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Awareness of the public about cutaneous leishmaniasis in an endemic area, Aseer region, Saudi Arabia

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Original Contribution and Literature Review

Editorial

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Integrating Clinical Insight and Emerging Evidence to Advance Patient Care

Healthcare today faces the dual challenge of managing complex chronic conditions while embracing innovation in diagnostics, therapeutics, and prevention. The articles compiled in this issue represent a spectrum of clinical investigations and reviews that together underscore the urgency of bridging clinical practice, population health, and translational science. One such example is the review on the FRAX tool in Qatar, which highlights the need for a systematic approach to osteoporosis screening in primary care. Despite the availability of country-specific tools, significant gaps in awareness and implementation persist among physicians. Closing this gap requires targeted training, integration of FRAX into routine health checks, and leveraging digital health solutions, including AI-assisted algorithms, to streamline risk prediction and referral pathways. Similarly, the study on ocular chemical injuries reveals knowledge deficits among both family and emergency medicine physicians. Developing standardized clinical pathways and offering simulation-based training could improve response times and patient outcomes in these time-critical cases.

Several contributions in this collection highlight the educational value of case reports. The unusual presentation of pulmonary embolism with abdominal pain and the two cases of testicular torsion with delayed diagnosis remind clinicians of the importance of maintaining a broad differential diagnosis and performing thorough examinations even when presentations are atypical. These cases illustrate that timely recognition and intervention can make the difference between full recovery and irreversible harm.

The article examining excess fat tissue as a primary driver of atherosclerosis reframes our understanding of cardiometabolic disease by positioning adiposity as a central, modifiable determinant of vascular aging. The authors argue that interventions aimed at weight reduction may exert greater long-term benefits on survival than those targeting smoking or other isolated risk factors. This perspective reinforces the need for preventive strategies focusing on diet, physical activity, and metabolic health.

At the population level, the cross-sectional survey on cutaneous leishmaniasis awareness in Saudi Arabia documents poor public knowledge of transmission and prevention, with younger and female participants exhibiting slightly better awareness. This underscores the necessity for region-specific health education campaigns that engage communities in active disease prevention efforts.

Equally important is the chapter on the neurobiology of dementia, which provides a detailed overview of molecular, cellular, and network-level mechanisms underlying cognitive decline. These insights are crucial for developing precision diagnostics, identifying biomarkers, and personalizing treatment. The paper calls for continued integration of neuroscience research into geriatric care models to support earlier interventions and slow disease progression.

Taken together, these contributions emphasize that the path forward lies in clinical vigilance, patient-centered risk stratification, and responsible adoption of technology. Emerging tools—whether risk calculators, machine learning models, or digital health platforms—must

be implemented alongside robust training, ethical oversight, and community education. Healthcare professionals, policymakers, and researchers must work together to build frameworks that ensure safety, equity, and transparency. The ultimate goal remains clear: to translate knowledge into practice in ways that enhance patient dignity, preserve function, and improve quality of life across diverse populations.

Warm regards,
Dr. Abdulrazak Abyad
Editor-in-Chief
Middle East Journal of Family Medicine

Awareness of the public about cutaneous leishmaniasis in an endemic area, Aseer region, Saudi Arabia

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Abstract

Background: Leishmaniasis is a group of chronic infections affecting humans and several animal species. Cutaneous leishmaniasis (CL) is a protozoal infection transmitted by bites of the infected female sandflies. CL is endemic throughout the desert of the Middle East. The awareness of the people is an important tool in the success of disease prevention and control programs.

Methods: We undertook a descriptive cross-sectional web-based study and a questionnaire in the Aseer region. The first part of the questionnaire included demographic data (age, gender, geographic location, personal and family history of CL). The second part of the questionnaire included the awareness of the participants regarding the frequency of infection, clinical signs, types, treatment methods, consequences, and preventive measures of CL.

Results: A total of 402 participants completed the questionnaires. Their age ranged from 18 to 65 years with a mean age of 34.1 ± 13.9 years. Good awareness about CL was statistically significantly higher among the following: i) participants less than 30 years (26.6%) as compared to those aged 50 years or more (6.9%), ii) females (17.6%) as compared to males (8.9%), and iii) participants who never had any previous exposure to CL (18.4%) as compared to those who exposed before (8.7%).

Conclusion: Overall, the public awareness regarding CL in Aseer region was very poor, especially the general knowledge including the nature of the disease, and mode of transmission. In KSA, more focus should be paid to improve public awareness regarding CL as a preventable disease.

Keywords:
Leishmaniasis, population, awareness, knowledge, prevalence, Kingdom of Saudi Arabia, and Aseer region.

Introduction

Leishmaniasis is a group of chronic infections affecting humans and animals that is endemic in more than 90 countries worldwide [1]. The annual global incidence of CL is 0.7 to 1 million new cases per year. In 2020, nearly 80% of CL was reported from seven countries: Afghanistan, Algeria, Brazil, Colombia, Iraq, Pakistan, and Syria [2]. The human gets infected through the bite of female sandflies (mostly the genera Phlebotomus and Lutzomyia) [3]. There are more than 20 species of Leishmania. The infection can cause protean clinical manifestations such as cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis, and visceral leishmaniasis [4]. CL is the most frequent type and is featured by the development of several dermal cutaneous lesions. The spontaneous healing of the latter leaves disfiguring scars, resulting in social and psychological stigma [5].

The Kingdom of Saudi Arabia (KSA) is the fourth most endemic area of CL in Western Asia [6] with an average number of 2500 cases per year [2]. CL is endemic in several regions of KSA. In the Eastern region, CL is endemic, especially in the Al-Hassa Oasis. Over there, the vector of the disease is the sandfly, and the desert rodents are the alternative natural hosts. The causative agent of CL in the Al-Hassa Oasis is L. Tropica [2, 7]. In the Eastern region, sand-fly is the most common vector, and L. major is the most causative agent. In the Southwestern region, L.Tropica is the most causative agent [8]. Alraey et al examined the epidemiology of 1565 CL in Aseer region over a period of 9 years (2011-2020). They used R statistic language (version 4.0.5), and the spatial distribution of cases was mapped using QGIS (version 3.20.0). 2011 to 2020. The highest risk of contracting CL was seen among children under the age of 13 years [9]. The highest areas of CL infection included Abha, Sarat-Abidah, and Khamis-Mushait. The face was the most commonly affected site [9].
Public awareness of certain diseases can improve the active participation of individuals and communities in disease prevention and control programs. In 1987, 1198 cases were reported among the Saudi populations of the Aseer region with an annual incidence of 12 per 10000 [10]. Khan et al examined the level of awareness regarding CL in the Malakand region (Pakistan). The authors conducted a cross-sectional survey on a total of 400 respondents. Most of the participants (61.2%) were aware of the role of the transmitting vector (sand flies). Most of the participants were not aware of the behavior of the sandflies. A quarter (24.5%) of the participants were not aware of the proper measures to control CL. Alarmingly, about half (49.8%) of the participants did not adopt any strategy to control CL [11].

To the best of our knowledge, there are no available reports about the public awareness of CL in the Aseer region. We conducted the current investigation to fill this existing gap in the literature. To achieve our goals, we conducted a descriptive cross-sectional web-based study in the Aseer region using two questionnaires.

Material and Methods

The current descriptive cross-sectional study was conducted to assess the public awareness of CL among 402 participants living in the Aseer region. The latter is a well-known endemic area of CL in KSA. The study included all individuals aged 18 years or older who consented to participate in the investigation. The exclusion criteria included individuals under 18 years old, people who declined to consent, or non-Arab language-speaking people. We designed the two-part questionnaire of the study based on a literature review and following consultation with experts in the field of epidemiology, community medicine, and infectious diseases residing in the Aseer region. The validity, applicability, and clearness of the questionnaire were assessed by the experts independently. Their suggestions were discussed thoroughly, and the appropriate ones were included in the final version of the questionnaire.

The final questionnaire was disseminated using social media platforms in the period between 1st of October 2022 to 31 December 2022. We encouraged the respondents to participate by emphasizing the strict confidentiality of their participation and clarifying the importance of this research to the health of their society. The first part of the questionnaire included the demographic data of the participants (age, gender, geographic location, personal and family history of CL). The second part of the questionnaire covered the general awareness of the participants, frequency of infection, clinical signs and types of leishmaniasis, treatment modalities, outcome, complications, and preventive measures against CL. All the questions had either one or more than one correct answer.

Data analysis

The data were collected, reviewed, and then fed to the Statistical Package for Social Sciences version 21 (SPSS: An IBM Company). All statistical methods were two-tailed. The alpha level of 0.05 is considered statistically significant if the P value is less than or equal to 0.05. The overall awareness level of CL was assessed by summing up discrete scores for different correct knowledge items. The overall awareness score was categorized as a poor level if the participant's score was less than 60% of the overall score. Alternatively, it was scored as a good level of awareness if the participant's score was 60% or more of the overall score. Descriptive analysis was done by prescribing frequency distribution and percentage for study variables, including respondents' data, medical, and family history of CL. The awareness regarding leishmaniasis, clinical signs, related treatment methods, consequences, and preventive measures was also tabulated, and overall awareness was graphed. Cross tabulation for showing the distribution of participants' overall awareness level by their data was carried out with the Pearson chi-square test for significance and the exact probability test if there were small frequency distributions.

Results

A total of 402 participants (233 females and 169 males) completed the questionnaire. The mean age of the participants was 34.1 ± 13.9 years old. Sixty-nine participants had a history of CL, whereas 111 participants had a family history of CL. A summary of these findings is shown in Table 1. We examined the public awareness regarding leishmaniasis in the Aseer region. The percentages of the participants aware of the following regarding CL were as follows: CL is a dangerous (43.8%), parasitic disease (26.6%) that is common in KSA (42.8%). CL is transmitted by sand-fly bite (28.9%), which can infect all age groups (60.4%), and can present as nodules or ulcers (35.8%). A summary of these findings is shown in Table 2.

Analysis of the public awareness regarding the treatment, consequences, and prevention of leishmaniasis in the Aseer region revealed several observations. The percentages of public awareness were as follows: CL infection can heal without treatment but with a scar (40.5%), and local injections are the most common treatment modality (27.6%). The infection can result in the development of scars and deformities (33.1%). The most effective preventive measure is to avoid sleeping in open areas (15.7%). A summary of these findings is shown in Table 3. The overall public awareness regarding leishmaniasis in the Aseer region was poor (86.1%; 346 participants), whereas 56 (13.9%, 56 participants) had a poor awareness level. A summary of these findings is shown in Table 2.

The factors associated with public awareness regarding CL included the following: age (26.6% of participants less than 30 years had a good awareness level versus 6.9% of those who were 50 years or more), gender (17.6% of female participants had a good awareness level versus 8.9% of male participants), and history of previous exposure to CL. A summary of these findings is shown in Table 4.

Table 1. Personal data of study participants, Saudi Arabia

Personal data	No	%
Age in years		
< 30	128	31.8%
30-39	170	42.3%
40-49	75	18.7%
50+	29	7.2%
Gender		
Male	169	42.0%
Female	233	58.0%
Have you ever had cutaneous leishmaniasis?		
Yes	69	17.2%
No	250	62.2%
I don't know	83	20.6%
Have any of your relatives had cutaneous leishmaniasis?		
Yes	111	27.6%
No	179	44.5%
I don't know	112	27.9%

Table 2. Public awareness regarding leishmaniasis and endemic area, Kingdom of Saudi Arabia

Domain	Awareness		No	%
General awareness	What is leishmaniasis?	Parasitic infection.	107	26.6%
		Bacterial infections	74	18.4%
		Viral infection	80	19.9%
		I don't know	141	35.1%
	How is leishmaniasis transmitted?	By sand-fly bite	116	28.9%
		By pets	19	4.7%
		By food & drink	24	6.0%
		By sexual relations	53	13.2%
		By breathing	73	18.2%
		I don't know	117	29.1%
	Is leishmaniasis contagious?	Yes	156	38.8%
		No	99	24.6%
		I don't know	147	36.6%
	Is leishmaniasis dangerous?	Yes	176	43.8%
		No	79	19.7%
		I don't know	147	36.6%
	Who are the vulnerable groups?	Children	47	11.7%
		Adults	112	27.9%
		All groups	243	60.4%
Leishmaniasis in Saudi Arabia	Is leishmaniasis common in Saudi Arabia?	Yes	172	42.8%
		No	65	16.2%
		I don't know	165	41.0%
	What are the most common areas of the Kingdom for Leishmaniasis?	Southern region	86	21.4%
		Central region	91	22.6%
		Northern region	25	6.2%
		Eastern region	17	4.2%
		Western region	38	9.5%
		I don't know	145	36.1%
	Is leishmaniasis common in the Aseer region?	Yes	195	48.5%
		No	69	17.2%
		I don't know	138	34.3%
Clinical data	Types of leishmaniasis	Cutaneous leishmaniasis.	205	51.0%
		Mucocutaneous leishmaniasis.	20	5.0%
		Intestinal leishmaniasis.	25	6.2%
		All of them	152	37.8%
	Places where leishmaniasis is common	Areas near valleys and dams.	82	20.4%
		Agricultural areas.	167	41.5%
		Overcrowded areas	22	5.5%
		In the city	15	3.7%
		I don't know	116	28.9%
	Signs of cutaneous leishmaniasis	Small nodule	163	40.5%
		Large nodule	25	6.2%
		Multiple nodules	39	9.7%
		Ulcer	31	7.7%
		All are signs	144	35.8%
	Most sites of infection	Face	157	39.1%
		Arms	31	7.7%
		Foot	9	2.2%
		Abdomen and back	9	2.2%
		All are sites	196	48.8%

Table 3. Public awareness regarding leishmaniasis and endemic area, Kingdom of Saudi Arabia, continued

Domain	Items		No	%
Treatment	Can the infection heal without treatment?	Yes, with scar	163	40.5%
		Yes, without scar	31	7.7%
		Never	208	51.7%
	Treatments for cutaneous leishmaniasis	Local injections	111	27.6%
		IM injections	54	13.4%
		Oral medications	57	14.2%
		Local creams	39	9.7%
		I don't know	141	35.1%
	Are there effective folk remedies for cutaneous leishmaniasis?	Yes	80	19.9%
		No	117	29.1%
		I don't know	205	51.0%
Consequences	Consequences of untreated cutaneous leishmaniasis	Leave scars and deformities.	133	33.1%
		No consequences	68	16.9%
		I don't know	201	50.0%
Prevention	Preventive measures of leishmaniasis?	Wearing long-sleeved clothes	57	14.2%
		Use of pesticides	49	12.2%
		Use insect repellent creams	59	14.7%
		Do not sleep in open areas	63	15.7%
		All of them	174	43.3%

IM: Intra-muscular

Table 4. Factors associated with public awareness regarding leishmaniasis, Kingdom of Saudi Arabia

Factors	Overall awareness level				p-value
	Poor		Good		
	No	%	No	%	
Age in years					
< 30	94	73.4%	34	26.6%	
30-39	155	91.2%	15	8.8%	.001*
40-49	70	93.3%	5	6.7%	
50+	27	93.1%	2	6.9%	
Gender					
Male	154	91.1%	15	8.9%	.013*
Female	192	82.4%	41	17.6%	
Have you ever had cutaneous leishmaniasis?					
Yes	63	91.3%	6	8.7%	.003*
No	204	81.6%	46	18.4%	
I don't know	79	95.2%	4	4.8%	
Have any of your relatives had cutaneous leishmaniasis?					
Yes	95	85.6%	16	14.4%	.306
No	150	83.8%	29	16.2%	
I don't know	101	90.2%	11	9.8%	

P: Pearson X2 test $: Exact probability test * P < 0.05 (significant)

Discussion

CL represents a major health problem in KSA. CL is endemic in KSA and as such, represents a major health problem. Hassanein and his colleagues examined the epidemiology of CL in the Tabuk region, the KSA, during the period from 2006 to 2021. Their study included 1575 CL patients. The patients with leishmaniasis included 53.1% Saudis and 46.9% non-Saudi citizens. They included 83.17% males and 16.83% females. Most of the participants were in the age group of 15-45 years. The continuous immigration to the region contributed to the increased incidence of CL in this region 12. Rasheed et al investigated the types of Leishmania species causing CL infection in the Qassim region, KSA. Examination of the DNA from 206 skin biopsies from CL patients revealed that the causative species included L. major (49.5%), L. tropica (28.6%), L. infantum, and L. donovani (3.9%) infections [1].

