. Flavonoids
o Flavonols:quercetin, kaempferol (onions, kale, leeks, broccoli, buckwheat, red grapes, tea, apples)
o Flavones: apigenin, luteolin (celery, herbs, parsley, chamomile, rooibos tea, capsicum pepper)
o Isoflavones: genistein, daidzein, glycitein (soya, beans, chick peas, alfalfa, peanuts)
o Flavanones: naringenin, hesperitin (citrus fruit)
o Anthocyanidins (red grapes, blueberries, cherries, strawberries, blackberries, raspberries, tea)
o Flavan-3-ols (tannins): catechins, epicatechin, epigallocatechin gallate (tea, chocolate, grapes)
o Flavanolols: silymarin, silibinin, aromadedrin (milk thistle, red onions)
o Dihydrochalcones: phloridzin, aspalathin (apples, rooibos tea)
2. Phenolic acids
o Hydrobenzoic acids: gallic acid, ellagic acid, vanillic acid (rhubarb, grape seed, raspberries, blackberries, pomegranate, vanilla, tea)
o Hydroxycinnamic acids: ferulic acid, P-coumaric acid, caffeic acid, sinapic acid (wheat bran, cinnamon, coffee, kiwi fruit, plums, blueberries)
3. Other non-flavonoid polyphenols
o Other tannins (cereals, fruits, berries, beans, nuts, wine, cocoa)
o Curcuminoids: curcumin (turmeric)
o Stilbenes: cinnamic acid, resveratrol (grapes, wine, blueberries, peanuts, raspberries)
o Lignans: secoisolariciresinol, enterolactone, sesamin (grains, flaxseed, sesame seeds)

Terpenoids **1. Carotenoid terpenoids** o Alpha, beta and gamma carotene (sweet potato, carrots, pumpkin, kale) o Lutein (corn, eggs, kale, spinach, red pepper, pumpkin, oranges, rhubarb, plum, mango, papaya) o Zeaxanthin (corn, eggs, kale, spinach, red pepper, pumpkin, oranges) o Lycopene (tomatoes watermelon, pink grapefruit, guava, papaya) o Astaxanthin (salmon, shrimp, krill, crab) **2. Non-carotenoid terpenoids** o Saponins (chickpeas, soya beans) o Limonene (the rind of citrus fruits) o Perillyl Alcohol (cherries, caraway seeds, mint) o Phytosterols: natural cholesterols, siosterol, stigmasterol, campesterol (vegetable oils, cereal grains, nuts, shoots, seeds and their oils, whole grains, legumes) o Ursolic acid (apples, cranberries, prunes, peppermint, oregano, thyme) o Ginkgolide and bilobalide (Ginkgo biloba)
Thiols o Glucosinolates: isothiocyanates (sulforaphane) and dithiolthiones (cruciferous vegetables such as broccoli, asparagus, brussel sprouts, cauliflower, horseradish, radish and mustard) o Allylic sulfides: allicin and S-allyl cysteine (garlic, leeks, onions) o Indoles: Indole-3-carbinol (broccoli, Brussel sprouts)
Other phytochemicals o Betaines found in beetroot o Chlorophylls found in green leafy vegetables o Capsaicin found in chilli o Peperine in black peppers

Table. 2 learning points

- Higher intake of phytochemical-rich foods such as colourful fruit, vegetables, herbs, pulses, spices and teas is associated with a lower risk of cancer and relapse after treatments.
- Their anti-oxidant properties help to protect our DNA from ingested or environmental carcinogens.
- Phytochemicals, particularly polyphenols have direct anti-cancer mechanism of action via inflammation, modulation of cellular and signalling events involved in growth, invasion and metastasis.
- Concentrating element of foods such as minerals, vitamins and phytoestrogenic polyphenols to potentially boost their health effects have largely been unsuccessful in preventing cancer in clinical trials.
- Whole food phytochemical-rich supplements have demonstrated significant benefits in phase II and well conducted RCT and their true potential is been evaluated in ongoing studies.

Clinical evidence for cancer prevention.

Although not all, many studies have linked a higher intake of phytochemical-rich foods, such as vegetables, fruit, legumes, nuts, herbs and spices, with a lower incidence of cancer as highlighted in the latest comprehensive review from the World Cancer Research Fund and other systemic reviews[2,3].

More specifically, certain elements of food have been addressed within a number of cohort studies. Carotenoids found in leafy green vegetables and carrots have been linked with a lower risk of breast cancer in a recent meta-analysis demonstrated[7] and a lower risk of ovarian and pancreatic cancers, especially among smokers in either questionnaire or serum-based studies[8, 9, 10]. Higher intake of cruciferous vegetables such as cabbage, cauliflower, Brussel sprouts, radishes and broccoli have been associated with a lower prostate cancer risk[11], as have foods rich in isoflavones such as pulses and soy products[12], lycopene rich colourful fruits and tomatoes[13]. Foods with abundant levels of flavonoids such as onions, rich in quercetin, have been shown to reduce the incidence of numerous cancers particularly those arising from the lung, especially amoung smokers[14, 15]. The anthoxanthins, in dark chocolate, have been reported to lower the risk of colon cancer[16] and higher green tea intake lowers the risk of breast, prostate, ovarian and oesophageal cancer, again particularly among smokers and alcoholics[17, 18]. Finally, coffee consumption has been shown to reduce the risk of non-melanomatous skin cancers and melanoma, even after removing other factors such as ultraviolet radiation exposure, body mass index, age, sex, physical activity, alcohol intake and smoking history[19,20].

Clinical evidence for a benefit after cancer

The benefits of healthy foods do not stop after a diagnosis, especially if combined with other healthy lifestyle habits. For example, breast cancer survivors who regularly consumed more than the government recommended five portions of fruit and vegetables a day, had a third lower breast cancer recurrence risk if combined with regular physical activity[21]. In another study, women with breast cancer who had the highest serum lignan levels, reflecting good intake of legumes, cereals, cruciferous vegetables and soya, were reported to have the lowest risk of death[22]. Likewise, a lignan and polyphenol rich diet was associated with a lower colorectal cancer relapse rate[23].

The large Shanghai Breast Cancer Survival Study demonstrated that women with the highest intake of the phytoestrogenic polyphenols isoflavones and flavanone found in soya and other beans, had a 29% lower risk of relapse and death[24]. Similar findings were seen for green tea after breast[25] and colorectal cancer[23]. Green tea also decreased the abnormal white cell count in 30% of patients with chronic leukaemia and reduced the levels of several markers of proliferation, as well as serum Prostate Specific Antigen (PSA) among men with prostate cancer[26]. A slowing of PSA progression has similarly been observed in other dietary studies, most notably the randomised trial involving a plant-based diet together with other lifestyle changes[27] and a phase II study of pomegranate juice[28].

Another cancer influenced by nutrition is skin cancer, as highlighted by a study of individuals who have been treated for basal cell carcinoma or squamous cell carcinoma, and who have a high risk of further lesions due to their on-going solar damage.

Those who consumed the highest levels of lutein and zeaxanthin-rich foods, such as leafy green vegetables, had the lowest levels of new cancer formation[29].

A number of other studies evaluating the impact of phytochemicals are underway, the largest and probably most comprehensive is the UK's DietCompLyf prospective trial involving 3159 women treated for breast cancer[30].

What are the likely anti-cancer mechanisms of phytochemicals?

The precise biochemical mechanisms through which phytochemicals exert their anti-cancer effects are still being explored, as their actions are wide-ranging and complex but significant advances have been made of late in the understanding the mode of action. The most quoted cancer prevention mechanism is via their antioxidant activity, elicited either through direct free radical absorption or through induction of antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione via a variety of molecular mechanisms[31, 32]. One of these mechanisms is activation of Nrf2, which switches on genes that code for antioxidant as well as detoxification enzymes[31, 32]. Phytochemicals, particularly the thiol class such as sulforaphane,have also been shown to inhibit the conversion of procarcinogens to their electrophilic, DNA damaging, chemicals[32,33].

A number studies involving known, common carcinogens have highlighted the antioxidant properties of phytochemicals. A good example of their protective effect was an experiment involving the known house-hold carcinogen triclocarban, commonly found in detergents and cleaning agents. Healthy cells exposed to triclocarban tend to mutate into pre-malignant cells, however, the amount and rate of carcinogenesiswas significantly reduced byadding curcumin to the petri dish culture feeds[34]. In another study, volunteers who ate a diet rich in kaempferol were found, on serum and urine analysis, to have improved SOD activity and higher urinary concentration of these polyphenols[35]. Rats exposed to cigarette smoke given indole-3-carbinol, a phytochemical rich in cruciferous vegetables, had a lower lung cancer rate than those not given idole-3-carbinol[36]. Subjects eating a meal of onions, which increased their serum levels of quercetin, demonstrated decreased levels of oxidative metabolites including 8-hydroxydeoxyguanosine (8-OHdG) a marker of DNA damage and repair16[18, 37]. Quercetin supplementation has also been shown to improving mitochondrial dysfunctions induced by the toxin 3-nitropropionic acid[38]. A clinical study in Singapore gave Chinese smokers 170g of watercress a day, rich in the indole-3-carbinol, and found a similar effect on urinary markers of DNA damage[39]. Finally, marinating meat in rosemary and thyme, has been reported to reduced the serum levels of carcinogenic heterocyclic amines (HCA) by 87% compared to subjects who eat the meat unseasoned[40].

Another key anti-cancer mechanism of phytochemicals appears to be their ability to reduce inflammation. It is now well established that inappropriate inflammation is intimately involved in the cancer process, particularly in the promotion and progression stages of cancer. Inflammation is closely associated with oxidative stress and activation of NF-kappa B family of transcription factors. These factors regulate more than 150 genes involved in mechanisms of cell survival and these target genes are not just pro-inflammatory but also oncogenic. Numerous phytochemicals have been shown to inhibit NF-kappa B signalling, particularly the green tea polyphenol epigallocatechin-3-gallate (EGCG), quercetin, curcumin, caffeic acid and caffeic acid phenethyl ester and the phytochemicals within bilberries[31,41].

More recently, it has been reported mainly from laboratory studies that phytochemicals have an affect on several cancer process through modulation of cellular and signalling events involved in growth, invasion and metastasis[32]. Pomegranate, for example, rich in the polyphenol ellagic acid, has been shown to directly inhibit cell growth and induce apoptosis in androgen sensitive and aggressive human prostate cancer cells[42]. Pomegranate extract has also been reported to inhibit processes involved in cancer metastasis in a study involving oestrogen sensitive and resistant breast cancer cell lines, showing increased markers of cell adhesion and migration in cancer but not normal cells[43]. In another study it inhibited a chemokine that attracts breast cancer cells to the bone[44]. Curcumin slows cancer cell growth by blocking the cell cycle, increasing the rate of apoptosis and preventing the invasion and migration of cells[45, 46, 47, 48]. It has also been found to halt the growth of stem cells that give rise to breast cancer without harming normal breast stem cells[49]. Curcumin has been shown to modulate miRNA expression in breast cancer cells leading to a reduced expression of Bcl-2[50] and stabilisation of tumour suppressor gene in colorectal cancer cell lines[52]. Green tea, rich in epigallocatechin gallate (EGCG), has demonstrated significant reduction of several factors that promote cancer cell proliferation by inhibiting DNA synthesis, de-differentiation and angiogenesis[26, 52, 53]. It has also been shown to block ornithine decarboxylase, an enzyme which signals cells to proliferate faster and bypass apoptosis[50, 54]. Resveratrol has demonstrated epigenetic regulatory properties which influence regulate proliferation, cell survival and apoptosis in prostate cancer by global modulation of gene expression through deacetylation of FOXO transcription factor[46]. Caffeic acid and phenethyl ester, as well as inhibiting NF-κB signaling, also have been shown to inhibit cell motility in vitro and inhibit metastasis of tumour models in vivo[47]. Luteolin, as well as inhibiting tumour growth and metastasis, inhibits epithelial mesenchymal transition which is a basic biological process related to cancer initiation and development[47].