Our current study took an aim to assess public awareness regarding CL in the Aseer region. Our study revealed several important observations. Importantly, the public awareness regarding CL was very poor, as nearly 14% of the participants were knowledgeable regarding leishmaniasis. Only one-fourth of the participants know that leishmaniasis is a parasitic disease, and more than one-fourth of them know that CL is transmitted by a sand-fly bite. Nearly the same percent knew that leishmaniasis is not contagious, but less than half (43.8%) knew that it is a dangerous infection, and less than two-thirds (60.4%) reported that leishmaniasis can infect all age groups. The level of awareness was higher among young participants, females, and those without a prior history of the disease.

Our results agree with previous studies in the other endemic areas of CL in the KSA, such as Al-Hassa [8,13], Tabuk [12], Qassim [1], and Tabuk [14], and the Malakand region (Pakistan). Amin et al conducted a cross-sectional descriptive survey including 1824 participants. The authors reported a low awareness regarding the epidemiological aspects of CL in Al-Hassa, located in the Eastern region of KSA [13]. Amin TT et al. reported that more than 76% of the participants (in the Al-Hassa region) recognized the clinical features of CL. Alternatively, the awareness regarding the vector, transmission, risk factors, and preventive methods was very poor [8]. Alatawi et al examined the attitude and knowledge regarding CL in 385 adult participants in the region of Tabuk, KSA, in the period from April to May 2022. They used an online survey14. The awareness regarding the risk factors of CL was prevalent among participants older than 61 years old and the Saudi male gender. The overall knowledge was poor regarding risk factors, transmitting vector, disease transmission, presentations, and gender prevalence [14].

Our results also call for the development of effective health strategies to combat the problem of CL. They include the improvement of public awareness regarding CL. The lack of sufficient knowledge about CL results in a delay in the diagnosis and treatment of patients afflicted by the disease.

To sum up, alarmingly, our work demonstrated overall poor public awareness of CL. The results of our investigations can help the health authorities fill the existing gap in knowledge regarding the public awareness of CL in the Aseer region. Our investigation calls for improving the public awareness of CL. This goal can be achieved through school education and public education campaigns. This will help improve public awareness to improve the policies to prevent and control CL in the endemic areas. More effort should be paid and focused on the role of sand-fly as a vector and the recognition/identification of sand-flies with the role of animal reservoirs in the spread of CL. This, in turn, will reduce the risk of outbreaks of CL in the future.

Conclusion and Recommendations

This study showed a significant defect in public awareness about cutaneous leishmaniasis (CL) in the Aseer region, despite it being an endemic area in Saudi Arabia. Only 13.9% of participants demonstrated a good level of knowledge about the disease's cause, symptoms, transmission, treatment, and prevention. Misconceptions were common, and understanding of preventive practices was particularly low. Notably, younger individuals, females, and those without prior exposure to CL were more likely to have better awareness. To improve public awareness of cutaneous leishmaniasis in the Aseer region, targeted health education campaigns should be implemented using schools, universities, and trusted media channels. Community outreach through healthcare providers and integrating CL education into routine medical visits can help correct misconceptions and promote preventive behaviors. Special focus should be placed on high-risk areas and vulnerable populations to enhance understanding and reduce disease transmission.

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Excess fat tissue may be the most significant atherosclerotic risk factor in the body

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Abstract

Background: Atherosclerosis may be the main cause of aging and shortened survival in human beings.
Methods: All patients with sickle cell diseases (SCD) were included.

Results: We studied 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, p>0.05, respectively). Smoking (23.8% vs 6.1%, p<0.001), alcohol (4.9% vs 0.4%, p<0.001), transfused red blood cells (RBC) in their lives (48.1 vs 28.5 units, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), stroke (12.1% vs 7.5%, p<0.05), chronic renal disease (9.9% vs 6.1%, p<0.05), cirrhosis (8.1% vs 1.8%, p<0.001), chronic obstructive pulmonary disease (25.2% vs 7.0%, p<0.001), coronary heart disease (18.0% vs 13.2%, p<0.05), leg ulcers (19.8% vs 7.0%, p<0.001), and clubbing (14.8% vs 6.6%, p<0.001) were all higher in males.

Conclusion: As an accelerated atherosclerotic process, hardened RBC-induced capillary endothelial damage initiated at birth terminates with multiorgan insufficiencies in early decades in the SCD. Diabetes mellitus (DM) may actually be one of the atherosclerotic endpoints of the pancreas. Although all of the above atherosclerotic consequences are frequent in SCD, we have not detected any case of DM probably due to the significantly lower body mass indexes of them. Similarly, just 20% of elderly have DM, but 55% of patients with DM are obese. So excess fat tissue may be much more significant than smoking, alcohol, or other chronic inflammatory or infectious processes for systemic atherosclerosis. Acarbose and metformin are safe, cheap, oral, long-term used, and effective drugs for loss of excess fat tissue.

Key words: Sickle cell diseases, excess fat tissue, capillary endothelial inflammation, atherosclerotic endpoints, diabetes mellitus, acarbose, metformin

Introduction

Chronic endothelial damage initiating at birth may be the most significant reason of aging and shortened survival via the atherosclerotic consequences in human body (1). Much higher blood pressures (BP) of the arterial system may be the strongest accelerating factor via the repeated injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are chiefly involved in the destructive process. Therefore venosclerosis is not a significant health problem. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, which terminally reduce blood supply to the end-organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical and mental inactivity, emotional stresses, animal-rich diet, smoking, alcohol, excess fat tissue, chronic inflammation, prolonged infection, and cancers for the development of atherosclerotic endpoints including obesity, hypertension (HT), diabetes mellitus (DM), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, chronic obstructive pulmonary disease (COPD), peripheric artery disease (PAD), stroke, abdominal angina, osteoporosis, dementia, early aging, and shortened survival (2, 3). Although early withdrawal of the accelerating factors can delay the consequences, the endothelial changes cannot be reversed, completely due to fibrotic natures. The accelerating factor and atherosclerotic endpoints of the destructive process on vascular endothelium have been researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature, extensively (4-6). Similarly, sickle cell diseases (SCD) are highly catastrophic process on vascular endothelium initiating at birth and terminating with an accelerated atherosclerosis-induced multiorgan insufficiencies in much earlier decades (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Loss of elasticity instead of shape may be the chief cause because sickling is rare in peripheric blood samples of patients with associated thalassemia minors (TM), and survival is not affected in hereditary spherocytosis or elliptocytosis in human being. Loss of elasticity is present during whole lifespan, but exaggerated with inflammation, infection, cancer, and additional stresses. The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with tissue hypoxia in whole body (9). As a difference from other causes of chronic endothelial damage, SCD keep vascular endothelium especially at the capillary level because the capillary system is the main distributor of the hardened RBC in the body (10, 11). The hardened RBC-induced chronic endothelial damage builds up an accelerated atherosclerosis in much earlier decades. Vascular narrowing and occlusions-induced tissue ischemia and end-organ insufficiencies are the terminal consequences, so the mean life expectancy is decreased 30 years or more in the SCD because we have patients with the age of 96 years without the SCD but just with the age of 59 years with the SCD in our clinic (8).

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All cases with the SCD were included. SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Smoking, alcohol, acute painful crises per year, transfused units of RBC in their lifespans, leg ulcers, stroke, surgical procedures, deep venous thrombosis (DVT), epilepsy, and priapism were researched in all patients. Patients with a history of one pack-year and one drink-year were accepted as smoker and drinkers, respectively. A full physical examination was performed by the Same Internist, and cases with disseminated teeth losses (<20 teeth present) were detected. Patients with acute painful crisis or any other inflammatory or infectious process were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography (CT) of brain, and magnetic resonance imagings (MRI) of brain and hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed via MRI (12). Associated TM were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since SCD with associated TM come with milder clinics than the sickle cell anemia (SCA) (Hb SS) alone (13). Systolic BP of the pulmonary artery of 40 mmHg or greater are accepted as pulmonary hypertension (14). Hepatic cirrhosis is diagnosed with full physical examination, laboratory parameters, and ultrasonographic evaluation of the liver. The criterion for diagnosis of COPD is a post-bronchodilator forced expiratory volume in one second/forced vital capacity of lower than 70% (15). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum, dyspnea, and hypoxia (16). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity. CRD is diagnosed with a continuously elevated serum creatinine level of 1.3 mg/dL or greater in males and 1.2 mg/dL or higher in females. Clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of greater than 1.0, and with the presence of Schamroth's sign (17, 18). An exercise electrocardiogram is taken in case of an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is performed in case of a positive exercise electrocardiogram. Finally, CHD was diagnosed either angiographically or with the Doppler

echocardiographic findings as movement disorders in the heart walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke was diagnosed by the CT and/or MRI of the brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in case of visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

We included 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, p>0.05, respectively) into the study, and there was not any patient above the age of 59 years. Associated TM were detected with similar prevalences in both genders (72.5% vs 67.9%, p>0.05, respectively). Both smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were higher in males (p<0.001 for both) (Table 1). Transfused units of RBC in their lives (48.1 vs 28.5, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), CRD (9.9% vs 6.1%, p<0.05), hepatic cirrhosis (8.1% vs 1.8%, p<0.001), COPD (25.2% vs 7.0%, p<0.001), CHD (18.0% vs 13.2%, p<0.05), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), and stroke (12.1% vs 7.5%, p<0.05) were all higher in males, significantly. Although the mean age of mortality (30.2 vs 33.3 years) was lower in males, the difference was nonsignificant, probably due to the small sample sizes of the study (Table 2). On the other hand, mean ages of the atherosclerotic consequences were shown in Table 3.

Table 1: Characteristic features of the study patients

Variables	Males with the SCD*	*p*-value	Females with the SCD
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated TM‡	72.5% (161)	Ns	67.9% (144)
Smoking	***23.8% (53)***	***<0.001***	***6.1% (13)***
Alcoholism	***4.9% (11)***	***<0.001***	***0.4% (1)***

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Thalassemia minors

Table 2: Associated pathologies of the study patients

Variables	Males with the SCD*	*p*-value	Females with the SCD
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBC‡	*48.1 ± 61.8 (0-434)*	*0.000*	*28.5 ± 35.8 (0-206)*
Disseminated teeth losses (<20 teeth present)	*5.4% (12)*	*<0.001*	*1.4% (3)*
CHD§	*18.0% (40)*	*<0.05*	*13.2% (28)*
Cirrhosis	*8.1% (18)*	*<0.001*	*1.8% (4)*
COPD¶	*25.2% (56)*	*<0.001*	*7.0% (15)*
Ileus	*7.2% (16)*	*<0.001*	*1.4% (3)*
Leg ulcers	*19.8% (44)*	*<0.001*	*7.0% (15)*
Digital clubbing	*14.8% (33)*	*<0.001*	*6.6% (14)*
*CRD***	*9.9% (22)*	*<0.05*	*6.1% (13)*
Stroke	*12.1% (27)*	*<0.05*	*7.5% (16)*
PHT***	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
ACS*****	2.7% (6)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)
Mean age of mortality (year)	30.2 ± 8.4 (19-50)	Ns	33.3 ± 9.2 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Coronary heart disease
¶Chronic obstructive pulmonary disease **Chronic renal disease ***Pulmonary hypertension
****Deep venous thrombosis *****Acute chest syndrome

Table 3: Mean ages of endpoints of the sickle cell diseases **Table 3: Mean ages of endpoints of the sickle cell diseases**

Variables	Mean age (year)
Ileus	29.8 ± 9.8 (18-53)
Hepatomegaly	30.2 ± 9.5 (5-59)
ACS*	30.3 ± 10.0 (5-59)
Sickle cell retinopathy	31.5 ± 10.8 (21-46)
Rheumatic heart disease	31.9 ± 8.4 (20-49)
Autosplenectomy	32.5 ± 9.5 (15-59)
Disseminated teeth losses (<20 teeth present)	32.6 ± 12.7 (11-58)
Avascular necrosis of bones	32.8 ± 9.8 (13-58)
Epilepsy	33.2 ± 11.6 (18-54)
Priapism	33.4 ± 7.9 (18-51)
Left lobe hypertrophy of the liver	33.4 ± 10.7 (19-56)
Stroke	33.5 ± 11.9 (9-58)
COPD†	33.6 ± 9.2 (13-58)
PHT‡	34.0 ± 10.0 (18-56)
Leg ulcers	35.3 ± 8.8 (17-58)
Digital clubbing	35.4 ± 10.7 (18-56)
CHD§	35.7 ± 10.8 (17-59)
DVT¶ and/or varices and/or telangiectasias	37.0 ± 8.4 (17-50)
Cirrhosis	37.0 ± 11.5 (19-56)
CRD**	39.4 ± 9.7 (19-59)

*Acute chest syndrome †Chronic obstructive pulmonary disease ‡Pulmonary hypertension §Coronary heart disease ¶Deep venous thrombosis **Chronic renal disease

Discussion

Excess fat tissue may be the most significant cause of vasculitis in human body. DM may actually be one of the atherosclerotic endpoints in human being. Although all of the atherosclerotic endpoints are frequent in the SCD, we have not detected any case of DM, probably due to the significantly lower mean body mass indexes (BMI) (10). The mean body weights and BMI were 57.8 vs 71.6 kg and 20.7 vs 24.9 kg/m2 in the SCD and control cases, respectively with the mean age of 28.6 years (p= 0.000 for both) (10). Additionally, the heaviest patient was 83 kg in weight in the SCD whereas 111 kg in the control groups (p= 0.000) (10). Interestingly, the mean body heights were similar in both groups (166.1 vs 168.5 cm, respectively, p>0.05) which may powerfully indicate that body height is determined, genetically (10). Similarly, just 20% of elderly have DM, but 55% of patients with DM are obese. So excess fat tissue may be much more significant than smoking, alcohol, or other chronic inflammatory or infectious processes for systemic atherosclerosis. Excess fat tissue leads to a chronic and low-grade inflammation on vascular endothelium, and risk of death from all causes increases parallel to the range of excess fat tissue (19). The low-grade chronic inflammation may also cause genetic changes on the endothelial cells, and the systemic atherosclerosis may even decrease the clearance of malignant cells by the natural killers terminating with the cancers (20). The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity (21, 22). Excess fat tissue is considered as a strong factor for controlling of C-reactive protein (CRP) because the fat tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines (23, 24). On the other hand, excess fat tissue will also aggravate myocardial hypertrophy and decrease cardiac compliance further. Fasting plasma glucose (FPG) and serum cholesterol increased and high density lipoproteins (HDL) decreased parallel to the increased BMI (25). Similarly, the prevalences of CHD and stroke increased parallel to the increased BMI (26). Eventually, the risk of death from all causes increased parallel to the severity of excess fat tissue in all age groups, and the cases with underweight may even have lower biological ages and longer survival (27). Similarly, calorie restriction prolongs survival and retards age-related chronic illnesses in human being (28).