Finally some polyphenols and other phytochemicals are also able to influence cancer via a hormonal mechanism.

Phytoestrogenic compounds, most notably isoflavones and lignans found in soy products, legumes and some cruciferous vegetables, weakly bind to the oestrogen receptor without stimulating proliferation of the cells, yet at the same time blocking the binding of more harmful oestrogens, including those produced endogenously[39]. This explains why in the previously mentioned Shanghai Breast Cancer Survival Study, women with the highest intake of isoflavones and flavanones-rich foods had a lower risk of death[24]. In men, phytoestrogenic compounds have been shown to affect 5 alpha reductase lowering endogenous testosterone levels. This may partly explain why men who eat phytoestrogenic foods such as beans and pulses have a lower risk of prostate cancer.

Can concentrating foods into supplements enhance their anti-cancer effect?

If certain foods have anti-cancer effects, then it is not unreasonable to hypothesise that concentrating them into a pill may be a good way to supplement individuals with poor diets or further enhance the benefits in those whoes diets are already adequate. People living with and beyond cancer (PLWBC) are certainly attracted to the potential health benefits of food supplements, as over 65% report regular intake[5,6]. There are two main categories of supplements commercially available: the first involves chemicals extracted from food, or made synthetically, such as minerals and vitamins; the second involves purifying and concentrating whole foods:

Vitamins and mineral supplements: The majority of studies, to date, have evaluated extracted chemicals such as vitamins and minerals. Some have shown a benefit. For example, a recent meta-analysis of studies reported that women who took supplements providing an average daily intake of vitamin C over 100mg had a reduced risk of breast cancer relapse[57]. The SU.VI.MAX study randomised French adults to a single daily capsule of ascorbic acid, vitamin E, beta carotene, selenium and zinc, or a placebo, and found no reduction in mortality or cancer-specific mortality overall[58], although a further analysis in men found a reduction in the risk of prostate cancer. The authors postulated that this difference between the sexes was related to French men having a lower baseline micro-nutrient status[59]. A major trial of selenium and vitamin supplements in a poor region of China, demonstrated reduced risks of oesophageal cancer; at the time this population was known to have widespread micro-nutrient deficiencies[60].

Unfortunately, most other studies of vitamin, minerals and other extracted nutrients have shown no benefit, or have actually shown an increased risk of cancer. For example, the CARET study found that beta carotene and retinol increased the risk of lung cancer[61]. The Health Professionals Follow-up study (HPFS) which followed the lifestyle habits of 51,529 male professionals for over 15 years found that men who took very high doses of zinc (>100mg/day), or took it for long durations were more than twice as likely to develop advanced prostate cancer compared with controls[62]. The randomised SELECT study demonstrated an increased prostate cancer incidence with vitamin E and selenium supplementation[63]. A further analysis of the HPFS found that of the 4,459 men who had developed prostate cancer, those who took selenium supplementation of ≥ 140 μg/d after diagnosis were associated with a 2.60-fold greater risk of prostate cancer mortality[64].

The negative effects of vitamin E and beta carotene were once again demonstrated in the ATBC study which found them to increase lung cancer risk, although subsequent analysis showed that men with pre-intervention low plasma levels of beta-carotene had a lower prostate cancer risk following supplementation, and that those with high levels had a higher risk, particularly in smokers[65]. This u-shaped distribution of risk was also observed in the EPIC study where those with folate-deficient diets and those with the highest intake both had a higher risk of cancer[66]. These data have prompted organisation such as the National Cancer Institute to issue statements stating that long term vitamin and mineral supplements should ideally be given to correct a known deficiency[67], which is rarely routinely detected unless individuals have self funded micro-nutrient analysis (cancernet.co.uk).

Whole food supplements: More recently academic attention has turned towards the evaluation of concentrated whole food supplements, particularly foods rich in polyphenols and other phytochemicals such as herbs, spices, green vegetables, teas and colourful fruits which have appeared to be beneficial in environmental cohort studies. Despite some initial encouragement from smaller evaluations, studies of extracted lycopene or genistein given on their own in more scientifically robust analyses have not demonstrate a benefit for either prostate cancer or benign prostatic hypertophy[68, 69, 70] neither were there links with the reduction in the risks of breast cancer with regular intake[5]. Of more concern, a randomised study from Memorial Sloan Kettering reported that serum taken from women who had take very high dose soy supplementation (25.8 g twice a day) added to laboratory tumour cells caused them to proliferate faster (Increased K67 expression) and overexpress the tumorigenic growth factor receptor FGFR2[71]. This supports the notion that phytoestrogen foods are healthy, but concentrating them into strong supplements is not recommended.

On the other hand, no study of non-phytoestrogenic foods supplements has shown any detrimental effects on cancer outcomes and some have beneficially influenced progression rates. For example, a study carried out at John Hopkins involving pomegranate seed extract, found that men taking the supplements had a reduction in PSA progression rate[72]. A study conducted at the Mayo Clinic found that green tea concentrate decreased the abnormal white cell count in 30% of patients with chronic leukaemia, and a small study from Louisiana University reported that green tea concentrate significantly reduced levels of several cancer-promoting growth factors as well as PSA levels in participants[26]. In the Vitamins and

Lifestyle (VITAL) cohort study, a regular intake of grapeseed extract was shown to be linked with a lower risk of prostate cancer[70], and another small RCT found that a dietary supplement containing isoflavones, plus other phytochemicals and anti-oxidants delayed PSA progression[73]. Interestingly one of the most popular supplements, Saw Palmetto, despite an effect in early small studies, showed no benefit for prostate cancer or benign prostatic hypertrophy in the largest randomised evaluation[74]. Likewise, another popular supplement, lycopene, despite similar suggestions from smaller non-randomised trials[68, 69], demonstrated no benefits in a more robust evaluation.

So far, the largest trial analysing phytochemical-rich food extracts was the National Cancer Research Network adopted Pomi-T study[75]. This study combined four different food types (pomegranate, green tea, broccoli and turmeric) in order to provide a wide spectrum of synergistically acting nutrients, whilst at the same time avoiding over-consumption of one particular phytochemical. It involved two hundred men, with localised prostate cancer managed with active surveillance or watchful waiting experiencing a PSA relapse, following initial radical interventions.

The results, presented as an oral presentation at the American Society of Clinical Oncology Conference (ASCO), Chicago, showed a statistically significant, 63% reduction in the median PSA progression rate compared to placebo in both men on active surveillance and experiencing a PSA relapse post-treatment. A further analysis of MRI images, demonstrated the cancers size and growth patterns correlated with PSA changes, excluding the possibility that this was just a PSA rather than tumour effect[75]. It was well tolerated, apart from some mild loosening of the bowels in 10% of men, and there was no effect on testosterone levels. At 6 months, significantly more men opted to remain on surveillance rather than proceeding to expensive radiotherapy, surgery or medical castration which can cause unpleasant effects such as depression, hot flushes, weight gain, osteoporosis and erectile dysfunction[75].

A number of other RCT's involving whole food phytochemical-rich supplement have demonstrated benefits for some of the distressing symptoms common after cancer treatments, such as fatigue[76] and urinary infections[77]. There are currently over ten, on-going studies registered with the National Institute of Health. In the UK, the Institute of Preventative Medicine has plans to include the Pomi-T supplement into the next national prostate cancer prevention study. This study will be recruiting men with a higher genetic risk of prostate cancer identified in the national RAPPER study, co-ordinated by the Institute of Cancer Research. Further trials are being designed involving men with prostate cancer already on androgen deprivation therapy and individuals with skin, colorectal and bladder cancer. In the meantime, a trial is passing through the regulatory process to investigate whether the natural anti-inflammatory properties of these ingredients could help joint pains after breast cancer.

Conclusion

There is increasingly convincing evidence to show that plant phytochemicals, particularly polyphenols have significant benefits for humans. Not only do they improve our daily lives by helping our food taste, smell and look appetising, they also reduce our risk of cancer and help people living with and beyond treatments. Living well programmes, slowly being introduced in the UK, are beginning to highlight the importance of phytochemical-rich diets, along side other lifestyle factors, largely being driving by the National Survivorship Initiative and guidelines from influential organisations such as ASCO. Going a step further and concentrating these foods, or extracted elements of these foods, into nutritional supplements gives an opportunity to boost their beneficial anti-cancer effects, but have their pitfalls. Studies of concentrated minerals, vitamins and phytoestrogenic supplements have reported detrimental effects. No study has reported detrimental effects of whole, non-phytoestrogenic food supplements and some have reported significant advantages. Despite these potential benefits and reports that over 60% of patients living with and beyond cancer take nutritional supplements, oncologists have been reluctant to discuss their pros and cons due to a lack of RCTs from academic institutions[55, 56]. Hopefully this trend will change, particularly following the success of the Pomi-T study[75] and ongoing studies registered with the National Cancer Institute.

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Review Article

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A Study On Clinical Features And Cost Incurred By Dengue Syndrome Patients Admitted To Tertiary Care Hospital

Manjunath M N, Chaithanya C Nair and Sharanya R

Abstract

Background: India is one of the seven identified countries in Southeast Asia regularly reporting dengue fever (DF)/dengue haemorrhagic fever (DHF) outbreaks. India may soon transform into a major niche for dengue infection in the future with more and more new areas being struck by dengue epidemics.

Objectives: 1) To study the clinical manifestations, trends and outcomes of all confirmed dengue cases admitted to a tertiary care hospital. 2) To study the cost incurred by these patients during hospital stay.

Materials and Methods: This record-based study was conducted on 757 serologically (NS1 Ag/ IgM/ IgG) positive dengue cases admitted to KIMS Hospital & Research Centre, Bangalore during January 2012 to December 2012. Required data from the entire laboratory confirmed cases were collected from the Medical Records Department (MRD) and analysed.

Results: The seropositive case rate for dengue was 61.5% with NS1 antigen\ IgM\ IgG. Males were commonly affected and the most vulnerable age group was found to be between 5 to15 years of age. The median age was 8 years. The percentage of cases presented as dengue fever without warning signs was 88.5%, the remaining being dengue with warning signs and severe dengue. Fever was the most common symptom seen followed by vomiting and abdominal pain. Haemorrhagic manifestations were seen in about 4.5% of cases of which majority presented with petechiae followed by haematemesis. The mortality rate was 8.6%.

Conclusion: Increased awareness, better transport facilities and case management according to the WHO guidelines is needed to further reduce mortality and cost burden of dengue cases.

Abbreviations: DF - Dengue Fever, DHF - Dengue Haemorrhagic Fever, DSS - Dengue Shock Syndrome, ARDS - Acute Respiratory Distress Syndrome, MODS – Multiple Organ Dysfunction Syndrome.

Introduction:

Dengue made its debut as early as 1780, when Benjamin Rush described the condition as "break bone fever". This hitherto unfamiliar infection has now grown to demand the attention of all public health care providers. It is a mosquito borne, fast emerging, viral infection manifesting in four serotypes [1]. Approximately 2.5 billion people, living mainly in urban areas of tropical and subtropical regions, are estimated to be at risk of acquiring dengue infection [2]. While dengue is endemic in more than 100 countries, most cases are reported from Southeast Asia and the western Pacific regions. Around 50 million cases and 24,000 deaths are estimated to occur in these 100 endemic countries. This includes hospitalisation of nearly half a million cases of dengue haemorrhagic fever (DHF), of which 90% are children. Treated (DHF)/dengue shock syndrome (DSS) is associated with a 1% mortality rate while mortality rate among untreated cases escalates to 20%[3,4].

India is one of the seven identified countries in the Southeast Asia region regularly reporting incidence of DF/DHF outbreaks. The first confirmed report of dengue infection in India dates back to 1940s, and since then more and more new states have been reporting the disease which mostly strikes in epidemic proportions often inflicting heavy morbidity and mortality, in both urban and rural environments.[5]

The various manifestations of dengue may not have a distinct line of demarcation: apart from the classic features, reports of rare presentations have recently become more frequent [6,7]. During recent outbreaks in India, the clinical manifestations which were shown by the patients were slightly different from those in previous years[8]. There have been many reports of difficulties in the use of the previous classification, which were summarised in a systematic literature review [9]. Difficulties in applying the criteria for dengue haemorrhagic fever in the clinical situation, together with the increase in clinically severe dengue cases which did not fulfil the strict criteria, led to the request for the classification to be reconsidered .Hence, WHO revised the dengue case classification into dengue (with or without warning signs), and severe dengue [10].The present study was done to analyse the clinical features, complications, cost incurred and outcome of cases admitted to a tertiary care teaching hospital in Bangalore.

Methodology:

A record based descriptive study was conducted in paediatric patients admitted with signs and symptoms suggestive of

dengue fever to KIMS hospital Bangalore, during the period between January 2012 to December 2012. SD BioLine kit was used for testing with NS1 antigen\ IgM\ IgG. The medical records were perused for collecting data about these cases using a pre-designed proforma. Data was analysed for the clinical presentations, outcome and direct cost incurred in respect to hospital charges and laboratory investigations.

Results:

Out of 1230 cases admitted with clinical signs and symptoms suggestive of dengue syndrome 757 (61.5%) cases were found to be NS1 antigen\ IgM\ IgG positive for dengue. Among the 757 positive cases, males were 499 (65.9%) and females 258 (34.1%). The majority of the cases were in the school going age group and this consisted of 310 cases (41%) and adolescent children which accounted for 249 cases (33%), the median age being 8 years of age. The least number of cases were seen in infants which accounted for 45 cases (6%).

Table 1. Sex distribution

Age group	Male	Female	Total
Infant	31	14	45
Toddler	114	39	153
School going	208	102	310
Adolescent	146	103	249
TOTAL	499 (65.9%)	258(34.1%)	757

The majority, 88.5% of cases presented as dengue fever without warning signs, 6.34% with dengue fever with warning signs and 5.15% with severe dengue. Of the cases with warning signs 92.3% of cases had fever, 42.5% cases had vomiting and 38.2% cases had abdominal pain. Haemorrhagic manifestations were seen in about 4.5% of cases of which majority (87%) presented with petechiae followed by haematemesis (9%) and epistaxis (4%). Rashes were seen in 4% and arthralgia in 13% of cases. Pleural effusion was seen in 21% of cases and ascites was seen in 16% of cases. Complications in the form of acute respiratory distress syndrome (ARDS) was seen in 12.06% cases, 6% cases showed neurological manifestations in the form of encephalopathy and 1.3% cases had renal failure.

Table 2. Severity of dengue

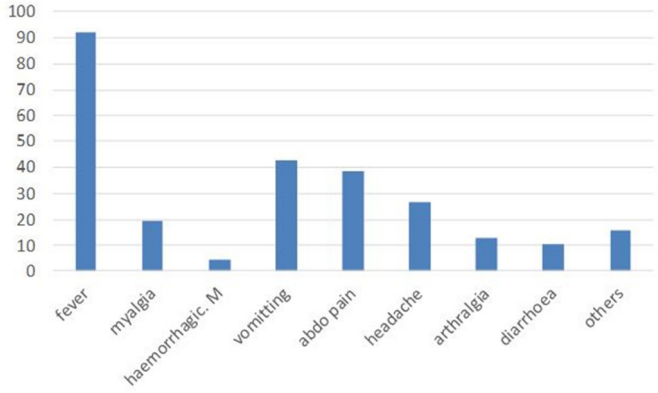
Severity	Percentage
DF without warning signs	88.5
DF with warning signs	6.3
Severe dengue	5.15

Haemoglobin level of > 12gm% was found in 73.4% cases, 9-12gm% in 23.4%, 6-9gm% in 2.1% and <6 gm% in 1.1% of cases. Platelet count of < 20,000 was found in 21.5% of cases, 20-50 thousand in 39.5% , 50,000 to 1.5 lakh in 36% of cases and >1.5 lakh was found in 3% of cases. Majority (65.5%) of cases were NS1 Ag positive alone or with IgM/ IgG/ or both positive.

Table 3. Presenting complaints

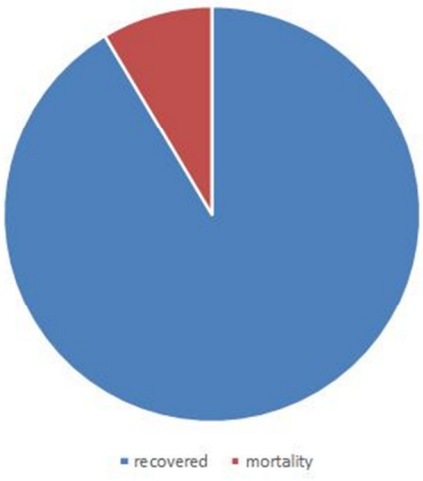
Presenting Complaints	Number (%)
Fever	699(92.3)
Myalgia	148(19.5)
Haemorrhagic manifestations	34(4.5)
Vomiting	321(42.5)
Abdominal pain	289(38.1)
Headache	201(26.5)
Arthralgia	99(13)
Diarrhoea	80(10.5)
Others	121(16)

Fig 1: presenting complaints.



Remaining were positive for either of the antibodies.13.7% cases werepositive for all the three i.e. Ag, IgM,& IgG. The mortality rate was found to be 8.6%.

Figure 2: outcome



Cost incurred which includes direct cost (transporting patient to the hospital, diagnostic testing and laboratory investigations, medications, hospitalisation, food) was found to been average of Rs.12,611=00. The indirect cost loss of wages of patient &attendants) was found to be an average of Rs.3, 109=00. The hidden cost (out of pocket expenses) was found to be an average of Rs.50=00. The cost of treatment of other co-morbid conditions was found to be an average of Rs.2, 275=00. The total cost of treating dengue syndrome was 18,045=00

Discussion:

In the present study it was found that males were commonly affected and the most common age group was between 5 to 15 yrs of age. Similar results were reported in a study by Faridi et al, 76% of all cases of DHF /DSS were aged 6 years or more[11].

In the present study, the most common presenting symptoms was fever followed by vomiting and abdominal pain which is similar to study done by Kumar A et al showed fever in 99.2% followed by myalgia (64.6%), vomiting (47.6%), headache (47.6%) and abdominal pain (37.5%) [12].

In the present study, the most common bleeding manifestation was haematemesis and epistaxis. In a study by Ratageri et al, common bleeding manifestations were gastrointestinal bleeding (22%) and petechiae (18%) [13]. The gastrointestinal tract was reported as the commonest site of bleeding (61%) in a study by Ahmed et al [14].

In the present study majority of cases had platelet count between 20,000 to 50,000/mm3.In a study by Kamath et al, platelet counts less than 50,000/mm were noted in 62.3% [15]. In our study complicated cases showed ARDS and neurological manifestations in the form of encephalopathy. Almost all the cases which expired were found to have ARDS. Dengue associated ARDS is associated with a high mortality [16]. Dengue infection is found to cause neurological manifestation ranging from non-specific symptoms to encephalitis and rarely Guillain-Barre Syndrome [17]. In our study the mortality rate was found to be 8.6% , in the study by Anju et al overall mortality seen was 6% [18], compared to 3% by Ahmed et al [14].

Conclusion:

The seropositivity for dengue was 61.5% with NS1 antigen\ IgM\ IgG. Males were commonly affected and most vulnerable age group was found to be 5-15 year olds. The median age was 8 years. 88.5% of cases presented as dengue fever without warning signs, the remaining being dengue with warning signs and severe dengue. Fever was the most common symptom seen followed by vomiting and abdominal pain. Haemorrhagic manifestations were seen in about 4.5% of cases of which majority presented with petechiae followed by haematemesis. The mortality rate was 8.6%. Acute Respiratory Distress Syndrom (ARDS) and multiple organ dysfunction syndrome (MODS) was found to be the most dreadful complications with high rates of mortality .

In this study it was found that cost incurred which includes direct cost (transporting patient to the hospital, diagnostic testing and lab investigations, medications, hospitalisation, food) was found to bean average of Rs. 12,611=00. Thus dengue syndrome also causes significant economic burden on the patients.

In the recent few years, the world has seen varied clinical presentation of the dengue fever in different epidemics, even in the same regions and even with the period of time. Where some known features are still manifesting, few atypical features are noted from several parts of the world. A continuous seroepidemiological surveillance and timely interventions are needed to indentify the cases, so that its complications, outbreak and mortality can be minimised.

Moreover community awareness, early diagnosis and management and vector control measures need to be strengthened, especially during peri-monsoon period, in order to curb the increasing number of dengue cases.

Competing Interests
None declared
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Review Article

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Current Management of Achalasia – A Review

Hanna Winter, Rajeev Shukla, Mohamed Elshaer and Amjid Ali Riaz

Abstract

Introduction: Achalasia is a rare oesophageal motility disorder characterised by oesophageal aperistalsis and incomplete relaxation on swallowing of the lower oesophageal sphincter. This review aims to identify and critique literature detailing the available management options for these patients and provide an up to date account of current thoughts and controversies in the treatment of achalasia.

Methods: An extensive literature search was performed for articles and reviews published on the management of achalasia, using Ovid MEDLINE, Cochrane library and PubMed search databases.

Results: The management of achalasia is controversial. Simple options such as pharmacological treatments and Botulinum toxin A injections do not provide sufficient relief of symptoms but may serve to treat those not suitable for surgery or dilatation. However, in those who are deemed suitable, the literature suggests that the optimum treatment is laparoscopic transabdominal Heller myotomy which has demonstrated the best long term results with few complications or perforations.

Conclusion: It is not possible to treat the underlying cause of achalasia but only to improve symptoms. Whilst the literature may suggest that the Heller myotomy is the best method to achieve this, it is clear that the outcomes are dependent on surgeon or physician technique and experience. It is important therefore that these patients are treated in a specialist centre with experience with such procedures. Recent advances in surgical and endoscopic technologies, with robotic Heller myotomy and per-oral endoscopic myotomy, provide promising progress for the treatment for achalasia

Keywords: Achalasia, manometry

INTRODUCTION

Achalasia is a rare oesophageal motility disorder, typically presenting with symptoms of dysphagia, regurgitation of food and retrosternal chest pain made worse on eating. The annual incidence in the UK, Ireland and USA is between 0.5 to 1.2 per 100,000[1] and seems to affect both sexes and all races equally.