Smoking may be the second most common cause of vasculitis all over the body. It may cause a systemic inflammation on vascular endothelium terminating with atherosclerotic end-organ insufficiencies in early decades (29). Its atherosclerotic effect is obvious in the Buerger's disease and COPD (30). Buerger's disease is an obliterative vasculitis in the small and medium-sized arteries and veins, and it has never been reported in the absence of smoking. Its characteristic features are chemical toxicity, inflammation, fibrosis, and narrowing and occlusions of arteries and veins. Claudication is the most significant symptom with a severe pain in feet and hands caused by insufficient blood supply, particularly by walking in the feet. It typically begins in extremities but may also radiate to central areas in advanced cases. Numbness or tingling of the limbs is also common. Skin ulcerations and gangrene of fingers or toes are the irreversible endpoints. Similar to the venous ulcers, diabetic ulcers, leg ulcers of the SCD, digital clubbing, onychomycosis, and delayed wound and fracture healings of the lower extremities, pooling of blood due to the gravity may be the major cause in the development of Buerger's disease, particularly in the lower extremities. Multiple narrowing and occlusions in the arm and legs are diagnostic in the angiogram. Skin biopsies may be risky, because a poorly perfused area will not heal, completely. Although most patients are heavy smokers, the limited smoking history of some patients may support the hypothesis that Buerger's disease may be an autoimmune reaction triggered by some constituent of tobacco. Although the only treatment way is complete cessation of smoking, the already developed narrowing and occlusions are irreversible. Due to the well-known role of inflammation, anti-inflammatory dose of aspirin in addition to the low-dose warfarin may be beneficial in prevention of microvascular infarctions. On the other hand, FPG and HDL may be negative whereas triglycerides, low density lipoproteins (LDL), erythrocyte sedimentation rate, and CRP positive APR in smokers (31). Similarly, smoking was associated with the lower BMI values due to the systemic inflammatory effects (32, 33). An increased heart rate was detected just after smoking even at rest (34). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (35). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (36). Smoking may be associated with a postcessation weight gain, but the risk is the highest during the first year, and decreases with the following years (37). Although the CHD was detected with similar prevalences in both genders, prevalences of smoking and COPD were higher in males against the higher white coat hypertension, BMI, LDL, triglycerides, HT, and DM in females (38). The risk of myocardial infarction is increased three-fold in men and six-fold in women with smoking, so smoking may be more harmful for women probably due to the higher BMI in them (39). Chemical toxicity of smoking can affect various organ systems. For instance, it is usually associated with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis with several possible mechanisms (40). First of all, smoking may have some anxiolytic properties. Secondly, smoking-induced vascular inflammation may disturb epithelial absorption and excretion in the gastrointestinal (GI) and genitourinary (GU) tracts (41). Thirdly, diarrheal losses-induced urinary changes may cause urolithiasis (42). Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the GI and GU tracts terminating with IBS and urolithiasis. Finally, immunosuppression secondary to smoking may terminate with the GI and GU tract infections and urolithiasis since some types of bacteria can provoke urinary supersaturation, and modify the environment to form crystal deposits. Actually, 10% of urinary stones are struvite stones which are built by magnesium ammonium

phosphate produced by the urease producing bacteria. As a result, urolithiasis was seen in 17.9% of cases with IBS and 11.6% of cases without (p<0.01) (40).

CHD is the other major cause of death in the human being together with the stroke. The most common triggering cause is the disruption of an atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade. The plaques are the gradual and unstable collection of lipids, fibrous tissue, and white blood cells (WBC), particularly the macrophages in arterial walls in decades of life. Stretching and relaxation of arteries with each heart beat increases mechanical shear stress on atheromas to rupture. After the myocardial infarction, a collagen scar tissue takes its place which may also cause life threatening arrhythmias because the scar tissue conducts electrical impulses more slowly. The difference in conduction velocity between the injured and uninjured tissues can trigger re-entry or a feedback loop that is believed to be the cause of lethal arrhythmias. Ventricular fibrillation is the most serious arrhythmia that is the leading cause of sudden cardiac death. It is an extremely fast and chaotic heart rhythm. Ventricular tachycardia may also cause sudden cardiac death that usually results in rapid heart rates preventing effective cardiac pumping. Cardiac output and BP may fall to dangerous levels which can lead to further coronary ischemia and extension of the infarct. This scar tissue may even cause ventricular aneurysm and rupture. Aging, physical inactivity, animal-rich diet, excess fat tissue, smoking, alcohol, emotional stress, prolonged infection, chronic inflammation, and cancers are important in atherosclerotic plaque formation. Moderate physical exercise is associated with a 50% reduced incidence of CHD (43). Probably, excess fat tissue may be the most important cause of CHD since there are nearly 20 kg of excess fat between the lower and upper borders of normal weight, 33 kg between the obesity, 66 kg between the morbid obesity (BMI ≥ 40 kg/m2), and 81 kg between the super obesity (BMI ≥ 45 kg/m2) in adults. In fact, there is a huge percentage of adults with heavier fat masses than their lean masses that brings a heavy stress both on the heart and brain.

Type 2 DM is the most common cause of blindness, non-traumatic amputation, and renal dialysis in adults. It is probably caused by insulin deficiency, insulin resistance, defective insulins, and/or defective insulin receptors. But excess fat tissue probably takes the major role in the development. Excess fat tissue in liver and pancreas are called as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic fatty pancreas disease (NAFPD). They are usually accepted as components of the metabolic syndrome. NAFLD progresses to steatohepatitis, cirrhosis, hepatocellular carcinoma, and hepatic failure. Blocking triglycerides secretion, subcellular lipid sequestration, lipolysis deficiency, enhanced lipogenesis, gluconeogenesis defects, or inhibition of fatty acid oxidation may be some of the development mechanisms (44). NAFLD may just be one of the atherosclerotic endpoints, and it is strongly associated with an accelerated atherosclerotic process not only in the liver instead all over the body. For example, NAFLD is seen in one-third of cases with hepatitis B virus-related chronic liver disease (45). Similarly, higher fatty liver ratios were observed in children with non-Hodgkin lymphomas (46). The liver density on contrast abdominopelvic CT of colorectal cancer patients was low which is consistent with NAFLD (47). As one of the acute phase reactants (APR), serum thrombopoietin levels increased in cases with NAFLD (48). Although serum levels of oxidizing agents including nitrate and advanced oxidation protein products increased, serum nitrite did not adequately increase as an antioxidant agent in cases with NAFLD (49). As a result, NAFLD is associated with an impaired carotid intima-media thickness (IMT) and flow-mediated dilation which are considered as early markers of systemic atherosclerosis (50). Carotid IMT was correlated with the BMI (p<0.001), age (p= 0.001), and grade 2-3 NAFLD (p<0.001) (51). Patients with NAFLD have more complex CHD, and carotid IMT and grade 2-3 NAFLD were associated with the severity of CHD (p<0.001 for both) (51-53). Similarly, there were reductions in hepatic artery flow volume, portal vein flow volume, and total flow volume in contrast to the increased NAFLD (54). Parallel to the liver, there may be reductions in blood flow volume of pancreatic arteries in NAFPD which is the most common benign pathologic condition of pancreas in adults (55). NAFPD is frequently related with the aging, obesity, and insulin resistance (56). Replacement of more than 25% of pancreas by fat tissue is associated with systemic atherosclerosis and increased risk of type 2 DM (57). Insulin is stored in vacuoles in beta cells of islets of Langerhans all over the pancreas and released via exocytosis. Pancreatic fat infiltration may lead to a reduced insulin secretion (58). NAFPD can lead to exocrine pancreatic insufficiency by fat droplet accumulation in pancreatic acinar cells and consequent lipotoxicity, destruction of acinar cells by both inflammation and fatty replacement, and by negative paracrine effect of adipocytes (59). It may cause pancreatic fibrosis and cancers. The patients with NAFPD have a higher risk of type 2 DM (57), and newly diagnosed patients with type 2 DM have significantly greater pancreatic fat content (60). Type 2 DM may actually be the pancretic fibrosis and cirrhosis. Age-related impairment of beta cells may actually be one of the atherosclerotic endpoints since 20% of elderly have type 2 DM, and just 55% of patients with type 2 DM are obese. Glucose tolerance progressively decreases with aging. It may be due to the progressively decreased physical and mental activity-induced excess fat tissue secreting adipokines. There is no term of malnutrition-related DM in the literature. Type 2 DM can be cured by gastric bypass surgery in 90% of morbid obese patients (61). The effect is not due to the weight loss instead decreased insulin requirement since it usually occurs just after days of surgery. This surgery reduced death rate from all causes by 40% (61). NAFPD is an independent risk factor for CHD, too (62). Similarly, the presence of NAFPD is associated with increased aortic IMT and epicardial adipose tissue (63). According to our opinion, NAFLD, cirrhosis, NAFPD, and DM may just be some of the atherosclerotic endpoints (64).

Acute painful crises are the severest symptoms of the SCD. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stresses are the most common precipitating factors of the crises (65). The increased basal metabolic rate during such stresses aggravates the sickling and capillary endothelial damage, inflammation, and edema terminating with tissue hypoxia and multiorgan insufficiencies. So the risk of mortality is much higher during such crises. Actually, each crisis may complicate with the following crises by leaving significant sequelaes on the capillary endothelial system all over the body. After a period of time, the sequelaes may terminate with multiorgan failures and sudden death with an acute painful crisis that may even be silent, clinically. Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCD. Unfortunately, most of the deaths develop just after the hospital admission, and majority of them are patients without hydroxyurea therapy (66, 67). Rapid RBC supports are usually life-saving for such patients, although preparation of RBC units for transfusion usually takes time. Beside that RBC supports in emergencies become much more difficult in terminal cases due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBC complicates the following transfusions by means of the blood subgroup mismacth. Due to the significant efficacy of hydroxyurea therapy, RBC transfusions should be kept just for acute events and emergencies in the SCD (66-68). According to our experiences, simple and repeated transfusions are superior to RBC exchange (69, 70). First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk patients. Secondly, transfusions of one or two units of RBC suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their relatives since RBC transfusions probably have the strongest analgesic effects during such crises (71). Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation all over the body. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of the simple transfusions will decrease transfusion-related complications including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary centers for the exchange. Terminally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that needs trained staff and additional devices. On the other hand, pain is the result of complex and poorly understood interactions between RBC, WBC, platelets (PLT), and endothelial cells, yet. Probably, leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes. The adverse effects of WBC on vascular endothelium are of particular interest for atherosclerotic endpoints in the SCD. For instance, leukocytosis even in the absence of any infection was an independent predictor of the severity of the SCD (72), and it was associated with the risk of stroke (73). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Due to the severity of pain, narcotic analgesics are usually required (74), but according to our experiences, simple and repeated RBC transfusions may be highly effective both to relieve pain and to prevent sudden deaths which may develop secondary to multiorgan failures on the atherosclerotic endpoints of the SCD.

Hydroxyurea may be one of the life-saving drugs for the treatment of the SCD at the moment. It interferes with the cell division by blocking the formation of deoxyribonucleotides via inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action may be the suppression of leukocytosis and thrombocytosis by blocking the DNA synthesis in the SCD (75, 76). By this way, the chronic inflammatory and destructive process of the SCD is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As in the viral hepatitis cases, although presence of a continuous damage of sickle cells on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' own WBC and PLT. So suppression of proliferation of them may limit the endothelial cells damage-induced edema, ischemia, and infarctions all over the body (77). Similarly, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels (78). The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with the SCA, and compared the results of patients treated with hydroxyurea or placebo (79). The study particularly researched effects of hydroxyurea on painful crises, ACS, and requirement of blood transfusion. The outcomes were so overwhelming in the favour of hydroxyurea group that the study was terminated after 22 months, and hydroxyurea was initiated for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations (79). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (79). But this study was performed just in severe SCA cases alone, and the rate of painful crises was decreased from 4.5 to 2.5, annually (79). Whereas we used all subtypes of the SCD with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7, annually ($p<0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p<0.000$) (66). Parallel to us, adult patients using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period (80). Although the underlying disease severity remains critical to determine prognosis, hydroxyurea may also decrease severity of disease and prolong survival (80).

The complications start to be seen even in infancy in the SCD. For example, infants with lower hemoglobin values were more likely to have higher incidences of ACS, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them (81). If started in early years, hydroxyurea may protect splenic function, improve growth, and delay atherosclerotic endpoints. Although RBC transfusions can also reduce the complications, there are the risks of infections, iron overload, and development of allo-antibodies causing subsequent transfusions much more difficult. Thus RBC transfusions should be kept just for emergencies as the most effective weapon at the moment.

Aspirin is a member of nonsteroidal anti-inflammatory drugs (NSAID). Although aspirin has similar anti-inflammatory effects with the other NSAID, it also suppresses the normal functions of PLT, irreversibly. This property causes aspirin being different from other NSAID, which are reversible inhibitors. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase (COX) enzyme. Aspirin inactivates the COX enzyme, irreversibly, which is required for the synthesis of prostaglandins (PG) and thromboxanes (TX). PG are the locally produced hormones with some diverse effects, including the transmission of pain into the brain and modulation of the hypothalamic thermostat and inflammation. TX are responsible for the aggregation of PLT to form blood clots. In another definition, low-dose aspirin irreversibly blocks the formation of TXA2 in the PLT, producing an inhibitory effect on the PLT aggregation during whole lifespan of the affected PLT (8-9 days). Since PLT do not have nucleus and DNA, they are unable to synthesize new COX enzyme once aspirin has inhibited the enzyme. But aspirin does not decrease the blood viscosity. The antithrombotic property of aspirin is useful to reduce the risks of myocardial infarction, transient ischemic attack, and stroke (82). Heart attacks are caused primarily by blood clots, and low-dose of aspirin is seen as an effective medical intervention to prevent a second myocardial infarction (83). According to the literature, aspirin may also be effective in prevention of colorectal cancers (84). On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Due to the risk of Reye syndrome, the US Food and Drug Administration recommends that aspirin should not be prescribed for febrile patients under the age of 12 years (85). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (86). Reye syndrome is a rapidly worsening brain disease (86). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (87). The syndrome mostly affects children, but it can only affect fewer than one in a million children, annually (87). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (86). Although the liver toxicity and enlargement typically occurs in most cases, jaundice is usually not seen (86). Although the death occurs in 20-40% of affected cases, about one third of survivors get a significant degree of brain damage (86). It usually starts just after recovery from a viral infection, such as influenza or chicken pox. About 90% of cases in children are associated with an aspirin use (87, 88). Inborn errors of metabolism are also the other risk factors, and the genetic testing for inborn errors of metabolism became available in developed countries in the 1980s (86). When aspirin use was withdrawn for children in the US and UK in the 1980s, a decrease of more than 90% in rates of Reye syndrome was seen (87). Due to the very low risk of Reye syndrome but much higher risk of death due to the SCD in children, aspirin should be added both into the acute and chronic phase treatments with an anti-inflammatory dose even in childhood in the SCD (89).