The aetiology of achalasia remains largely unknown. However, suggested influences include a genetic predisposition, infection and autoimmunity[2,3]. The changes responsible for achalasia include a combination of both poor oesophageal contractility and impairment of relaxation of the lower oesophageal sphincter resulting in oesophageal distension and symptoms described above. Reaching a diagnosis relies on oesophageal manometry in addition to barium swallow and oesophagogastroduodenoscopy (OGD).

The condition was first described by a British physician in 1674, Sir Thomas Willis, and treated with dilatation using a sponge attached to a whale bone[4]. It was not until many years later in 1913 that a German surgeon, Heller, performed the first cardiomyotomy[5]. The optimal treatment for achalasia remains controversial with treatment largely dependent on the preference of the physician. Cases are few and far between and therefore large studies reviewing the optimal treatments are limited.

This review aims to identify and collaborate relevant literature detailing the management options available to treat achalasia.

METHODS

An extensive literature search was performed using Ovid MEDLINE, Cochrane library and PubMed databases for relevant articles relating to medical, endoscopic and surgical management of patients with achalasia. Keywords including achalasia, Heller's myotomy and balloon dilatation were used and relevant articles included.

MANAGEMENT

Diagnosis

All patients presenting with dysphagia should initially be investigated with OGD to exclude a mitotic lesion. OGD has little value however in diagnosing achalasia but remains an essential component of the investigation of the upper gastrointestinal tract. The gold standard for diagnosing achalasia is oesophageal manometry[6,7]. This typically shows a high resting pressure in the lower oesophageal sphincter which fails to relax on swallowing with associated impaired oesophageal contractility. A barium swallow may show very little in early disease, but in more advanced disease may demonstrate a 'bird's beak' appearance or a sigmoid oesophagus, distension due to longstanding obstruction at the gastro-oesophageal junction (GOJ)[8].

Achalasia Subtypes

Whilst the diagnosis of achalasia is dependent upon the above, high resolution manometry can further classify achalasia into

three subtypes dependent on the pattern of oesophageal peristaltic abnormalities and oesophageal pressure dynamics (Figure 1). The three subtypes differ in responsiveness to treatment and as such, can be used to guide the most appropriate treatment and counsel patients appropriately.

Figure 1: The Chicago classification for achalasia subtypes[9]

Type I (classic)	Achalasia with minimal oesophageal pressurisation
Type II	Achalasia with oesophageal compression
Type III	Achalasia with oesophageal spasm

Treatment

The treatment for achalasia is aimed entirely at symptom control. The underlying pathological processes which lead to myenteric plexus neurodegeneration are not fully understood and as such, cannot as yet be prevented or reversed. Current treatment options exist therefore to reduce the contractility of the lower oesophageal sphincter and hence improve the obstruction to passage of food and symptoms of dysphagia.

Various options exist for this, including pharmacological therapies which are available in the form of nitrates, calcium channel blockers, anticholinergic agents and beta agonists. Endoscopic therapy is a preferable alternative, with pneumatic balloon dilatation or intrasphincteric Botulinum toxin injection being the most commonly used techniques. The ultimate and generally accepted optimal treatment, however, is the surgical Heller's myotomy (Figure 2).

Figure 2: Treatment options available for the management of achalasia

Pharmacological options	Oral nitrates (GTN, Isosorbide dinitrate) Calcium channel blockers (Nifedipine, verapamil) Anticholinergics Opioids (loperamide) Phosphodiesterase inhibitors •$_2$ agonists Nitric oxide agonists
Endoscopic techniques	Pneumatic balloon dilatation Botulinum toxin injections Peroral endoscopic myotomy (POEM)
Surgical options	Heller's cardiomyotomy (transabdominal or transthoracic / open or laparoscopic)

Medical

Pharmacological therapies as treatment for achalasia have been largely superseded by improvements in both endoscopic and surgical techniques. However, their potential role still exists in those with early disease, in elderly patients unsuitable for surgery or dilatation and in whom Botulinum toxin injections have failed. They may also have potential use in patients awaiting surgery for interim symptom control[10,11,12]. Most trials reviewing the effect of drug therapy for achalasia are limited by small numbers and short follow up so long-term benefits remain poorly understood[13].

As with all achalasia treatments, the aim of drug therapy is to relax the lower oesophageal sphincter. Nitrates have been used as vasodilators within cardiovascular disease since the 1970s. Within the smooth muscle of the gastrointestinal tract, they behave similarly by increasing the production of cyclic GMP and in turn, causing dephosphorylation of the myosin light chain and subsequent inhibition of smooth muscle contraction. It is with this concept in mind that medical treatment with nitrates can cause relaxation of the lower oesophageal sphincter. There are only two randomised controlled trials which have reviewed the effect of nitrates on patients with achalasia and compared them to alternative treatment modalities[14,15]. However, as a Cochrane review has established, the results of these studies cannot be reliably interpreted due to both the methodology and the limitations with regards to follow up[13]. Regardless, nitrates are not without side effects and can cause headaches and changes in blood pressure. In view of this, their routine use is not recommended.

Calcium channel blockers, including Nifedipine, are more commonly used and are given sublingual 15-30 minutes before meals[16]. These limit the intracellular uptake of calcium and hence reduce the contractility of muscle cells. Reports of success as high as 65-80% have been documented[17,18,19]. However, up to 30% experience significant side effects.

Additional agents that have been described include β_2- agonists, anticholinergics and phosphodiesterase inhibitors, the latter of which induces nitric oxide release and thereby relaxation of lower oesophageal sphincter muscle but can also result in significant side effects, including angina, and so routine use is again not advised[20,21]. It is for these reasons, that progress has been encouraged elsewhere with developments in both endoscopic and surgical techniques for the treatment of achalasia.

Endoscopic

Endoscopic treatments are again aimed at reducing the contractility of the lower oesophageal sphincter and several options exist for this. Injection of Botulinum toxin A is the most commonly performed and has fewer associated side effects and complications than its alternatives, hence is often used as first line treatment and especially in patients not suitable for surgical intervention. Alternative options include pneumatic balloon dilatation and more recently, per-oral endoscopic myotomy (POEM).

Botulinum toxin A is used as an intrasphincteric injection and exerts its action by inhibiting the release of acetylcholine, necessary for muscular contractions. This in turn lowers the tone and pressure of the lower oesophageal sphincter. 80-100 units of Botulinum toxin A are injected in divided doses in all four quadrants at the level of the squamocolumnar junction via endoscopic guidance. Patients recover quickly and can go home the same day[22], typically seeing improvements in symptoms between days 1-3[23]. Results are variable. Certainly the side effects are minimal and it appears to be a safe procedure without the risk of perforation seen with other techniques[24,25]. Short term improvement in symptoms is described as high as 85%. However, over time this is seen to decrease significantly to only 30% at one year. Most will require further injections or alternative treatments such as pneumatic balloon dilatation or surgical myotomy[24].

Pneumatic balloon dilatation includes inflating a 30mm balloon at the level of the GOJ[26,27]. This process fractures the muscular fibers of the lower oesophageal sphincter hence disrupting the sphincter mechanism. It can be performed under fluoroscopic or endoscopic guidance dependent on operator experience and preference. The major risk is oesophageal perforation, which in experienced hands occurs in 1.9% (range 1-16)[28]. In addition, gastro-oesophageal reflux post procedure can be troublesome, affecting 4-16% of patients[29].

A Cochrane review compared outcomes with Botulinum toxin injections and pneumatic balloon dilatation[30]. Whilst little difference in short term improvement was noted, longer term remission rates were considerably higher in those treated with balloon dilatation. However, even with balloon dilatation, up to a quarter require further treatments at five years[31,32].

An emerging endoscopic technique is the peroral endoscopic myotomy (POEM). This is performed by incising the mucosa endoscopically, dissecting and developing a plane in the submucosal layer and performing a myotomy inferiorly to beneath the gastro-oesophageal junction. The mucosa is thereafter closed with staples. Studies have shown it to be both safe and effective with short term results demonstrating similar relief in dysphagia and improvements in Eckardt scores as patients undergoing laparoscopic myotomy[33,34]. The added benefit of POEM is the potential for faster return to normal activities[34] and with preserving the need for surgery, dissection at the hiatus can be avoided which may reduce symptoms of post-operative reflux. However, it is technically challenging and studies demonstrating long term outcomes are not yet available.

Surgical

The surgical treatment for achalasia involves performing a myotomy at the level of the gastro-oesophageal junction. There has been controversy regarding the most appropriate method of achieving this and experience includes open versus laparoscopic, transthoracic versus transabdominal. Further controversy exists in the importance of performing simultaneous antireflux surgery.

With the development of laparoscopic abdominal surgery, there is little doubt that this has lowered the complications and improved patient recovery and inpatient hospital stay[35,36,37]. Not only is the approach to the GOJ easier via the abdomen, also single lung ventilation is not required and so pulmonary complications are fewer.

Surgical myotomy offers superior long-term relief of achalasia-related symptoms compared to medical and endoscopic alternatives, alleviating dysphagia in 88%-94% at ten years following surgery[36,38]. Improvements have also been demonstrated in patient satisfaction and quality of life post operatively[39]. Performing a complete myotomy is essential to outcome and prevention of recurrent symptoms, hence accuracy and precision is paramount[40]. Where this is concerned, robotic surgery is becoming more accessible and early results would suggest improvements over conventional laparosopic surgery[41].

The risk of perforation is small with laparoscopic myotomy[42] and even smaller with robotic surgery. The main complication associated with performing a myotomy is symptomatic reflux. Controversy exists regarding simultaneous anti-reflux procedure and some would argue that in the absence of posterior dissection at the level of the GOJ, there is not the need[43]. A meta-analysis performed by Lyass et al reviewed patients undergoing surgery for achalasia[44]. The authors concluded that the rates of reflux post operatively were no different between those who had anti-reflux procedures and those who did not. Ultimately, the decision to proceed with anti-reflux surgery will vary surgeon to surgeon. However, what is generally accepted is that a complete 360 degree Nissen's fundoplication is not required, and may serve only to give the patient ongoing symptoms of dysphagia. Therefore, Toupet (posterior 270 degrees) or Dor (anterior 180 degrees) fundoplication are more commonly used, the latter providing cover to the myotomy and thus potentially protecting any unidentified mucosal breach[45].

Surveillance

Studies have demonstrated that patients with a diagnosis of achalasia have an increased risk of squamous cell carcinoma of the oesophagus[46]. For this reason, guidelines developed by the American Society for Gastrointestinal Endoscopy suggest surveillance oesophagogastroduodenoscopy every 1-3 years for 15-20 years[47].

CONCLUSIONS

Achalasia is a difficult condition to diagnose and treat. All treatments are aimed at disrupting the lower oesophageal sphincter mechanism and none are without risk or complication. Treatment modalities vary in their short and long term success rates. Pharmacological treatments are of limited

value and Botulinum toxin injections have limited long term results but both may play a role in patients who cannot tolerate more invasive procedures[48]. The main debate has historically lain between advocating the use of endoscopic dilatation versus laparoscopic Heller myotomy.

Studies looking at endoscopic dilatation versus myotomy have comparable initial symptomatic relief. Direct comparison between the long term outcomes does, however, favour laparoscopic myotomy[49,50]. Traditionally, endoscopic dilatation has been the first line treatment, with surgery reserved for those in whom dilatation has failed[51]. However, subsequent intervention is common and there are many studies examining outcomes of second treatment with either surgery or dilatation. In cases where initial treatment has failed and recurrent symptoms of dysphagia present, dilatation has been shown to be more effective in those who have had surgery rather than those who have had previous dilatations or Botulinum toxin injections[52,53]. Importantly, there is not a greater risk of perforation in these patients than in those who have not undergone myotomy[54].

Performing a surgical myotomy after previous treatment with dilatation or injection may complicate the surgery slightly and has been shown to increase complications and failure of myotomy[55,56], providing an argument for surgery as first line treatment. That said, surgery is still recommended in these patients as the most successful option[57].

Ultimately, the optimal treatment will vary dependent on physician or surgeon technique and experience. Cases are limited and so it is recommended that these patients are treated in a specialist Upper GI unit where all options are presented to the patient and the risks and benefits of each counselled appropriately. It is an exciting time for achalasia as new treatment options including POEM come to light and robotic surgery becomes more available.

Competing Interests
None declared
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Case Report

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Topical medicament allergy: the importance of patch testing

Amelia Cussans, Natalia Spierings, Amanda Woods and Lucy Ostlere

ABSTRACT
A 41-year-old woman with a 6-year history of mild psoriasis presented with a rash under her breasts. She was prescribed Trimovate cream (GlaxoSmith Kline) and had a florid weeping eczema within 48 hours of application. This settled with the withdrawal of Trimovate. Contact dermatitis is type IV allergy and usually appears within 2-3 days after contact with an external allergen. Detection of the allergen, or allergens, is important, as avoidance results in resolution of the eczema. Our patient was patch tested and showed positives to three components of Trimovate; cetearyl alcohol, sodium metabisulphite, and clobetasone butyrate. These are important allergens to identify, because they are also present in other products. Clobetasone butyrate is often used in facial and flexural psoriasis. Cetearyl alcohol is particularly significant, as it is found in many products including commonly used moisturizers such as Diprobase (MSD), Cetraben (Genus) and Epaderm (Mölnlycke) cream, and most steroid creams. Our patient highlights the fact that is insufficient to simply advise a patient to avoid the topical medicament that has caused a reaction. Patch testing is necessary to identify which components the patient is allergic to, so that they can be avoided in all products. This is of particular significance for our patient given her history of psoriasis, as she will likely require moisturizers and topical steroid preparations in the future. Since she began avoiding these allergens, she has had no recurrence of eczema. To conclude, GPs should consider sending their patients with contact dermatitis for patch testing, as the identification of all allergens is valuable to management.
Keywords: patch testing, contact dermatitis, concomitant sensitivity, Trimovate cream, sodium metabisulphite, clobetasone butyrate, cetearyl alcohol.

Case Report

A 41-year-old woman with a 6-year history of mild psoriasis presented with a rash under her breasts. The differential diagnosis included flexural psoriasis, an allergy to the nickel in her under wired bra, and intertriginous dermatitis (moisture-associated skin damage). She was prescribed Trimovate cream (GlaxoSmith Kline) and developed a florid weeping eczema within 48 hours of application (Figure 1). The eczema settled with the withdrawal of Trimovate and application of Betnovate RD cream (GlaxoSmith Kline). The history was very suggestive of a contact dermatitis to Trimovate cream.

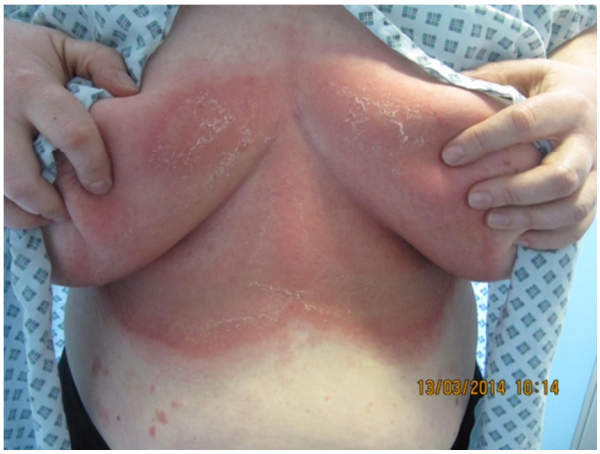

Figure 1 showing eczema

She was referred to the Dermatology department and was patch tested to the European standard, medicament and steroid batteries. She had a number of positives including cetearyl alcohol, sodium metabisulphite, and clobetasone butyrate. These are all components of Trimovate. She was given advice sheets on all her allergens and on avoiding them she has had no recurrence of eczema.

Discussion

Contact dermatitis is a type IV allergy and usually appears within 2 to 3 days after contact with an external allergen. This case is likely to be an example of concomitant sensitisation, where one sensitivity facilitates the acquisition of another sensitivity to a chemically unrelated ingredient within a product. Whilst there has been a previous case report of concomitant sensitivity to sodium metabisulphite and clobetasone butyrate in a patient using Trimovate cream,[1] this is the first report of a patient reacting to three of the ingredients found in Trimovate - sodium metabisulphite, clobetasone butyrate, and cetearyl alcohol. Allergy to clobetasone butyrate is rare, with only 5 previously reported cases.[1, 2, 3] Allergy to sodium metabisulphite is not uncommon, producing a positive reaction in approximately 4% of patients who are patch tested.[4, 5] Allergy to cetearyl alcohol is also rare, with one study estimating the incidence of positive reactions to be 0.8% among 3062 patients that were patch tested.[6]

Detection of the allergen, or allergens, is important, as avoidance results in resolution of the eczema. Our patient highlights the fact that it is insufficient to simply advise a patient to avoid the topical medicament that has caused a reaction. Ideally, patients with a topical medicament allergy should be patch tested to identify which components the patient is allergic to, so that they can be avoided in all products. In this case, in addition to Trimovate, there are a number of

other products that our patient will now avoid. This is of particular significance in view of her history of psoriasis, for which she has used moisturizers and topical steroid preparations in the past, and will likely need again in the future. Clobetasone butyrate is often used in facial and flexural psoriasis. Cetearyl alcohol is a particularly important allergen to identify, as it is found in many products including a number of commonly used moisturizers such as Diprobase (MSD), Cetraben (Genus) and Epaderm (Mölnlycke) cream, and most steroid creams although not steroid ointments. Our patient was therefore advised to use only steroid ointments and has had no recurrence of the contact dermatitis. To conclude, GPs should consider sending their patients with contact dermatitis for patch testing, as the identification of all allergens is valuable to management.

Competing Interests
None declared
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Case Report

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Blue Macular Skin Lesions of Unknown Cause in a Tyre Factory Worker: A Case Report

Mohammed Al Abadie, Dilhara Karunaratne, Nabeel Salmons, Audrey Fong Juan Chin, Soha Ammar and Nisal Karunaratne

ABSTRACT
This report describes the case of a 61 year old gentleman who developed blue macular skin lesions of unknown cause. Biopsy of the lesion showed pigment deposition in the dermis that had the appearance of tattoo pigment, but oddly the patient had never been tattooed in the past. Carbon black is a chemical which can be used to give blue tattoos their colour. The patient was exposed to carbon black in his job as a tyre maker and it may have accumulated in the dermis by an unknown route. An occupational exposure may be the cause of the skin lesions and this case may play a part in the identification of more cases and a confirmation of the true diagnosis.
Keywords: Macular lesion, dermis, carbon black, tattoo, tyre worker, occupational exposure

Case Report

Blue discolouration of the skin can have a multitude of causes, including Mongolian spots, blue naevi, the naevi of Ito and Ota and metallic discolouration[1] or the use of drugs such as minocycline. Here we report the case of a 61 year old gentleman who developed blue macular skin lesions that were not attributable to any obvious cause and may be the result of an unidentified occupational exposure.

A 61 year old Caucasian gentleman developed blue macular skin lesions over a 14 year period. The very first lesion appeared in the middle phalanx of the right middle finger (figure 1). It was light blue and pinpoint, eventually darkening and increasing in size to approximately 1mm x 1mm, at which point becoming permanent and non-evolving. The lesion had no notable associated features and the patient was in otherwise good health.

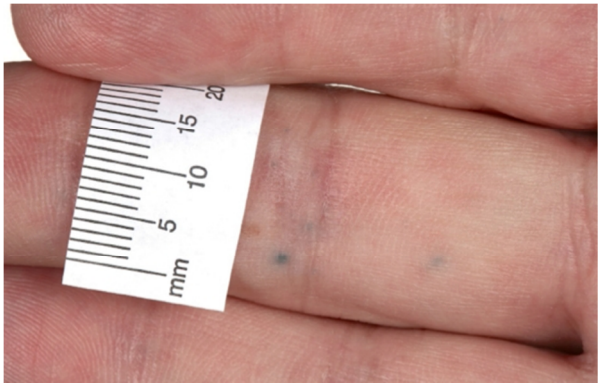

Figure 1: The first blue macular lesion on the middle phalanx of the right middle finger.

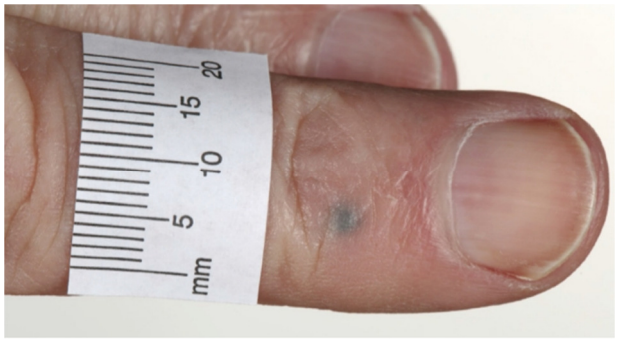

Figure 2: A blue macular lesion on the terminal phalanx of the left middle finger.

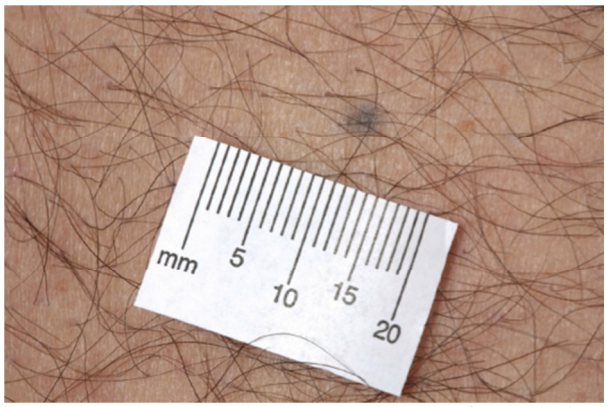

Figure 3: A lesion on the anterior abdomen from which a punch biopsy was taken.

At present, he has approximately thirteen blue macular lesions in total, all of which have developed in the same manner. They are distributed predominantly on his hands with one on his left forearm and one on the right abdominal flank. New spots still continue to arise on his hands (figure 2).