Warfarin is an anticoagulant, and it does not have any effect on blood viscosity, too. It can prevent formation of blood clots and reduce the risk of thromboembolism. Warfarin is the best suited for anticoagulation in areas of slowly flowing blood such as veins and the pooled blood behind artificial and natural valves and dysfunctional cardiac atria. It is commonly used to prevent blood clots formation as in DVT and pulmonary embolism, and to protect against stroke in atrial fibrillation (AF), valvular heart disease, and artificial heart valves. Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery. The warfarin initiation regimens are simple, safe, and suitable to be used in the ambulatory settings (90). Warfarin should be initiated with a 5 mg dose, or 2 to 4 mg in the elderlies. In the protocol of low-dose warfarin, the target international normalised ratio (INR) value is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR value is between 2.5 and 3.5 (91). When warfarin is used and INR is in therapeutic range, simple discontinuation of the drug for five days is enough to reverse the effect, and causes INR to drop below 1.5 (92). Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability. The anticlotting protein C and protein S are also inhibited, but to a lesser degree. A few days are required for full effect, and these effects can last for up to five days. The consensus agrees that current self-testing and management devices are effective methods of monitoring oral anticoagulation therapy, providing outcomes possibly better than achieved, clinically. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is just 1-3%, annually (93). All types of bleeding may occur, but the severest ones are those involving the central nervous system (92). The risk is particularly increased once the INR exceeds 4.5 (93). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (94). Thirteen publications

from 11 cohorts including more than 48.500 patients with more than 11.600 warfarin users were included in the meta-analysis in which in patients with AF and non-end-stage CRD, warfarin resulted in a lower risk of ischemic stroke (p= 0.004) and mortality (p<0.00001), but had no effect on major bleeding (p>0.05) (95). Similarly, warfarin is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (96). Whereas recurrent ICH occured in 6.7% of patients who used warfarin and 7.7% of patients who did not use warfarin (p>0.05) (96). On the other hand, patients with cerebral venous thrombosis (CVT) anticoagulated either with warfarin or dabigatran had lower risk of recurrent venous thrombotic events (VTE), and the risks of bleeding were similar in both regimens (97). Additionally, an INR value of 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted with no increase in the number of men ever reporting minor bleeding episodes (98). Non-rheumatic AF increases the risk of stroke, presumably from atrial thromboemboli, and long-term use of low-dose warfarin is highly effective and safe with a reduction of 86% in the risk of stroke (p= 0.0022) (99). The mortality rate was markedly lower in the warfarin group, too (p= 0.005) (99). The frequencies of bleedings that required hospitalization or transfusion were similar in both groups (p>0.05) (99). Additionally, very-low-dose warfarin was safe and effective for prevention of thromboembolism in metastatic breast cancer in which the average daily dose was 2.6 mg, and the mean INR value was 1.5 (100). On the other hand, new oral anticoagulants had a favourable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleedings as for warfarin, but increased GI bleeding (101). Interestingly, rivaroxaban and low-dose apixaban were associated with increased risks of all cause mortality compared with warfarin (102). The mortality rates were 4.1%, 3.7%, and 3.6% per year in the warfarin, 110 mg of dabigatran, and 150 mg of dabigatran groups, respectively (p>0.05 for both) with AF in another study (103). On the other hand, infection, inflammation, medical or surgical emergency, and emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction or stroke may cause sudden deaths (104). So anti-inflammatory dose of aspirin plus low-dose warfarin may be the other life-saving regimen to decrease severity of capillary endothelial inflammation, and to prevent atherosclerotic endpoints even at childhood in the SCD (105).

COPD is the third leading cause of death in human being (106, 107). Aging, smoking, alcohol, male gender, excess fat tissue, chronic inflammation, prolonged infection, and cancers may be the major causes. Atherosclerotic effects of smoking may be the most obvious in the COPD and Buerger's disease, probably due to the higher concentrations of toxic substances in the lungs and pooling of blood in the extremities. After smoking, excess fat tissue may be the second common cause of COPD due to the excess fat tissue-induced atherosclerotic endpoints all over the body. Regular alcohol consumption may be the third leading cause of the systemic accelerated atherosclerotic process and COPD, since COPD was one of the most common diagnoses in alcohol dependence (108). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (109). Probably an accelerated atherosclerotic process is the main structural background of functional changes that are characteristics of the COPD. The inflammatory process of vascular endothelial cells is exaggerated by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may actually be the pulmonary endpoint of the systemic atherosclerotic process. Beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body in COPD (110). For instance, there may be close relationships between COPD, CHD, PAD, and stroke (111). Furthermore, two-third of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5.887 smokers (112). When hospitalizations were researched, the most common causes were the cardiovascular diseases, again (112). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (113). Finally, COPD may be the pulmonary endpoint of the accelerated atherosclerotic process in the SCD (106).

Leg ulcers are seen in 10% to 20% of the SCD (114). Its prevalence increases with aging, male gender, and SCA (115). The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (114). Similar to Buerger's disease, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow (114). The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes (115). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened RBC-induced venous insufficiencies may also accelerate the process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also be important for the development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood may be the cause of delayed wound and fracture healings in the lower extremities. Smoking and alcohol may also have some additional atherosclerotic effects on the leg ulcers in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCD (116). It is an oral, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (11). Its main action may be the suppression of hyperproliferative WBC and PLT in the SCD (117). Although presence of a continuous damage of hardened RBC on vascular endothelial cells, severity of the destructive process is probably exaggerated by the immune system. Similarly, lower WBC counts were associated with lower crisis rates, and if a tissue infarct

occurs, lower WBC counts may decrease severity of tissue damage and pain (78). Prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBC and PLT counts-induced exaggerated capillary endothelial cell inflammation and edema.

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (118). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (119). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, clubbing is frequently associated with the pulmonary, cardiac, renal and hepatic diseases, and smoking those are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect their functions in a short period of time. On the other hand, clubbing is also common in the SCD with a prevalence of 10.8% in the present study, too. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, edema, and fibrosis, particularly at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of clubbing in males (14.8% vs 6.6%, $p<0.001$) may also indicate some additional role of male gender about the atherosclerotic endpoints.

CRD is also increasing that can also be explained by aging of the human being and increased prevalence of excess weight all over the world (120). Aging, animal-rich diet, excess fat tissue, smoking, alcohol, inflammatory or infectious processes, and cancers may be the major causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarcts (121). Excess fat tissue-induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance can cause tissue inflammation and immune cell activation (122). For instance, age ($p= 0.04$), high-sensitivity CRP ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT (120). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess fat tissue (123). Excess fat tissue also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (123). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (124). With prolonged excess fat tissue, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM, CRD progresses much more easily (123). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (125). Although some authors reported that alcohol was not related with the CRD (125), various metabolites of alcohol circulate in blood vessels of kidneys and give harm to the endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature (124). Due to the systemic nature of atherosclerosis, there are close relationships between CRD and other atherosclerotic endpoints of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (126, 127). For example, the most common causes of death were the CHD and stroke in the CRD, again (128). The hardened RBC-induced capillary endothelial damage cell may be the major cause of CRD in the SCD, again (129).

Stroke is the other terminal cause of death, together with the CHD, and it develops as an acute thromboembolic event on the chronic atherosclerotic background. Aging, male gender, smoking, alcohol, excess fat tissue, chronic inflammatory or infectious processes, cancers, and emotional stress may be the major underlying causes. Stroke is also a common atherosclerotic endpoint of the SCD (130). Similar to the leg ulcers, stroke is particularly higher in cases with the SCA and higher WBC counts (131). Sickling-induced capillary endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic capillary endothelial cell damage, inflammation, edema, and fibrosis (132). Probably, stroke does not have a macrovascular origin in the SCD, and acute onset diffuse capillary endothelial cell damage, inflammation, and edema may be much more significant. Eventually, permanent neurological deficits of stoke are rare in cases with the SCD. Infection, inflammation, medical or surgical emergency, and emotional stresses may precipitate stroke by increasing basal metabolic rate and sickling. Decreased stroke with hydroxyurea can also suggest that a significant proportion of cases is developed due to the increased WBC and PLT counts-induced an acute onset accelerated capillary endothelial cell edema in the SCD (133).

Acarbose is a pseudotetrasaccharide produced as a natural microbial product of Actinoplanes strain SE 50. It is an alpha-glucosidase inhibitor. Acarbose binds to oligosaccharide binding site of alpha-glucosidase enzymes in the brush border of the small intestinal mucosa with a dose-dependent manner, reversibly and competitively. It inhibits glycoamylase, sucrase, maltase, dextranase, and pancreatic alpha-amylase. It has little affinity for isomaltase but does not have any effect on beta-glucosidases such as lactase. By this way, it delays the intestinal hydrolysis of oligo- and disaccharides mainly in the upper half of the small intestine. As a result, the absorption of monosaccharides is delayed, and transport into the circulation is interrupted. Actually, it does not have

any direct effect on glucose absorption. It should be taken with the first bite of the meal, and its effects may prolong up to 5 hours. The suppression of alpha-glucosidases is persistent with long-term use without any treatment failure. Its usage results with carbohydrates appearing in the colon where bacterial fermentation occurs, accounting for the frequency and severity of GI adverse effects such as flatulence, loose stool, and abdominal discomfort (134). If started with a lower dosage and titrated slowly, it tends to cause tolerable GI side effects (135). Long-term use increases colonic bacterial mass that of lactobacteria in particular. The finally impaired carbohydrate absorption, increased bacterial carbohydrate fermentation, and fecal acidification mimic effects of lactulose in portosystemic encephalopathy. So acarbose has a favourable therapeutic profile for the long-term use even in cirrhosis. Similarly, observed changes in bacterial flora and decreased stool pH and beta-hydroxybutyrate may be associated with anti-proliferative effects on the epithelial cells of colon that may potentially decrease carcinogenesis. After oral administration, less than 2% of the unchanged drug enters into the circulation. Thus there is no need for dosage adjustment in mild renal insufficiency. After a high carbohydrate meal, acarbose lowers the postprandial rise in blood glucose by 20% and secondarily FPG by 15% (136). The initial improvement in blood glucose tends to be modest, but efficacy steadily improves with the long-term use, and is maintained over several years. Its beneficial effects on serum lipids were also seen with a dose-dependent manner (136), because dietary carbohydrates are key precursors of lipogenesis, and insulin plays a central role for postprandial lipid metabolism. Carbohydrate-induced postprandial triglycerides synthesis is reduced for several hours, so acarbose lowers plasma triglycerides levels (136). The same beneficial effect is also seen in non-diabetic patients with hypertriglyceridemia, and acarbose reduced LDL significantly, and HDL remained as unchanged in hyperinsulinemic and overweight patients with impaired glucose tolerance (IGT) (137). Significantly elevated ursocholic acids in the stool appear to be the additive endpoint of a decreased rate of absorption and increased intestinal motility due to the changes of intestinal flora. Acarbose may lower LDL via increased fecal bifido bacteria and biliary acids. Acarbose together with insulin was identified to be associated with a greater improvement in the oxidative stress and inflammation in type 2 DM (138). Probably, acarbose improves release of glucagon-like peptide-1, inhibits PLT activation, increases epithelial nitrous oxide synthase activity and nitrous oxide concentrations, promotes weight loss, decreases BP, and eventually prevents endothelial dysfunction (136). So it prevents all atherosclerotic endpoints of excess fat even in the absence of IGT or DM (139-141). Although some authors reported as opposite (142), it should be used as the first-line antidiabetic agent. Based on more than 40 years of use, numerous studies did not show any significant side effect or toxicity (143).

Metformin is a biguanide, and it is not metabolized, and 90% of absorbed drug is eliminated as unchanged in the urine. Plasma protein binding is negligible, so the drug is dialyzable. According to literature, antihyperglycemic effect of metformin is largely caused by inhibition of hepatic gluconeogenesis, increased insulin-mediated glucose disposal, inhibition of fatty acid oxidation, and reduction of intestinal glucose absorption (144, 145). Precise mechanism of intracellular action of metformin remains as unknown. Interestingly, 25.9% of patients stopped metformin due to the excessively lost appetite (146). Additionally, 14.1% of patients with overweight or obesity in the metformin group rose either to normal weight or overweight group by weight loss without a diet regimen (146). According to our opinion, the major effect of metformin is a powerful inhibition of appetite. Similar results indicating the beneficial effects on the BMI, BP, FPG, and lipids were also reported (147-149). Probably the major component of the metabolic syndrome may be excess fat tissue and its atherosclerotic endpoints which can be prevented by suppression of appetite. So treatment of excess fat tissue with metformin will probably prevent not only the IGT or DM but also most of the other atherosclerotic consequences. Because of the low risk of side effects, metformin can be initiated for majority of cases with excess fat, but clinicians must be careful above the age of 70 years due to risks of debility induced weight loss. Although 25.9% of patients stopped metformin due to an excessive anorexia (146), only 10.6% stopped acarbose due to an excessive flatulence or loose stool (150). So acarbose intolerance is lower than metformin in the society ($p<0.001$) (146). Finally, acarbose can be used in a larger population than metformin, and we should not put a lower limit of age to start acarbose for cases with excess fat.

As a conclusion, hardened RBC-induced capillary endothelial damage initiated at birth terminates with multiorgan insufficiencies in early decades of life in the SCD. DM may actually be one of the atherosclerotic endpoints of the pancreas. Although all of the above atherosclerotic endpoints are frequent in the SCD, we have not detected any case of DM probably due to the significantly lower BMI of them. Similarly, just 20% of elderly have DM, but 55% of patients with DM are obese. So excess fat tissue may be much more significant than smoking, alcohol, or other chronic inflammatory or infectious processes for the systemic atherosclerosis. Acarbose and metformin are safe, cheap, oral, long-term used, and effective drugs for loss of excess fat tissue.

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Neurobiology of dementia

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Abstract

Dementia encompasses a group of progressive neurodegenerative disorders marked by cognitive, behavioural, and functional decline, underpinned by complex neurobiological processes. This chapter outlines the anatomical, cellular, and molecular mechanisms that drive disease onset and progression. Structural vulnerability of the hippocampus, cerebral cortex, white matter, and cognitive networks underlies characteristic clinical manifestations. At the microscopic level, neuro-inflammation, mitochondrial dysfunction, oxidative stress, excitotoxicity, impaired protein clearance, and synaptic loss converge to promote neuronal injury. Distinct proteinopathies—including amyloid-β plaques and tau tangles in Alzheimer's disease, α-synuclein inclusions in Lewy body dementia, and TDP-43 or tau aggregates in frontotemporal lobar degeneration—define specific dementia subtypes, yet share overlapping cascades of pathology. Vascular contributions, such as ischemia, hypoperfusion, and blood–brain barrier disruption, further compound neuronal vulnerability, highlighting the prevalence of mixed dementias. Collectively, these mechanisms illustrate dementia as a multifactorial disorder of network disintegration and cellular stress. Advancing insights into these processes are driving the development of biomarkers and disease-modifying therapies, paving the way for more precise, personalized approaches to diagnosis and care.

Introduction

Dementia represents a constellation of progressive neurodegenerative disorders characterized by cognitive, behavioural, and functional decline. While clinical syndromes often overlap, advances in neurobiology have elucidated diverse yet interconnected molecular, cellular, and anatomical mechanisms driving disease onset and progression. A unified understanding of dementia's neurobiology is crucial for refining diagnostic accuracy, developing biomarkers, and targeting novel therapeutic interventions.

The symptoms of dementia vary from person to person and may include memory problems or mood changes or difficulty walking, speaking or finding their way. While dementia may include memory loss, memory loss by itself does not mean that a person has dementia. While some mild changes in cognition are considered a part of the normal aging process, dementia is not.

This chapter delves into the fundamental aspects of brain anatomy, cellular and molecular pathophysiology, and specific proteinopathies that characterize various forms of dementia.

Brain Anatomy

The human brain, a marvel of biological engineering, orchestrates all our thoughts, emotions, and actions. Its intricate structure comprises various specialized regions, each contributing to specific cognitive functions and behaviour [1]. Dementia typically involves damage to these regions and their interconnected networks.

• **Cerebral Cortex:** The outermost layer of the brain, is responsible for higher-level functions such as memory, language, perception, and executive functions. Different lobes (frontal, parietal, temporal, occipital) contribute distinctively to these processes. Damage here often manifests as prominent cognitive deficits.

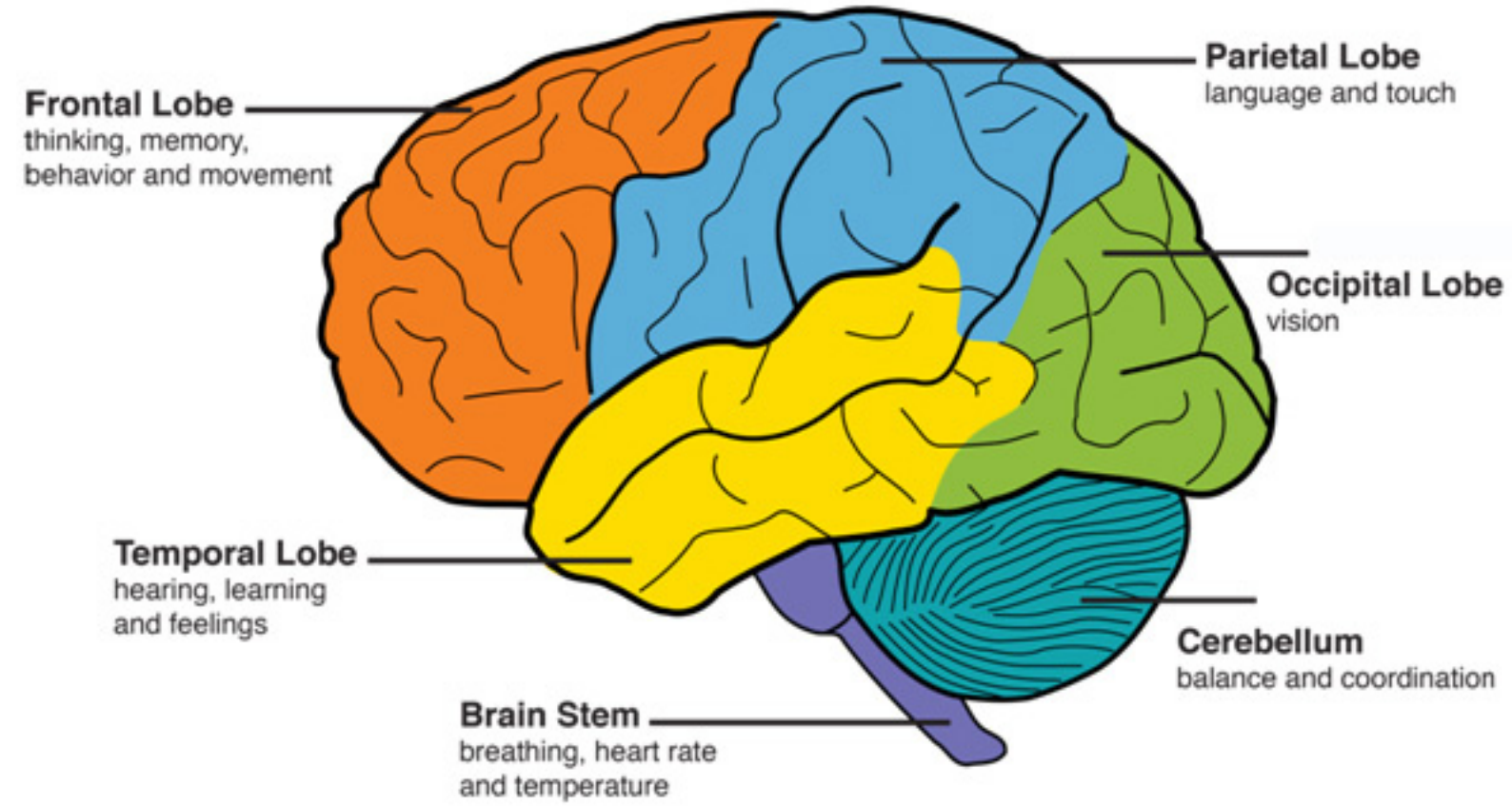

Figure 2.1: A detailed diagram of the human brain

• **Hippocampus:** Located within the temporal lobe, this seahorse-shaped structure is critical for the formation of new memories (episodic and spatial). Its degeneration is a hallmark of Alzheimer's disease, leading to classic memory impairment.

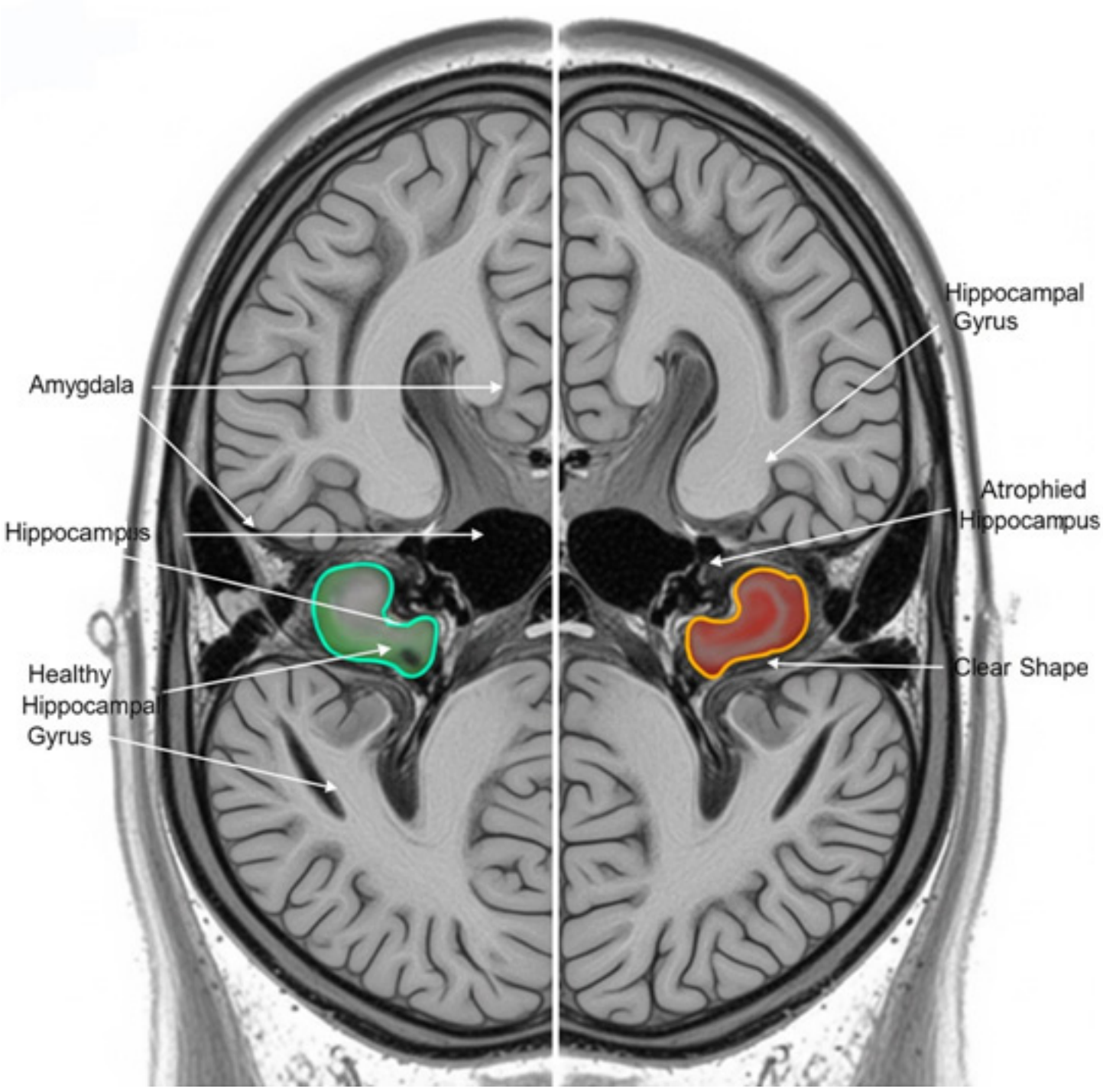

Figure 2.2: An anatomical illustration or an MRI slice clearly showing the location of the hippocampus within the temporal lobe, perhaps comparing a healthy hippocampus to an atrophied one.

• Basal Ganglia: **A group of subcortical nuclei involved in motor control, learning, and executive functions. Dysregulation** here can contribute to motor symptoms seen in some dementias, such as Parkinson's disease dementia and Lewy Body Dementia.

• **Thalamus:** A relay station for sensory and motor information, also playing a role in consciousness and alertness.

• **White Matter:** Composed of myelinated axons, forming communication pathways between different brain regions. Damage to white matter, often seen in vascular dementia, disrupts these vital connections, leading to widespread cognitive decline.

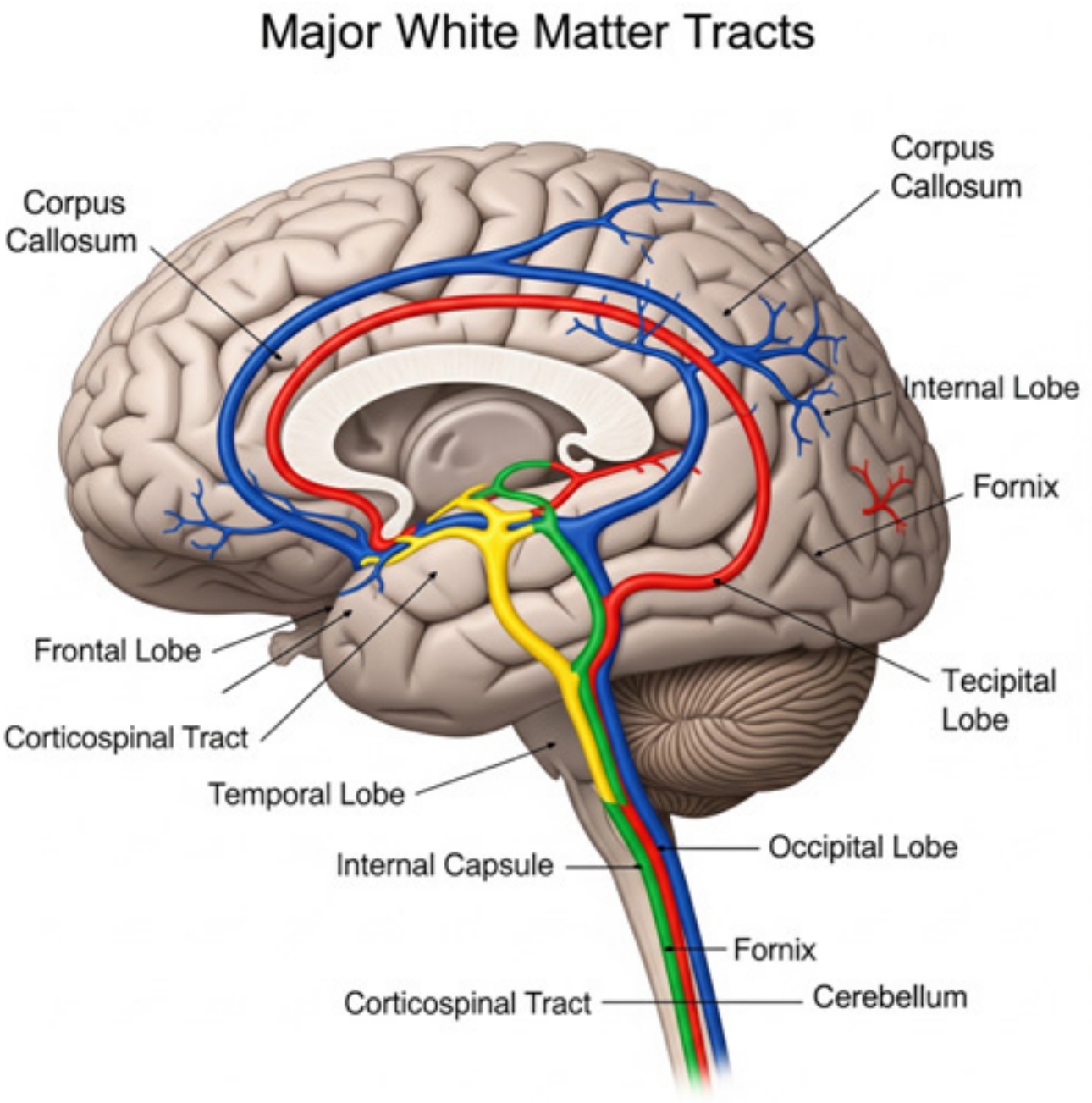

Figure 2.3: A diagram illustrating major white matter tracts (e.g., corpus callosum, internal capsule) and how they connect different brain regions.

The Key areas affected in dementia are shown in Table 1:

Table 1: Brain Regions and Their Roles in Dementia

Brain Region	Primary Function	Impact in Dementia
Hippocampus	Memory formation and consolidation	Early atrophy in Alzheimer's disease (AD), leading to episodic memory loss [2].
Cerebral Cortex	Higher cognitive functions (language, decision-making)	Degeneration causes aphasia, apraxia, and executive dysfunction [3].
Basal Forebrain	Cholinergic neurotransmission	Loss of acetylcholine-producing neurons contributes to memory deficits [4].
Frontal & Temporal Lobes	Behaviour, personality, language	Atrophy in frontotemporal dementia (FTD) leads to disinhibition and speech deficits [5].
Thalamus	Sensory and motor signal relay	Disrupted connectivity contributes to cognitive slowing in vascular dementia (VaD) [6].
Striatum	Motor control and reward processing	Lewy body accumulation in LBD leads to parkinsonism and cognitive fluctuations [7].

Cognitive Networks

Cognitive processes rely on distributed brain networks rather than isolated regions. Neurodegeneration disrupts these networks, leading to specific clinical syndromes.

The default mode network (involved in self-referential thought and memory retrieval), the salience network (detecting important stimuli), and the central executive network (working memory and problem-solving) are particularly vulnerable in dementia, leading to characteristic cognitive profiles. Disruption of these networks underpins the disconnection syndrome often observed.