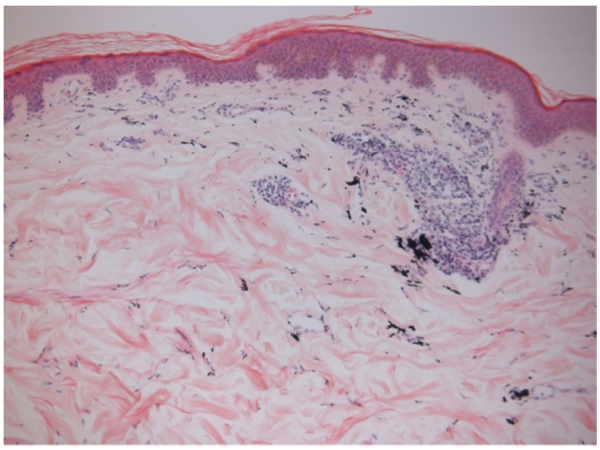

Figure 4: Haematoxylin and Eosin stained slide at 10x magnification. Abdominal skin biopsy showing dermal interstitial and perivascular distribution of black coloured pigment deposits

A punch biopsy of the abdominal lesion (figure 3) was carried out. The histological findings were those of skin with normal intact epidermis and the presence of black coloured pigment granular deposits, located largely within the papillary dermis and occasional smaller deposits in the superficial reticular dermis (figure 4). The deep reticular dermis and subcutaneous fat were normal. The pigment had a perivascular distribution and in dendritic histiocytic cells, with close association to fibroblasts. Histiocytic cells form part of the mononuclear phagocyte system and these cells are abducted mainly for phagocytosis removal or storing material[2]. Apart from the pigment, the remaining skin was normal. The use of light microscopy alone does not identify all substances on examination of a Haematoxylin and Eosin (H&E) stained section of tissue. Applying polarisation light microscopy enables the identification of numerous structures, for example crystals, pigments, bone and amyloid[3]. However, the black coloured material here was non polarisable (no refractile foreign material could be identified). These appearances as seen on light microscopy alone are most frequently seen where there is a history of tattoo artistry, but tattoo pigment is typically identified as showing reflective properties using polarisation[4]. Interestingly, the patient had no clinical history of deliberate tattooing and other causes were considered.

Discussion

The discovery of black coloured deposits in the dermis excludes the diagnoses of Mongolian spots or blue naevi and the naevi of Ito and Ota, all of which are disorders of dermal melanocytes. Another important differential is malignant melanoma, but it is not the diagnosis as the histopathological findings did not find any evidence of dysplasia or malignancy.

In a disorder known as anthracosis, similar findings of black coloured deposits can be seen in other organs such as within the lung and draining lymph nodes. It is often found in smokers and urban populations and reflects the deposition of carbon which is the most commonly identified exogenous mineral substance within tissue sections. The skin is not a site where such carbon pigment is typically seen and therefore, this is not a credible diagnosis in this case.

Agyria is a condition that occurs as a result of silver particle impregnation of skin leading to blue-grey skin discolouration. Silver exposure may be due to occupational or surgical exposure (by use of silver sutures) or medication with silver salts. On interview, the patient denied any occupational exposure to silver and the use of silver salts. Although the patient had had previous shoulder surgery, silver sutures are no longer used in modern day surgical practice and therefore this cannot be the cause of his skin discolouration.

Unfortunately, histological examination of paraffin embedded tissue sections can only confirm the presence and distribution of an exogenous substance and it is not possible to precisely differentiate the exact type of material which is present. The use of an electron probe micro analyser may have been useful in identifying the substance, however, such equipment is not currently available and was not used in this case.

Interestingly, in tattoo artistry, carbon black may be used to give blue tattoos their colour[5] and this is also a component of tyres and industrial rubber products[6]. This provided us with a link to occupational exposure, given that this gentleman is a tyre worker and has been involved in both the manufacture and assembly of tyres for 34 years. Carbon can cause discoloration of the skin, depending on the extent of deposition.

It is notable that in his 34 years of working with tyres, this gentleman did not routinely use gloves or protective uniform until only 10 years ago. This was as workplace safety precautions were not as strongly enforced in previous times. He admitted to have been in direct contact with the materials involved in tyre building and also suffered accidental superficial cuts on his hands whilst working, which may be a route by which carbon may have been introduced into the dermis. This is supported by the observation that the majority of the blue macular lesions were on the hands. Adding credibility to this theory is the identification of a colleague of this gentleman's (who did not wish to be identified), whose job also involved the manufacture and assembly of tyres, who also has a similar single blue macular lesion on his hand.

In addition to this we have identified a forum on the internet[7] that reports other similar cases of blue pin-point macular lesions appearing on the skin of tyre factory workers – some of whom worked for the same tyre company that this gentleman did. This may suggest that there is an association between exposure to a chemical, possibly carbon black, involved in the manufacture of tyres, and the appearance of these blue macular lesions.

In this case report, the identity of the material deposited and the route by which it accumulated in the dermis is unclear, but may have been related to an occupational exposure – this was in keeping with the general consensus upon presentation of this case at the West Midlands Dermatology Conference at New Cross Hospital Wolverhampton. We welcome any new case reports or literature that may be able to shed further light on this subject.

Competing Interests
None declared
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Case Report

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Malignant Syphilis as an Initial Presentation of Underlying HIV Infection: A Case report

Ashok R Devkota, Rabindra Ghimire, Mirela Sam and Oo Aung

Abstract
There is a higher rate of HIV coinfection among men who have sex with men (MSM) infected with syphilis. HIV positive patients present more often with secondary syphilis and disease course is more aggressive. Here we present a patient, with diffuse papulo-nodular and ulcerative skin lesion and newly diagnosed human immunodeficiency virus. Biopsy of skin lesions confirmed the diagnosis of malignant syphilis, supported by serology results and he responded very well to doxycycline. It is important to recognize and diagnose malignant syphilis early and institute appropriate treatment as complete cure can be achieved.
Keywords: Malignant syphilis, human immunodeficiency virus (HIV), MSM

Introduction

The rate of primary and secondary syphilis reported in the United States is gradually increasing. Reported cases of syphilis decreased during the 1990s, were lowest in 2000, after which it gradually increased annually during 2001-2009[1]. In a recent report published by CDC, primary and secondary syphilis rates have increased among men of all ages, races and ethnicities, largely among MSM, from 5.1 cases per 100,000 population in 2005 to 9.8 in 2013. Rates of 50%–70% HIV coinfection among MSM infected with primary and secondary syphilis have been reported[2]. Syphilis and the behaviours associated with acquiring it, increase the likelihood of acquiring and transmitting HIV. Although the incidence of HIV has remained stable, the incidence of syphilis has been increasing disproportionately possibly due to adaptive behaviour like serosorting among HIV concordant couples and oral sex that decrease transmission of HIV but not syphilis[3].

Syphilis may manifest differently in patients with HIV. HIV positive patients present more often with secondary syphilis and the disease course is more aggressive[4]. Malignant syphilis also known as lues maligna or ulceronodular syphilis is a severe form of secondary syphilis and is more common among HIV infected persons[5]. Although HIV patients present with varied clinical symptoms, it is uncommon to present with florid secondary syphilitic skin lesions. Here we present a case report of a patient, who presented with diffuse ulceronodular skin lesions, whose serology and skin biopsy confirmed syphilis and was subsequently found to have HIV.

Case report

A 20-year-old African American man was admitted to Interfaith Medical Center with a generalised body rash for a month. He noticed a rash on his chest, which in few days spread centrifugally to his whole body, face and arms, including palms and soles. The rash was non-pruritic, painless, progressive in size and gradually oozed and crusted (Figure 1a). Besides significant unintentional weight loss of 26 pounds in the last two months, he did not report any other systemic complaints. He denied any travel or unwell contacts. He is a homosexual man and has had two male sexual partners in the last two years; one of them was treated for syphilis two years ago. He denied smoking, alcohol or drug use.

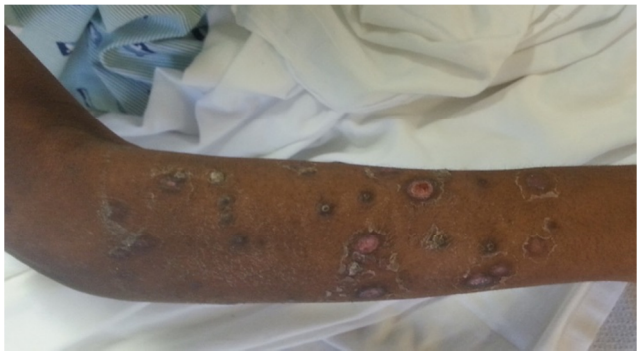

Figure 1a - Skin lesions reveal papulosquamous nodular and ulcerative changes in upper limbs

On admission, he was afebrile with normal vital signs. His physical examination revealed widespread papulonodular and ulcerated lesions on his whole body including the scalp and oral mucosa, and measured up to 2-3 cm. Skin lesions were prominent on his face, some with sero-purulent discharge and some covered with crusts and scabs, which would bleed on removal of crusts and scabs. No skin lesions were noted in genital area. Besides bilateral enlarged axillary lymph nodes, no significant lymphadenopathy was noted. Other systemic examinations were within normal limits.

His full blood count showed microcytic hypochromic anaemia with a mean corpuscular volume of 77.2 fL (normal reference range, 80-100 fL) and thrombocytosis with platelets of 546 per microliter (reference range, 130-400 per microliter). Renal and hepatic function tests were normal. He tested positive for HIV using serum enzyme linked immunosorbent assay (ELISA), rapid plasma reagin was 1:128 (reference range, nonreactive), fluorescent treponemal antibody absorption test was reactive (reference range, nonreactive) and neurosyphilis was ruled out with negative spinal fluid studies. Hepatitis B and Cserologieswere negative. Nucleic acid amplification test of the urine sample was negative for Neisseria gonorrhea and Chlamydia trachomatis. The patient was treated with doxycycline100 mg every 12 hours for secondary syphilis as he was allergic to penicillin.

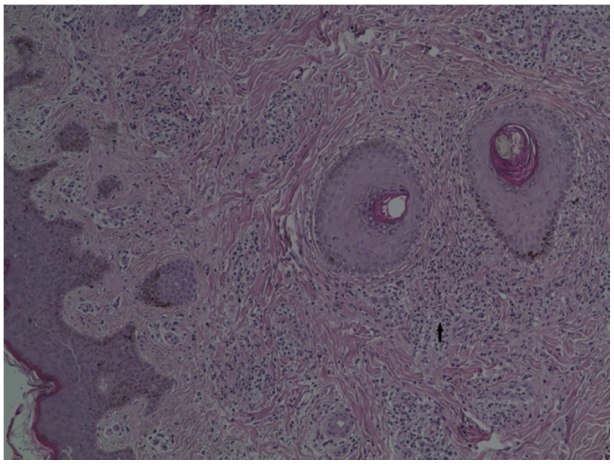

Figure 1b - A lymphocyhistiocytic infiltrate was present in the dermis and extended around blood vessels.

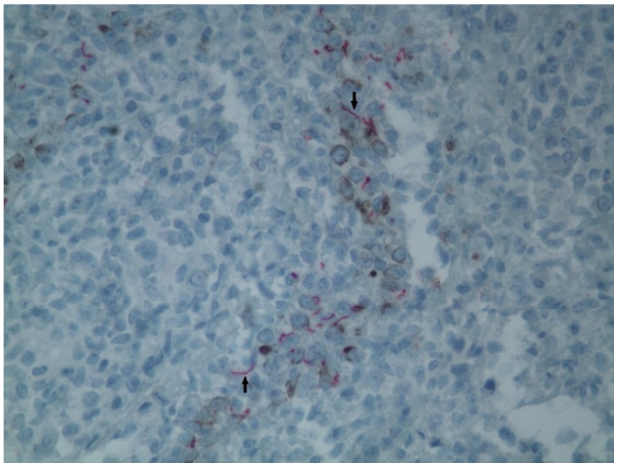

Figure 1c - Immunohistochemical stain showing delicate and spiral shaped spirochaetes, highly specific and sensitive of Treponema pallidum

The patient developed chills, fever, sweating, tachycardia and hypotension 18 hours after treatment with doxycycline. A Jarisch-Herxheimer reaction was suspected, which was managed with observation, intravenous hydration and a single dose of methylprednisone. Despite being on antibiotics, he had intermittent fever for two weeks, possibly related to the syphilis and its treatment. Further investigations included blood and urine culture, chest x-ray, CT scan of the head, chest, abdomen and pelvis and a gallium scan, which were unremarkable. Brucella IgM antibody, Q fever phase I and II antibodies, coccidioides antibody, histoplasma urine antigen, cryptococcal antigen and blood culture for acid fast bacilliwere all negative. His EBVserologies suggested past infection and CMV serologies for IgG and IgM were positive. Wound culture taken from the purulent skin lesions grew methicillin sensitive Staphylococcus aureus (MSSA)which was treated with antibiotics. His HIV-1 RNA was 1050118 (reference range, <20) and CD4 was 276 cells per microlitre (reference range, 317-1868 cells per microlitre), CD4 was 17.4% (reference range, 25.7-62.8%) and CD4:CD8 ratio was 0.32 (reference range, 0.20-3.50). Skin biopsy from the left forearm lesion showed lichenoid lymphohistiocytic infiltrate with plasma cells (Figure 1b). Immunochemical stain was positive for spirochetes, which confirmed secondary syphilitic skin lesions (Figure 1c). After three weeks of doxycycline therapy, significant clinical improvement in the skin lesions were noted. The skin lesions healed well with hyperpigmentation. Combination anti-retroviral therapy was initiated upon discharge and on follow-up a month later, the skin lesions had resolved and the RPR titre was 1:32; showing a four-fold reduction.

Discussion

Skin lesions of secondary syphilis in patients with HIV may have varied appearance that mimic other diseases like cutaneous lymphomas, mycobacterial infections, bacillary angiomatosis, fungal infections or Kaposi's sarcoma[6]. Detail workup was done in our patient and systemic fungal and bacterial infections were ruled out. He had secondary infection of the skin lesions due to MSSA and was treated with doxycycline. Skin biopsy confirmed secondary syphilitic skin lesions. Histology showed abundant plasma cells and lymphocytesandtreponomes were demonstrated in the special immuno-histochemical stains. Fisher's diagnostic criteria for lues maligna include strongly positive RPR titre, a severe Jarisch-Herxheimer reaction, characteristic gross and microscopic morphology and rapid resolution of the lesions with antibiotics[7]. Our patient had all of these features. Because of variable presentation of skin lesions and increased rate of false negative serological tests due to prozone phenomenon in patients with HIV, alternative diagnostic techniques like biopsy of skin lesions and special stains should be performed[8,9]. The relative paucity of spirochetes in the biopsy of skin lesions makes the demonstration of microorganisms difficult. Yanagishawa et al were able to find 6 published cases of pathologically confirmed malignant syphilis with the demonstration of spirochetes[10]. Treatment of secondary syphilis in HIV infected patient is the same as that of HIV non infected patients. Benzathine penicillin is first line therapy and doxycycline is an alternative drug for penicillin allergic patients[11]. A severe Jarish-Herxheimer reaction occurred in our patient, which might not be observed in some cases with HIV and syphilis due to concurrent immunosuppression[10]. Experience from case reports

have shown that malignant syphilitic skin lesions respond very well to antibiotics regardless of CD4 count[12]. With the increasing incidence of syphilis in HIV infected patients, it is important to recognise and diagnose malignant syphilis early and institute appropriate treatment as complete cure can be achieved.

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Competing Interests
None declared
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Case Report

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Phenobarbital induced Pellagra

Youssef kort, Naziha Khamassi, Heykel Abdelhedi and Ouahida Cherif

Abstract

Background: Pellagra is a nutritional disorder due to an insufficiency in vitamin B3 also called vitamin PP for "pellagra preventing" vitamin. The disease was characterized by the "3D" consisting in dermatitis, dementia and diarrhea. The insufficiency can be due to drug use as anti epileptics. We describe a case of Phenobarbital-induced pellagra.

Observation: We report here a 61 years old woman who developed pellagra after a 45 years use of Phenobarbital. The diagnosis was suspected by the association of dermatological, neurological and gastro intestinal signs. It was confirmed by the good response to the niacin treatment and Phenobarbital discontinuation.

Conclusion: Pellagra should be considered in patients taking anti epileptic drugs because of its very good prognosis if treated and fatal issue if misdiagnosis.

Keywords: Pellagra, Phenobarbital, epilepsy

Introduction

Pellagra is a nutritional disorder due to an insufficiency in vitamin B_3 also called vitamin PP ('Pellagra preventing'). The disease was characterized by the following '3 D's': 'Dermatitis', 'Dementia' and 'Diarrhoea'. When it is misdiagnosed, it can lead to the fourth 'D' which is 'Death'.[1] It was very common in past centuries, particularly in populations that had an exclusively maize diet. Nowadays, this diet problem is rare in developed countries, so the disease is less frequent. However, many recent studies suggest that the disease has not been eradicated and can be under-diagnosed. Alcohol, drugs and malabsorption seem to be the new aetiologies of the disease. So, it is important to recognize the '3 D's' triad in such situations to avoid fatalities.

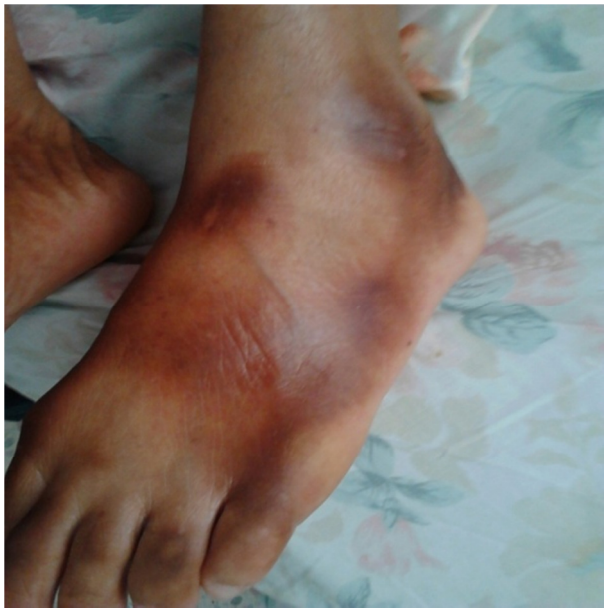
Observation

A 61-year-old patient presented to the Internal Medicine Department with an 8-month history of deterioration in her general state. She had a medical history of Epilepsy treated by Phenobarbital since she was 16.

Review of systems revealed gastrointestinal symptomatology consisting of intermittent diarrhoea (6-7 watery stools a day without blood), dysphagia and diffuse abdominal pain. The patient also reported a skin photosensitive eruption affecting her hands and feet.

Physical examination showed a listless patient with a low Body Mass Index (17 kg/m²).

On dermatological examination, symmetric, well-defined, brown-coloured and scaly eruption was observed on the dorsa of her feet (Picture 1) and hands (Picture 2). The mucous examination showed a commissural Cheilitis and Glossitis.



Picture 1: Brown well-defined patches on feet.

The nervous system examination revealed a pyramidal and cerebellar syndrome. The response to neurocognitive tests was altered suggesting Dementia.

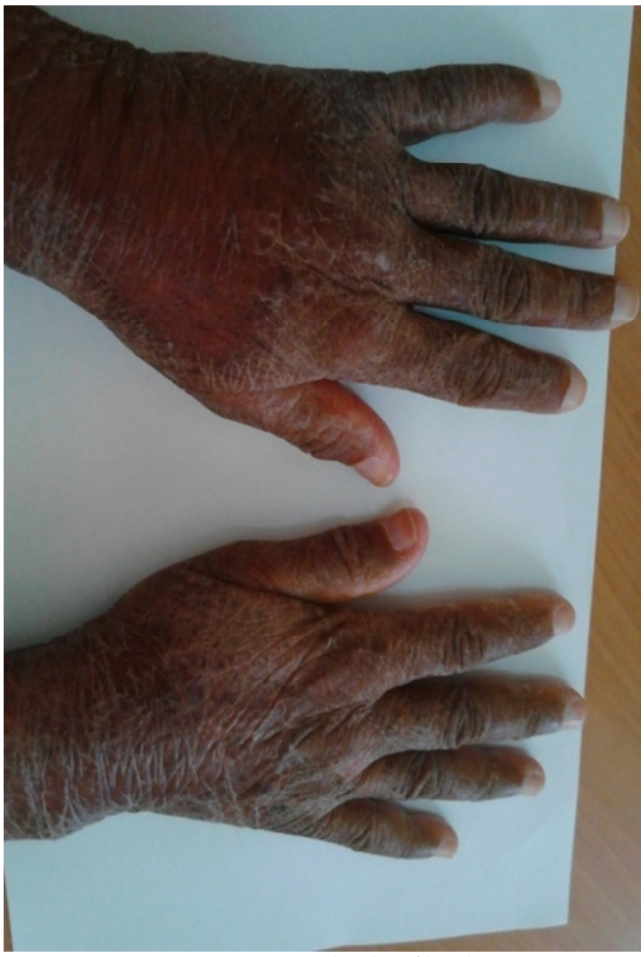
The rest of physical examination was normal. In particular, there were neither peripheral lymph nodes, nor spleen or liver enlargements, nor abdominal mass.

The laboratory tests (glucose, calcaemia, creatinine, liver function tests, urine analysis, haemoglobin, hematocrit, sedimentation rate, C-reactive protein and protein electrophoresis) were within normal limits.

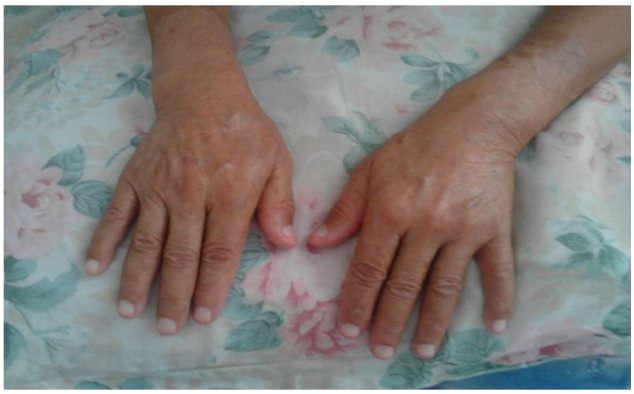
Oesogastroduodenal endoscopy was normal. The cranial, thoracic and abdominal CT scans were normal.

The diagnosis of Pellagra was made on dermatological, abdominal and neurological signs. The patient was treated by

Niacin (1000 mg/day) and multivitamin complex. Phenobarbital was discontinued and switched to Clobazam. The patient's symptoms started to improve quickly. Ten days after the treatment began the skin lesions (Picture 3) and gastrointestinal signs completely disappeared.



Picture 2: Brown pigmentation and scales of hands.



Picture 3: Hands aspect after treatment.