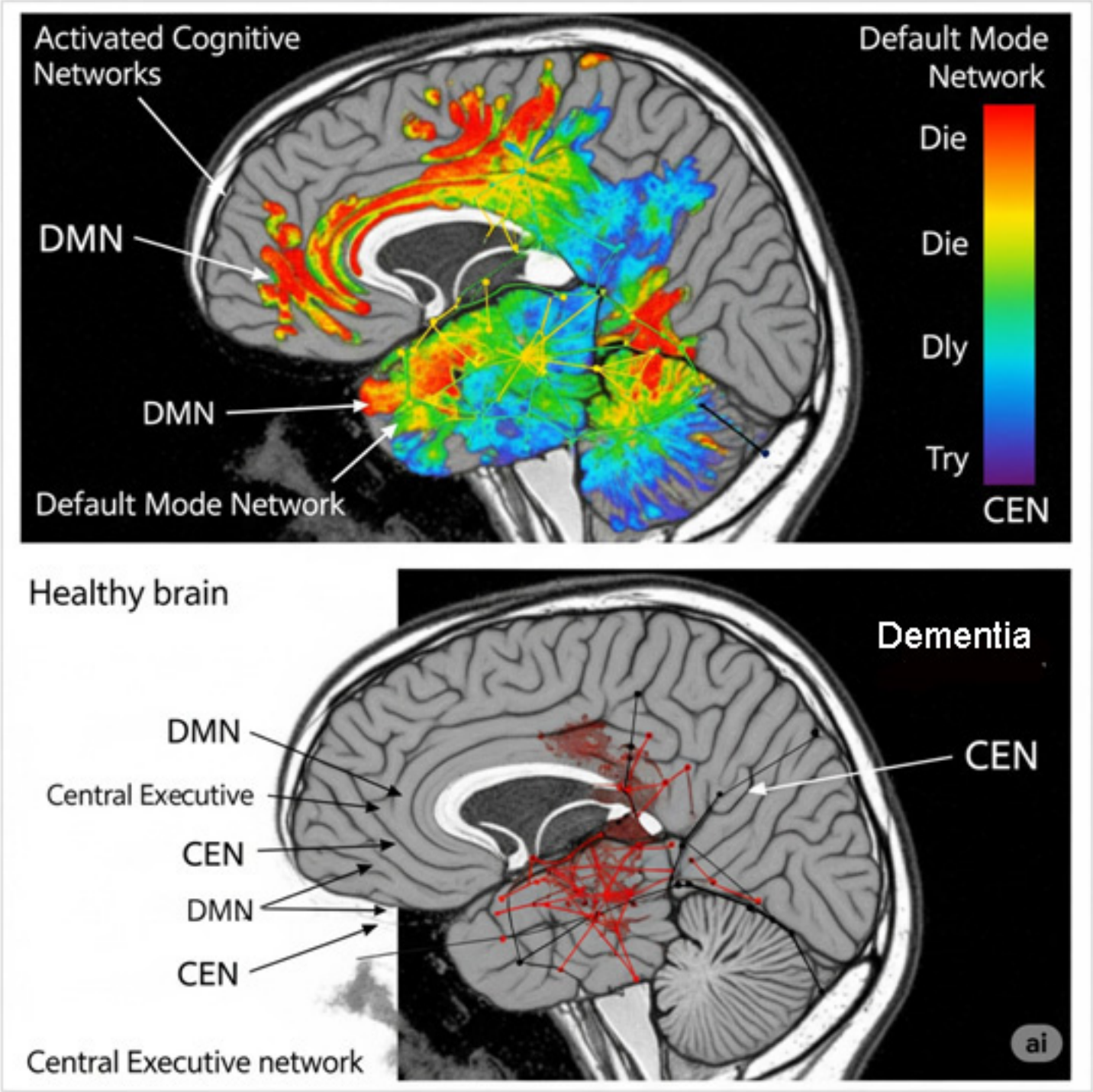

Figure 2.4: A functional MRI (fMRI) image depicting activated cognitive networks (e.g., default mode network, central executive network) and how their connectivity might be impaired in dementia.

Default Mode Network (DMN)
• Includes medial prefrontal cortex, posterior cingulate cortex, precuneus, and lateral parietal regions [8].
• Active during internally focused processes such as memory retrieval, future planning and self-referential thought.
• In Alzheimer's disease (AD), DMN regions show early amyloid deposition and hypometabolism on FDG-PET, correlating with episodic memory impairment [9,10].
Salience Network
• Anchored in anterior insula and anterior cingulate cortex [11].
• Detects and integrates emotionally or biologically significant stimuli.
• Dysregulated in behavioural variant frontotemporal dementia (bvFTD), contributing to impaired social cognition and emotional blunting [11].
Executive Control Network
• Frontal and parietal regions coordinate goal-directed behaviours, working memory, and problem-solving [12].
• Vulnerable in vascular cognitive impairment and subtypes of FTD.

Neuroimaging studies reveal network-specific disruptions that precede overt atrophy, offering potential early diagnostic biomarkers [13].

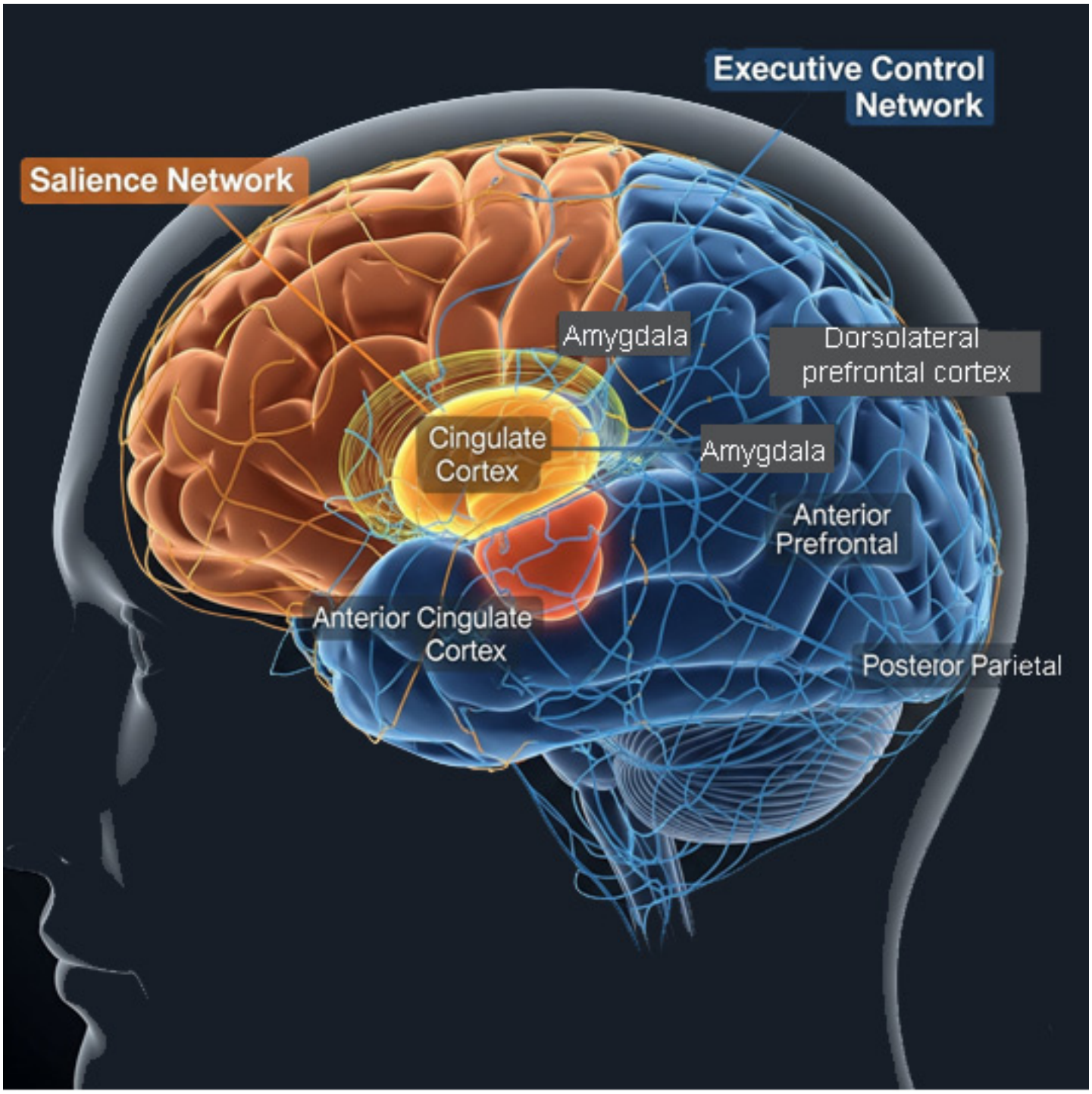

Figure 2.5: Salience and Executive control networks.

Cellular and Molecular Pathophysiology
At the microscopic level, dementia is characterized by a cascade of cellular and molecular events that ultimately lead to neuronal dysfunction and death. Neurodegeneration in dementia arises from multiple interacting pathways [14]:

Neuroinflammation
• Chronic activation of microglia and astrocytes leads to sustained production of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) [15].
• In AD, amyloid plaques act as persistent immune stimuli, perpetuating neuroinflammatory cascades.
• Neuroinflammation is increasingly recognized as a driver, rather than mere consequence, of neurodegeneration [16].

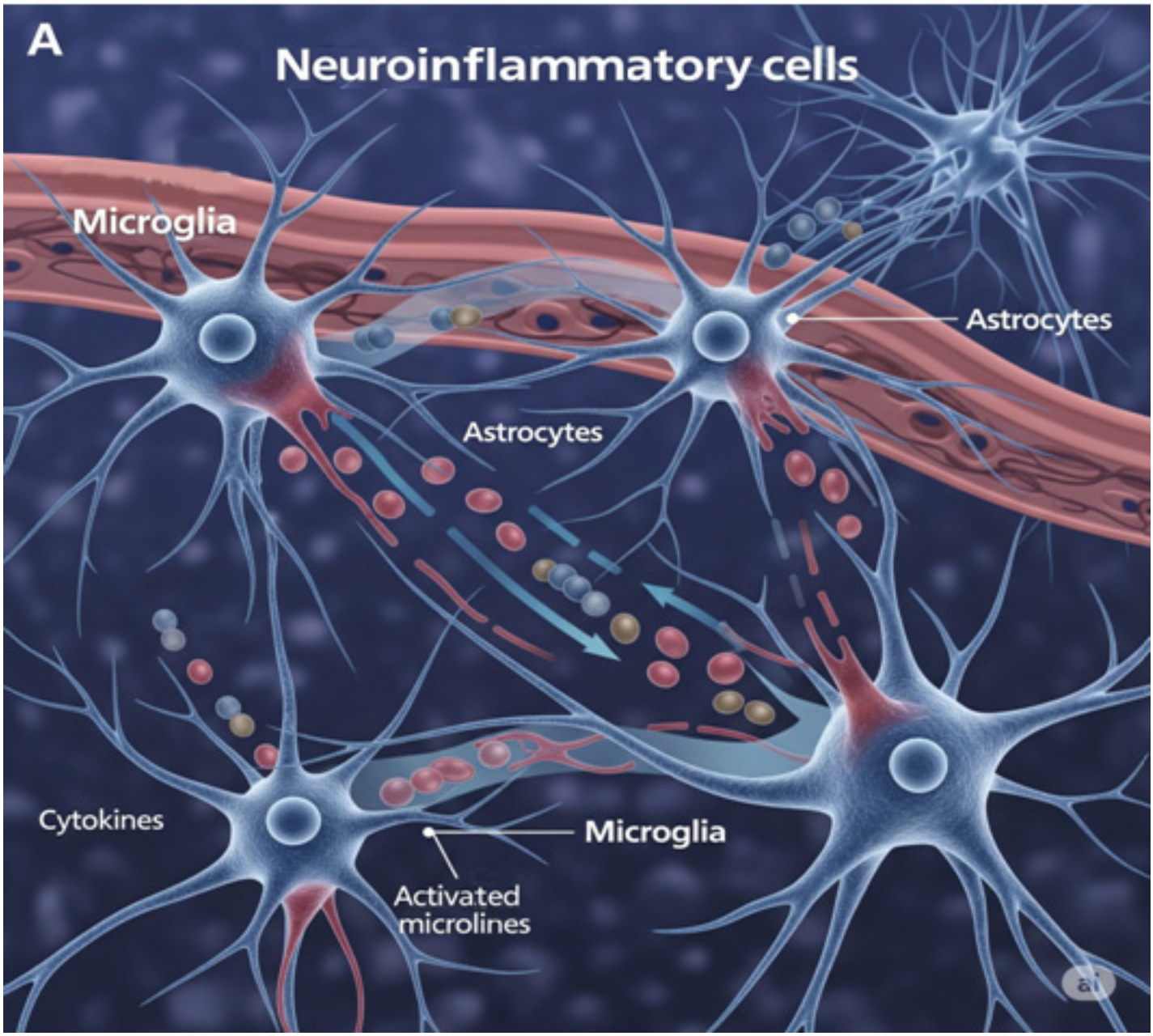

Figure 2.6: An illustration showing activated microglia and astrocytes (neuroinflammatory cells) in neural tissue, depicting their interaction with neurons and the release of inflammatory mediators.

Mitochondrial Dysfunction

Mitochondria, the powerhouses of the cell, are vital for neuronal energy production. Impaired mitochondrial function leads to energy deficits, increased oxidative stress, and ultimately, neuronal vulnerability and death. This is a common theme across various neurodegenerative diseases.

Oxidative Stress

• An imbalance between the production of reactive oxygen species (free radicals) and the body's ability to detoxify them.
• Mitochondrial dysfunction in neurons leads to excess reactive oxygen species (ROS) production.
• ROS damage DNA, proteins, and lipid membranes, accelerating synaptic failure and cell death [17].
• Biomarkers like 8-hydroxy-2′-deoxyguanosine (8-OHdG) are elevated in neurodegenerative diseases, reflecting oxidative DNA damage [18].

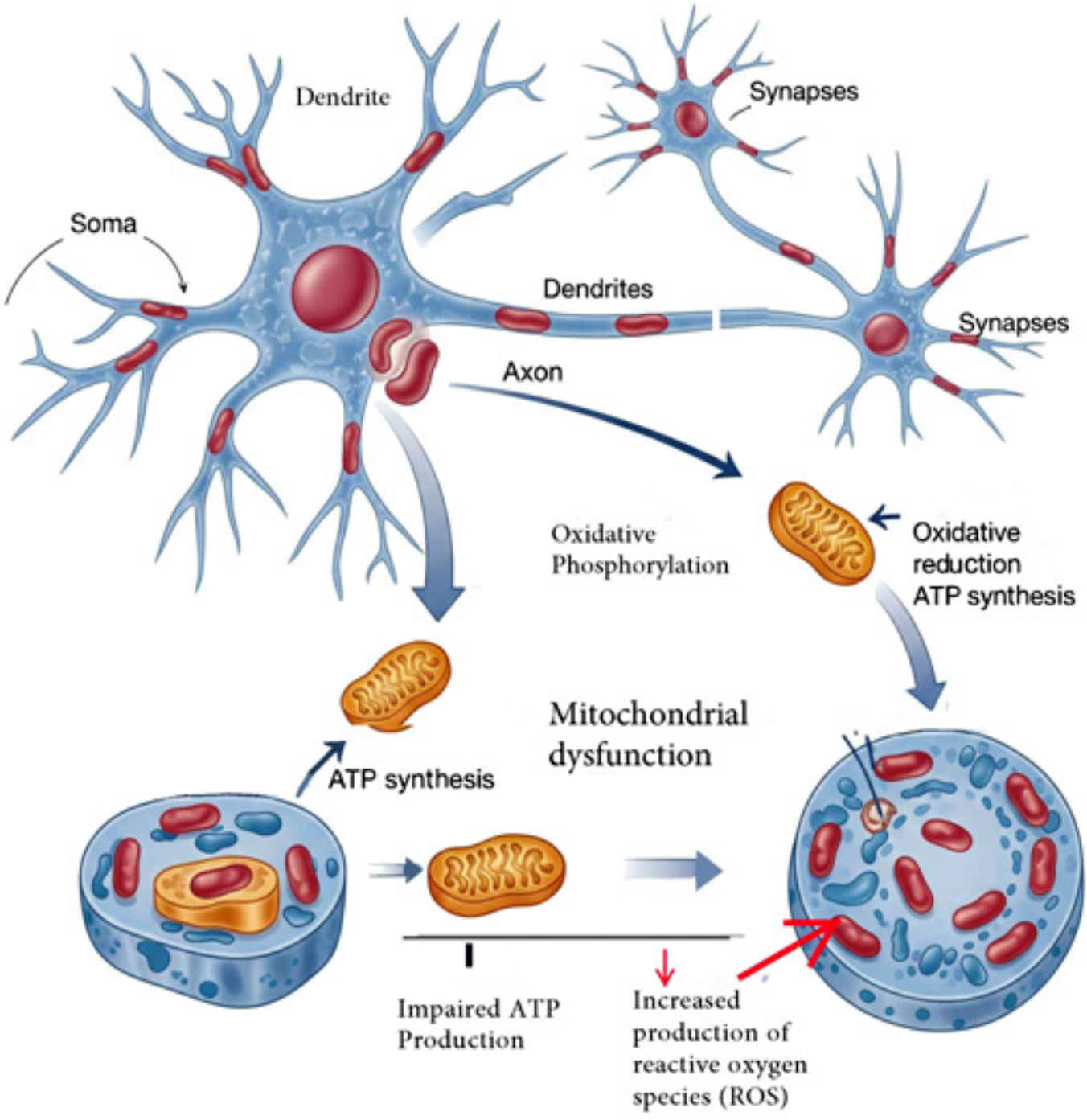

Figure 2.7: A diagram of a neuron with mitochondria highlighted, illustrating their role in producing ATP (energy) and showing how dysfunction might lead to reduced energy and increased reactive oxygen species

Explanation of the Diagram:
This diagram illustrates the crucial role of mitochondria within a neuron, particularly in energy production, and how their dysfunction can lead to detrimental effects.