Discussion

Pellagra was diagnosed clinically in our patient based on the skin aspects. The skin lesions have been described since 1771 by Frapolli whose name was given to the disease: Pellagra which means rough skin in Italian.[1] The typical lesions consist of a brown pigmentation and scales with a photosensitive distribution and well-defined borders as seen in our patient. The face, the neck and the dorsa of the hands are the preferential locations.[2] The skin lesions are not always found, and cases of Pellagra Sine Pellagra have been described.[3] The extra-cutaneous manifestations are less specific, but their association with pellagrous skin lesions are sufficient to reach a diagnosis. The neurological involvement is classically a Dementia syndrome, but 'Pellagrous Encephalopathy' can also consist of delirium, insomnia, depression, cerebellar and extrapyramidal syndrome.[4] The gastrointestinal signs are non-specific; they can be Glossitis, dysphagia, nausea, vomiting and abdominal pain. An intractable diarrhoea may occur in advanced stages of disease and can quickly lead to death.[5]

In 1929, Goldberger attributed such clinical manifestations to a Niacin (vitamin B_3 or PP) deficiency. Niacin is a precursor for two important coenzymes namely 'Nicotinamide Adenine Dinucleotide (NAD)' and 'NAD-Phosphate' which are essential for many oxidative reactions. This probably explains why Pellagra affects tissues with a high rate of cell turnover such as the skin and digestive tract.[4]

Niacin can be directly absorbed by the gastrointestinal tract or synthesized from Tryptophan.

Primary Pellagra occurs when the diet is deficient in Niacin or Tryptophan as in poor populations with an exclusive maize diet (which contain Niacin but in an indigestible form).

Table 1: List of drugs predisposing to Pellagra.

Predisposing Drugs
Antituberculosis agents: Isoniazid Pyrazinamide
Antiepileptic drugs: Hydantoins Ethionamide Phenobarbital Diazepam
Chemotherapy and immunosuppressive drugs 6-Mercaptopurine 5-Fluorouracil Chlorambucil Azathioprine Chloramphenicol

Despite sufficient dietary Niacin, Secondary Pellagra may be caused by a problem in Niacin absorption or metabolism. Many causes of Secondary Pellagra were identified as alcohol, intestinal malabsorption, carcinoid tumours, Hartnup's Syndrome, Anorexia Nervosa and drugs (Table 1).[5] Our patient did not consume alcohol and had no biological signs of malabsorption, but she was taking Phenobarbital for about 45 years. In the English literature, we found only two cases of Phenobarbital-induced Pellagra, and with a fatality in one case.[6,7] The underlying mechanism of Pellagra caused by Phenobarbital, or other antiepileptic drugs, is an alteration in Niacinamide synthesis due to an enzymatic induction.[5]

The treatment is first based on correction of predisposing factors. In our patient, it consisted of using another antiepileptic drug instead of Phenobarbital. Second-line treatment is a vitamin therapy based on Niacin. There is no consensus on the doses, form and duration of the treatment, but the minimal dose is 300 mg of Niacin/day. A multivitamin complex containing other B-vitamins is often necessary because of the frequency of other deficits in such patients.[2] With treatment, the skin lesions and gastrointestinal symptoms generally disappear within a few hours or days, as in the case of our patient, and it is a good argument for a retrospective diagnosis of pellagra.[1] Testing for Niacin levels or urinary metabolites is not frequently available and it's not necessary for the diagnosis.

Conclusion

We described a typical case of Pellagra in which the '3 D's' were present. In such a case, we should begin the treatment before the results of the laboratory investigations are known. The improvement of all symptoms within a few days is sufficient to confirm the diagnosis. However, the '3 D's' triad is not always present, and the clinician should consider the diagnosis in face of unexplained abdominal or neurological signs in certain patient groups.

Competing Interests
None declared
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Case Report

Familial dilated cardiomyopathy linked with hearing loss in brothers: Case Report

Jing Lin, Jianhong Tao, Guangre Xu and Li Cai

Abstract
Dilated cardiomyopathy (DCM) is the third leading cause of severe heart failure and the most common cause of heart transplantation. Many cases (25–30%) of DCM are familial, indicating a genetic contribution to the etiology. The diagnosis of Familial dilated cardiomyopathy (FDC) is clinically based on the clinical manifestation, with at least two affected members from the same family. More than 30 genes associated with FDC have been identified, but still theses explain only a minority of the etiology of FDC. Here we present a strange case of FDC accompanied by hearing loss and rapid progressive course. The manifestations of FDC in this family was really rare and it is anticipated that more susceptibility genes may be discovered.
Keywords: familial dilated cardiomyopathy; hearing loss; rapid progressive course

Introduction

Dilated cardiomyopathy (DCM) is a cardiac muscle disease, characterized by dilatation and impaired contraction of the left ventricle or both ventricles, and leads to progressive heart failure and sudden or heart failure-related death [1]. The life expectancy is limited and varies according to the underlying etiology with a median survival time of about 5 years after diagnosis [2]. Although the pathogenesis of this disease has been extensively studied for decades, it remains ambiguous. Currently, myocarditis, immunological abnormalities, toxic myocardial damage, and persistent cardio-tropic viral infection are all assumed to be causes of DCM [3]. Dilated cardiomyopathy occurring in families, or the familial dilated cardiomyopathy (FDC) may occur in 25% to 35% of DCM cases, implicating a genetic contribution to the etiology [4-7]. More than 30 susceptibility genes have been shown to be associated with an increased risk of developing a DCM. Here we report three strange cases of FDC accompanied by hearing loss and rapid progressive course in brothers from Sichuan Province of China. The presentation of the family was really rare and it is anticipated that more susceptibility genes may be discovered.

Case report

The patient was a boy from Sichuan Province, and had lost his hearing when he was five years old. At the age of eight, the boy presented with cough and acute onset breathlessness. On examination, he had blood pressure (BP) of 90/60mmHg, heart rate (HR) 105/min, raised jugular venous pressure (JVP), crackles over the lung bases and a pansystolic murmur at the apex. A huge cardiomegaly was seen on chest X-ray (CXR), and the cardiothoracic ratio (CT ratio) was 0.721. ECG revealed primary atrioventricular block and left ventricular hypertrophy (LVH). Echocardiography (Echo) showed enlargement of both ventricles of the heart, a decreased left ventricular ejection fraction (LVEF), and severe mitral regurgitation (MR). The patient was treated in line with congestive cardiac failure (CCF). However, he died three months after the acute onset of breathlessness.

Surprisingly, the progression was nearly the same as two of his older brothers. Both of them also lost hearings at the age of five. Then presented with acute onset breathlessness and they were diagnosed with DCM aged seven to eight years. They also died three months later after the acute onset of breathlessness. Because of the terrible experience of his older brothers, the boys' parents took him to hospital every year to be examined. ECG and Echo images were normal 6 months before the onset of breathlessness. Moreover, the boy had no symptoms 1 month before his presentation.

Discussion

The definition of FDC is clinically based on manifestation with at least two affected members from the same family [5]. The most common mode of inheritance is the autosomal dominant type, while X-linked, autosomal recessive and mitochondrial forms are less common [8, 9]. Although most people affected die in early adulthood, the age of onset, rate of progression, disease complications, as well as overall prognosis and outcome vary within families [5, 10]. Nevertheless, the age of onsets in this family were similar and with a rapid progressive course. All of the sons in the family suffered from DCM as well as hearing loss. The manifestation of the brothers hasn't been reported

before. We traced back three generations of this family finding no other affected members. As all the patients were male, we speculated that the possible mode of inheritance in this family is X-linked. Regrettably, the parents had no daughters and we were not able to investigate the possible association between gender and FDC of this kind. Because of the rapid progressive course, we hypothesize that autoimmune abnormalities might be the pathogenic factors for this disease, but we do not have any solid evidence yet. Fortunately, we were able to get the blood samples from the patient and the relatives. Further studies are needed to explore new susceptibility genes as well as the molecular mechanisms that are involved in the disease.

Competing Interests
None declared

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EYE: "A clue to diagnosis"

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A 38 year male presented to our centre with a two-month history of jaundice. Past medical & family history was insignificant. Clinical examination revealed a icterus and greenish brown ring in both eyes (Figure 1). Laboratory investigations revealed a mild thrombocytopenia (platelet count-1.2 lakh/mm3) and a prolonged prothrombin time. Liver function tests showed elevated serum levels of alanine aminotransferase & aspartate aminotransferase. Serology for hepatotropic viruses was negative. Serum ceruloplasmin was 9.8 mg/dl (reference range 20-60mg/dl) and 24 hour urinary copper was elevated.

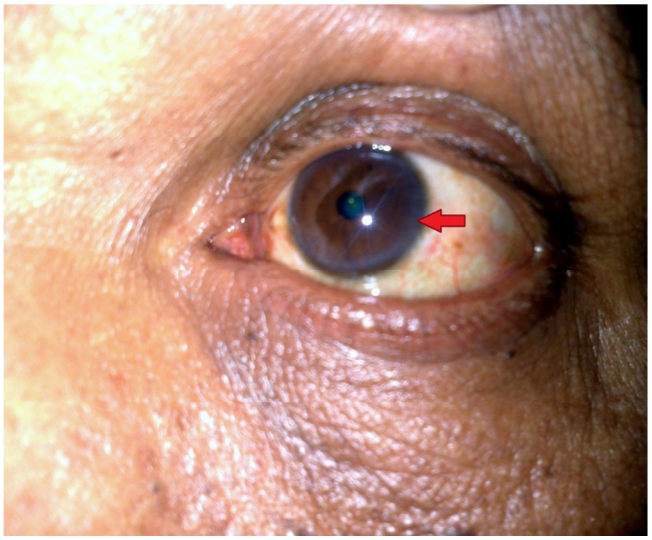

Figure 1

What is the eye finding?

1. Arcus Senilis
2. Pterygium
3. Kayser Fleischer ring
4. Phlycten

Correct Answer:

3. Kayser Fleischer ring

Discussion:

Wilson's disease is a consequence of defective biliary excretion of copper. This leads to its accumulation in the liver and brain [1]. It is due to mutations of the ATP7B gene on chromosome 13, which codes for a membrane-bound copper transporting ATPase [2].

Kayser-Fleischer ring is an outcome of abnormal copper deposition in the membrane in the limbus of cornea. Slit-lamp examination by an experienced observer is required to identify a K-F ring. The colour may range from greenish gold to brown. When well developed, a K-F ring may be readily visible to the naked eye. K-F ring is observed in most individuals with symptomatic Wilson disease and are almost invariably present in those with neurologic manifestations. They are not entirely specific for Wilson's disease, since they may also be found in patients with chronic cholestatic diseases.

Clinical presentation is variable and patients presenting with chronic hepatitis, cirrhosis & at times acute liver cell failure. The most common presenting neurologic feature is asymmetric tremor. The characteristic tremor is coarse, irregular proximal tremulousness with a "wing beating" appearance.

Typically, the combination of K-F rings and a low serum ceruloplasmin (<0.1 g/L) level is sufficient to establish a diagnosis of Wilson's disease [3]. However delayed diagnosis in patients with neuropsychiatric presentations is frequent and was in one case as long as 12 years [4].Our patient was treated with a none copper diet, oral zinc and d pencillamine. His liver functions became normal over 6 months of treatment and without progression of liver disease.

Arcus Senilis is a grey band of apacity near the sclero-corneal margin, commonly found in the elderly and associated with hypercholesterolemia. Pterygium is a benign wedge shaped fibrovascular growth of conjunctiva that extends onto the cornea. Phylecten is consequence of allergic response of the conjunctive & corneal epithelium usually associated with tuberculosis, staphylococcus protein and moraxella.

Competing Interests
None declared
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