- **Neuron Structure:** The diagram shows a typical neuron with its key components:
  - Soma (Cell Body): The main part of the neuron, containing the nucleus and other organelles.
  - Dendrites: Branch-like extensions that receive signals from other neurons.
  - Axon: A long, slender projection that transmits signals to other neurons.
  - Synapses: Junctions where neurons communicate with each other.

- **Mitochondria (Highlighted):** These are depicted as oval-shaped organelles, highlighted within the neuron. Mitochondria are often referred to as the "powerhouses" of the cell because they are responsible for generating most of the cell's supply of adenosine triphosphate (ATP), which is used as a source of chemical energy.

- **Role in ATP Production (Energy**):
  - The diagram illustrates the process of oxidative phosphorylation within the mitochondria. This is a metabolic pathway that uses oxygen to generate ATP.
  - Glucose (from food) is broken down, and its energy is used to create a proton gradient across the mitochondrial inner membrane.
  - The flow of protons back across the membrane drives the enzyme ATP synthase to produce large amounts of ATP. This ATP is then used to power all cellular processes, including neuronal signaling, maintaining ion gradients, and synthesizing neurotransmitters.

- **Mitochondrial Dysfunction and its Consequences:**
  - **Reduced Energy (ATP):** When mitochondria are dysfunctional (e.g., due to genetic mutations, oxidative stress, or toxins), their ability to produce ATP is compromised. This leads to an energy deficit within the neuron. Neurons are highly energy-demanding cells, and a lack of sufficient ATP can impair their ability to function correctly, leading to problems with signal transmission, maintenance of cellular integrity, and overall neuronal health.

  - **Increased Reactive Oxygen Species (ROS):** Mitochondrial dysfunction can also lead to an increase in the production of reactive oxygen species (ROS), also known as free radicals. ROS are highly reactive molecules that can cause oxidative damage to cellular components, including DNA, proteins, and lipids. This oxidative stress can further damage mitochondria, creating a vicious cycle, and contribute to neuronal degeneration.

Protein Homeostasis and Autophagy

• Neurons depend on efficient clearance of misfolded proteins via autophagy lysosomal pathways.
• Impaired proteostasis results in toxic accumulation of aggregated proteins (e.g., amyloid-beta, tau, alpha-synuclein) [19].
• Genetic mutations affecting autophagy (e.g., mutations in progranulin, TMEM106B) are linked to familial dementia syndromes [20].

Excitotoxicity

Excessive activation of excitatory neurotransmitter receptors, particularly N-methyl-D-aspartate (NMDA) receptors by glutamate, can lead to an influx of calcium into neurons [21]. While calcium is essential for neuronal function, excessive levels can trigger a cascade of events leading to neuronal damage and death.

Lysosomal Dysfunction

Lysosomes are cellular organelles responsible for waste degradation and recycling. Impaired lysosomal function leads to the accumulation of misfolded proteins and cellular debris, contributing to neurodegeneration.

Axonal Transport Deficits

Neurons are highly dependent on efficient axonal transport to deliver essential molecules and organelles along their long axons. Disruptions in this transport system can lead to impaired synaptic function and ultimately, axonal degeneration.

Mechanism	Description	Associated Dementia Types
Mitochondrial Dysfunction	Impaired ATP production, oxidative stress, and neuronal energy failure [22].	AD, LBD, FTD
Neuroinflammation	Chronic microglial activation releases pro-inflammatory cytokines (TNF-α, IL-6) [23].	AD, VaD, LBD
Excitotoxicity	Excessive glutamate causes Ca^{2} overload, leading to neuronal death [24].	AD, VaD
Impaired Protein Clearance	Dysfunctional autophagy and ubiquitin-proteasome systems lead to toxic aggregates [25].	AD (Aβ, tau), LBD (α-synuclein)

Table 2: Key Pathophysiological Mechanisms in Dementia

Proteinopathies and Neurodegeneration

A defining feature of most neurodegenerative diseases, including many dementias, is the abnormal accumulation and aggregation of specific proteins within or outside neurons. These “proteinopathies” disrupt normal cellular processes and lead to neuronal dysfunction and death [26].

A defining feature of neurodegenerative dementias is selective vulnerability to misfolded proteins:

Misfolding and Aggregation: Proteins must fold into specific three-dimensional structures to function correctly. In proteinopathies, proteins misfold and aggregate into insoluble clumps, which are toxic to neurons. Misfolded proteins disrupt synaptic function, impair intracellular trafficking, and ultimately trigger cell death via apoptosis or necroptosis pathways. These aggregates can spread throughout the brain, contributing to disease progression [27].

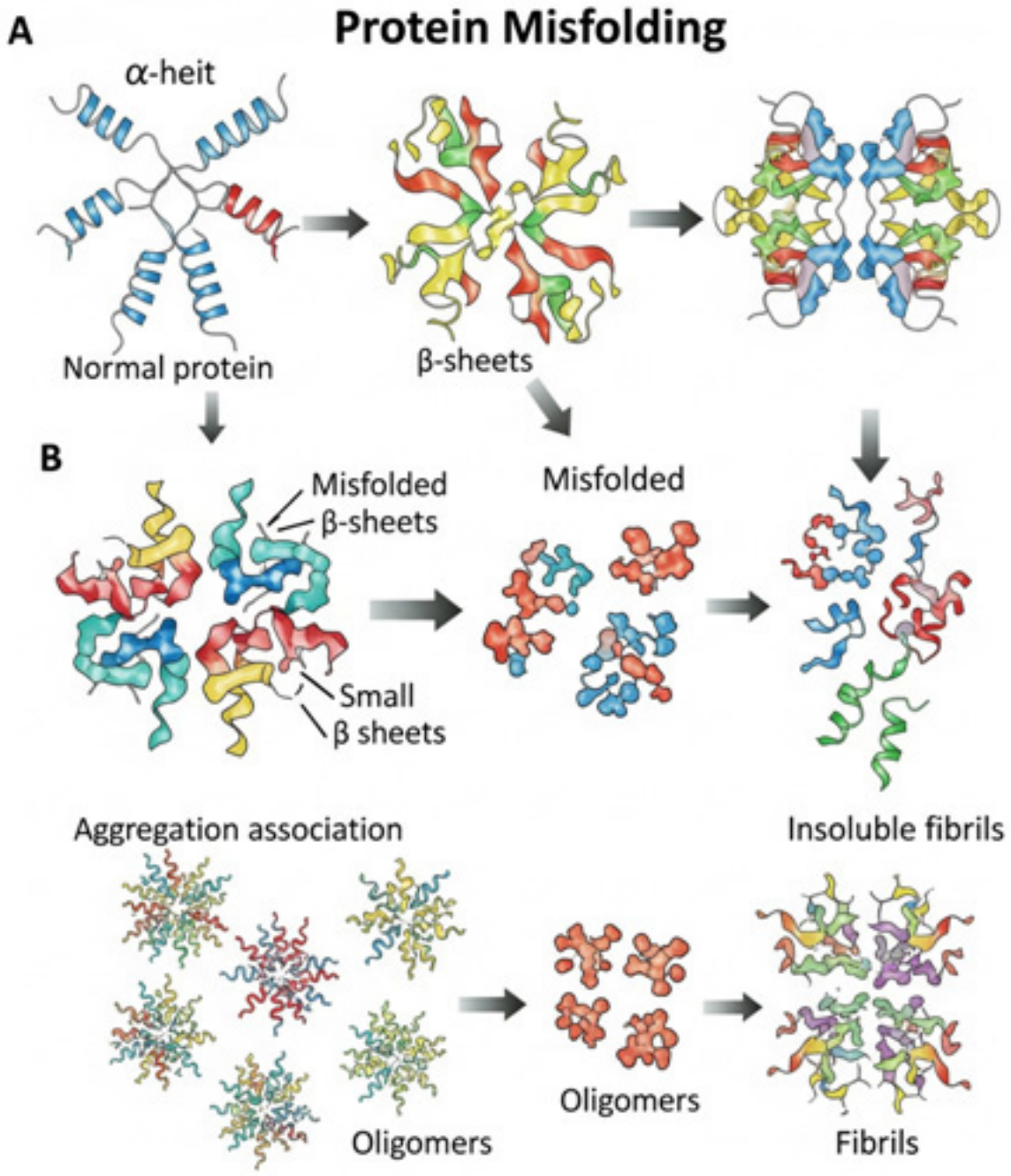

Figure 2.8: A schematic illustrating the process of protein misfolding (e.g., from alpha-helix/beta-sheet structures to misfolded beta-sheets) and subsequent aggregation into oligomers and insoluble fibrils.

Prion-like Spread: Emerging evidence suggests that some misfolded proteins, such as amyloid-beta and tau, can act in a "prion-like" manner, seeding the misfolding of normal proteins and propagating pathology across interconnected brain regions [28].

- Alzheimer's Disease: Amyloid-β plaques and tau tangles.
- Lewy Body Dementia: Alpha-synuclein inclusions.
- Frontotemporal Lobar Degeneration (FTLD): TDP-43, tau, or FUS aggregates.

Protein	Aggregate Form	Associated Disease	Consequences
Amyloid-β (Aβ)	Extracellular plaques	Alzheimer's disease	Synaptic toxicity, inflammation, neurodegeneration [29].
Tau	Neurofibrillary tangles	AD, FTD	Disrupts microtubules, impairs axonal transport [30].
Alpha-synuclein	Lewy bodies	LBD, Parkinson's	Disrupts dopamine and acetylcholine signaling [31].

Table 3: Major Proteinopathies in Dementia

Neuronal Damage and Synaptic Loss

The ultimate consequence of the aforementioned pathological processes is the progressive damage and loss of neurons (neurodegeneration) and, critically, the degradation of synapses.

There are stages that synapses path through:

• **Synaptic Plasticity and Function:** Synapses, the junctions between neurons, are where communication occurs. They are crucial for learning and memory through a process called synaptic plasticity (the ability of synapses to strengthen or weaken over time).

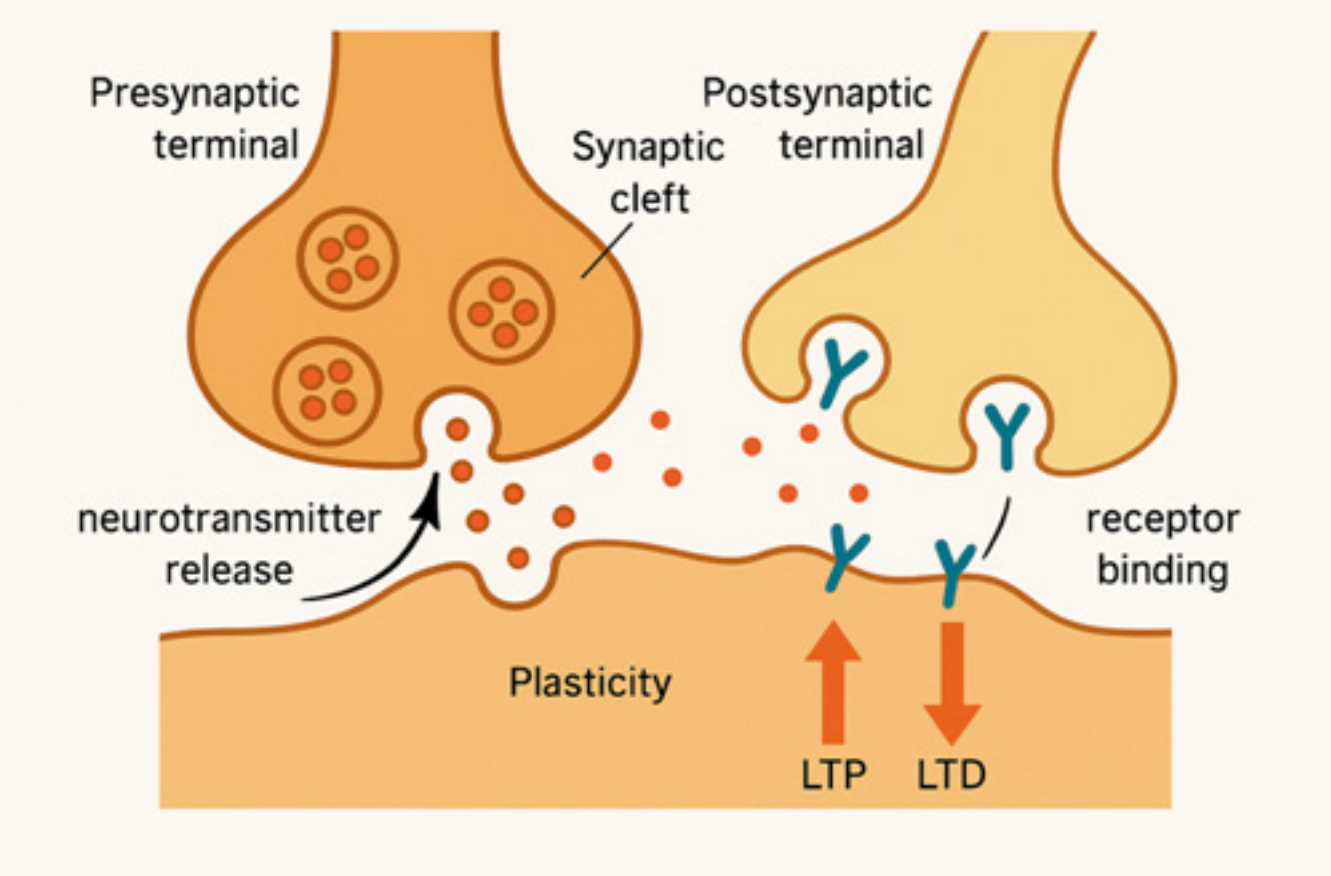

Figure 2.9: A detailed diagram of a synapse, showing the presynaptic terminal, synaptic cleft, and postsynaptic terminal. Illustrates neurotransmitter release, receptor binding, and the concept of long-term potentiation (LTP) or depression (LTD) as examples of plasticity.

• **Early Synaptic Dysfunction:** In many dementias, synaptic dysfunction and loss occur before significant neuronal death [32]. This early impairment in synaptic communication contributes significantly to cognitive deficits, particularly memory problems.

• **Neuronal Atrophy and Death:** As the disease progresses, sustained cellular stress and protein accumulation lead to neuronal atrophy (shrinking) and eventually, programmed cell death (apoptosis) or other forms of cell death. The pattern of neuronal loss varies depending on the specific dementia type, explaining the diverse clinical presentations.

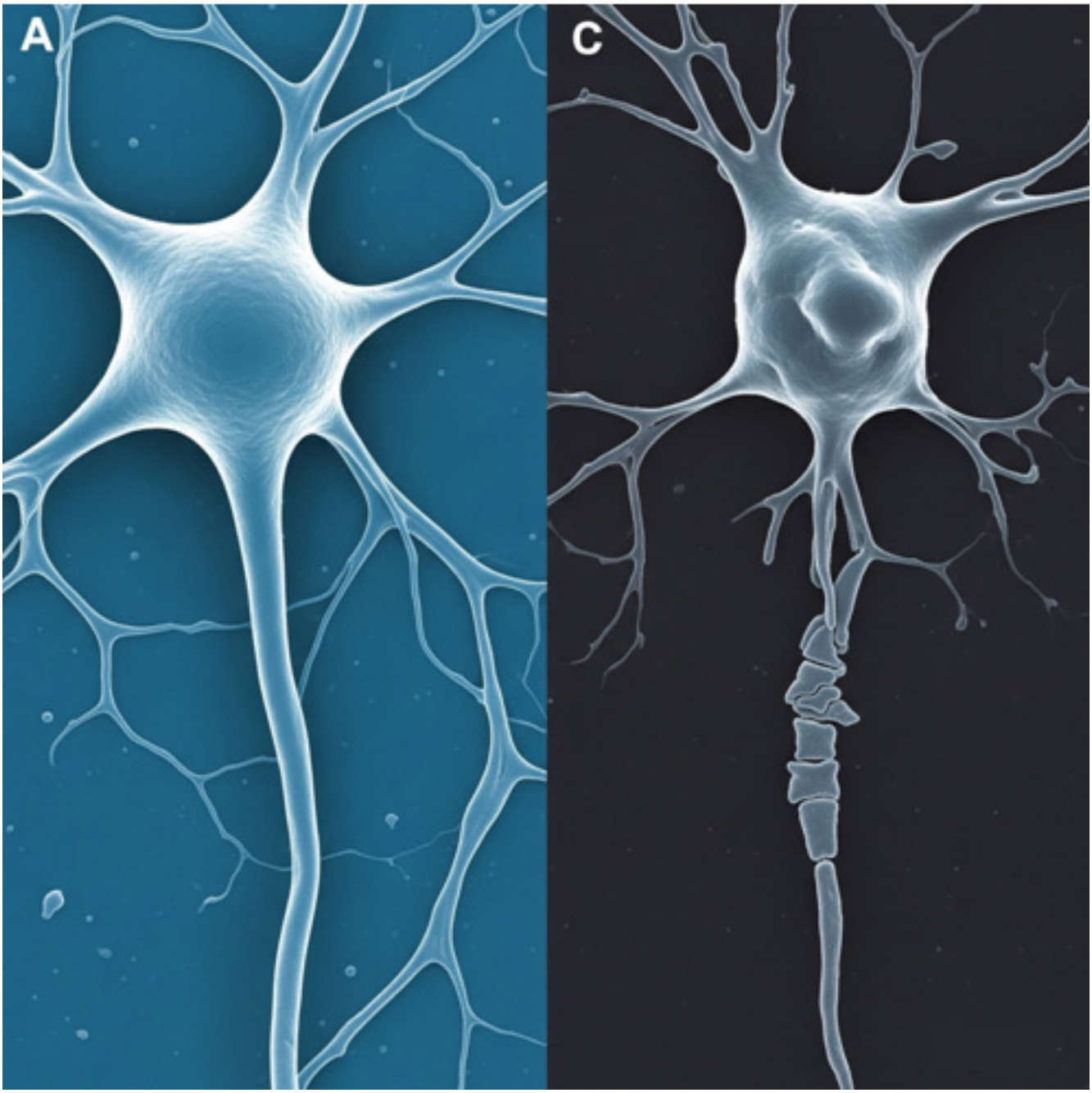

Figure 2.10: Microscopic images comparing a healthy neuron (A) (well-defined soma, dendrites, axon) to an atrophied or degenerating neuron (C), highlighting morphological changes.

Synaptic dysfunction is a pivotal early event in dementia pathophysiology:
• Dendritic spine loss observed in hippocampus and cortex in AD, correlating with memory deficits [33].
• Neurotransmitter system changes, such as cholinergic deficits in AD and dopaminergic dysfunction in Lewy body dementia, contribute to cognitive and motor symptoms [34].
• Synaptic vesicle proteins (e.g., synaptophysin) decrease before neuronal death, indicating synapse-specific vulnerability [35].

Synaptic disconnection leads to reduced network efficiency and cognitive slowing. Cognitive reserve may mitigate the clinical impact of early synaptic loss, explaining variable symptom severity [19].

Role of Amyloid Plaques and Tau Tangles (Alzheimer's Disease)

Alzheimer's Disease (AD) is the most common cause of dementia, characterized by two hallmark proteinopathies [36]:

Amyloid-β Pathophysiology

• Derived from sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases.
• Oligomeric Aβ species are neurotoxic, interfering with NMDA receptor signaling, long-term potentiation (LTP), and synaptic plasticity [37].

Amyloid plaques are thought to initiate a cascade of events leading to
Amyloid Plaques trigger microglial activation, further driving neuronal dysfunction, neurodegeneration and neuroinflammation.

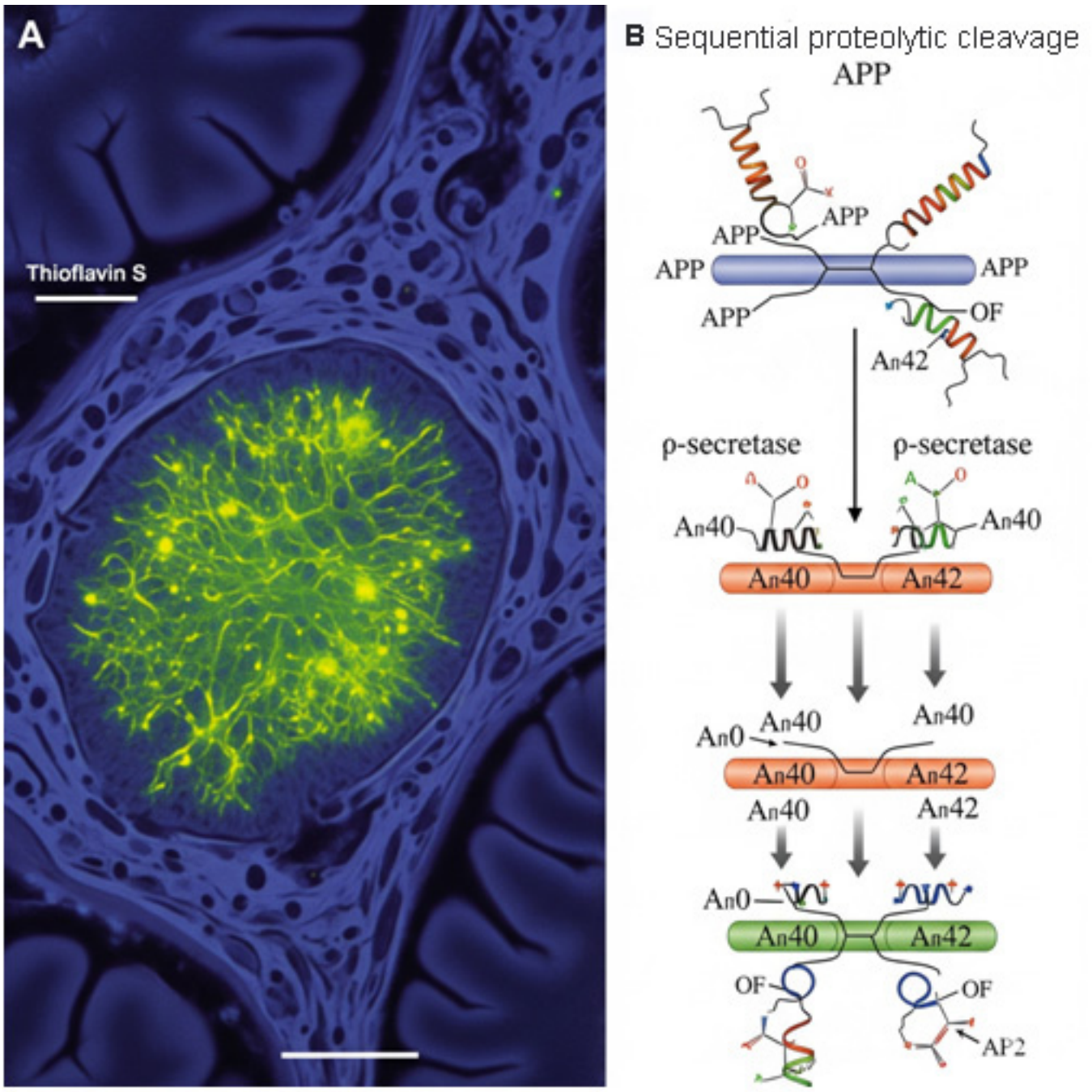

Figure 2.11: A microscopic image of an amyloid plaque in brain tissue (e.g., stained with Congo red or thioflavin S) A schematic showing the sequential proteolytic cleavage of APP by β-secretase and γ-secretase to produce Aβ peptides.

Tau Pathology
Tau is a microtubule-associated protein that normally helps stabilize microtubules, which are essential for axonal transport and neuronal structure.

• Hyperphosphorylated tau aggregates into paired helical filaments forming neurofibrillary tangles (NFTs).
• Tau pathology spreads anatomically in a stereotyped pattern (Braak stages), beginning in transentorhinal cortex and progressing to neocortex [38].

While amyloid pathology may initiate the disease, tau pathology appears to be more directly linked to the progression of neuronal damage and clinical symptoms [39, 40].

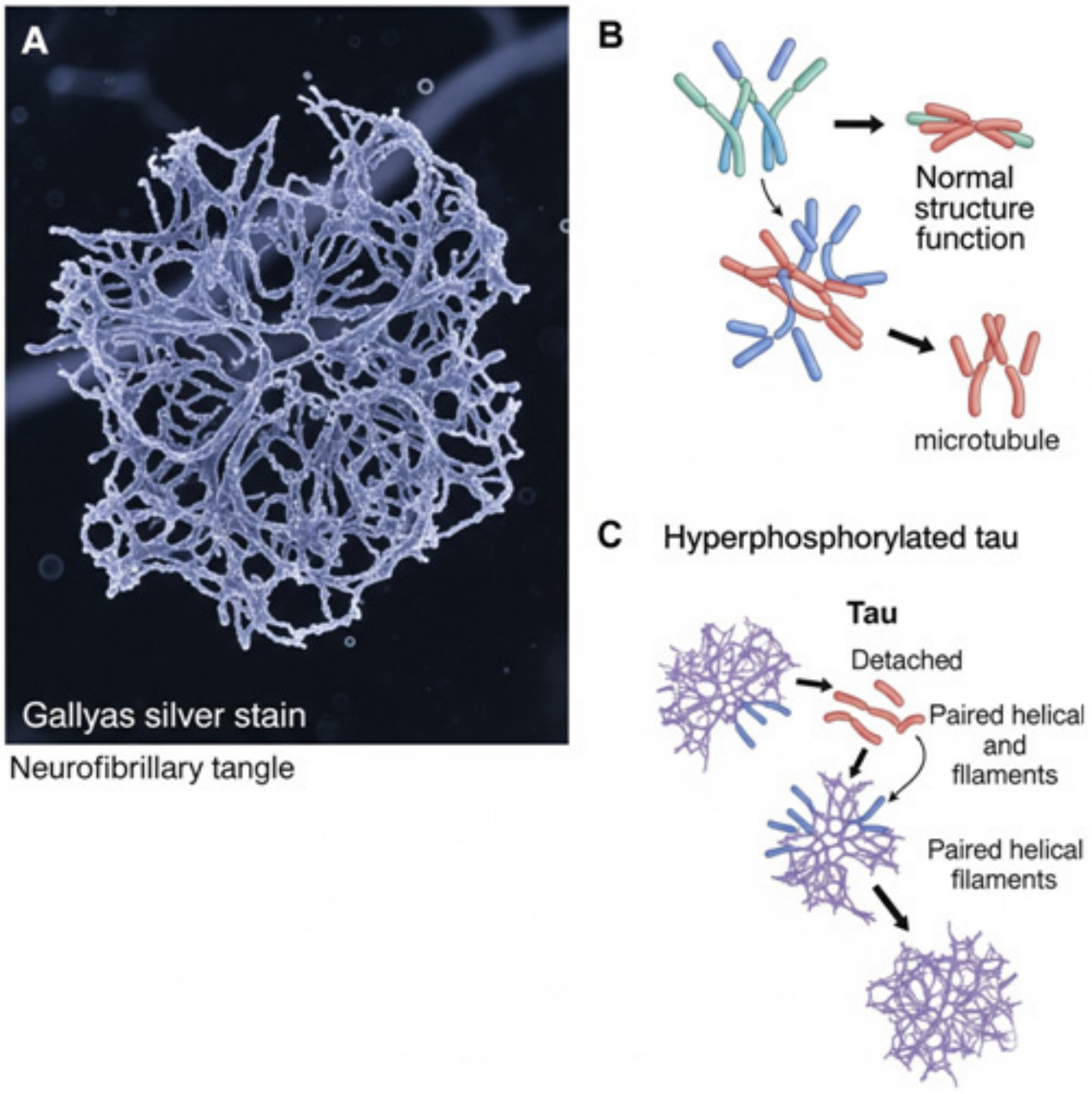

Figure 2.12: A microscopic image of a neurofibrillary tangle (e.g., stained with Gallyas silver stain or an anti-tau antibody). Diagram showing normal tau protein binding to microtubules versus hyperphosphorylated tau detaching and forming paired helical filaments that aggregate into tangles.

Vascular Changes in Vascular Dementia

Vascular Dementia (VaD) is the second most common type of dementia, resulting from cerebrovascular disease that impairs blood flow to the brain [41].

Vascular dementia (VaD) encompasses:

Cerebral Ischemia and Hypoxia

Reduced blood flow (ischemia) or complete lack of oxygen (hypoxia) to brain regions leads to neuronal damage and death.

This can be due to:
o Strokes (infarcts): Both large vessel strokes (e.g., affecting major arteries) and small vessel disease (affecting tiny blood vessels deep within the brain) can cause brain damage.
o Chronic Hypoperfusion: Sustained reduction in blood flow, even without overt strokes, can lead to cumulative neuronal damage over time, particularly affecting white matter. (42)
o Chronic small vessel ischemia results in white matter hyperintensities, lacunar infarcts, and microbleeds [42].

These may lead to slowed information processing, executive dysfunction, and gait disturbances.

Cerebral Amyloid Angiopathy (CAA)

•c Amyloid deposits in vessel walls cause microhemorrhages and cortical superficial siderosis.
• Strongly associated with Alzheimer's pathology [26].
Mixed dementia, where vascular pathology coexists with neurodegenerative changes, is increasingly recognized in elderly populations [42].

Blood-Brain Barrier Disruption

The blood-brain barrier (BBB) normally protects the brain from harmful substances. Vascular changes can compromise the BBB, leading to leakage of blood components and inflammatory molecules into the brain, further contributing to neuronal damage (43).

White Matter Lesions

Small vessel disease often leads to widespread damage in the brain's white matter, disrupting communication pathways between different brain regions and manifesting as cognitive slowing and executive dysfunction [44].

Microbleeds

Small hemorrhages in the brain, often associated with amyloid angiopathy (amyloid deposition in blood vessel walls), can contribute to cognitive decline and increase the risk of larger strokes.

Alpha-Synuclein in Lewy Body Dementia

Alpha-synuclein is a small protein normally found in presynaptic terminals, involved in synaptic vesicle function and neurotransmitter release. In LBD, alpha-synuclein misfolds and aggregates into insoluble clumps called Lewy bodies (intracellular inclusions primarily found in neurons) and Lewy neurites (abnormal protein deposits in neuronal processes) [45].

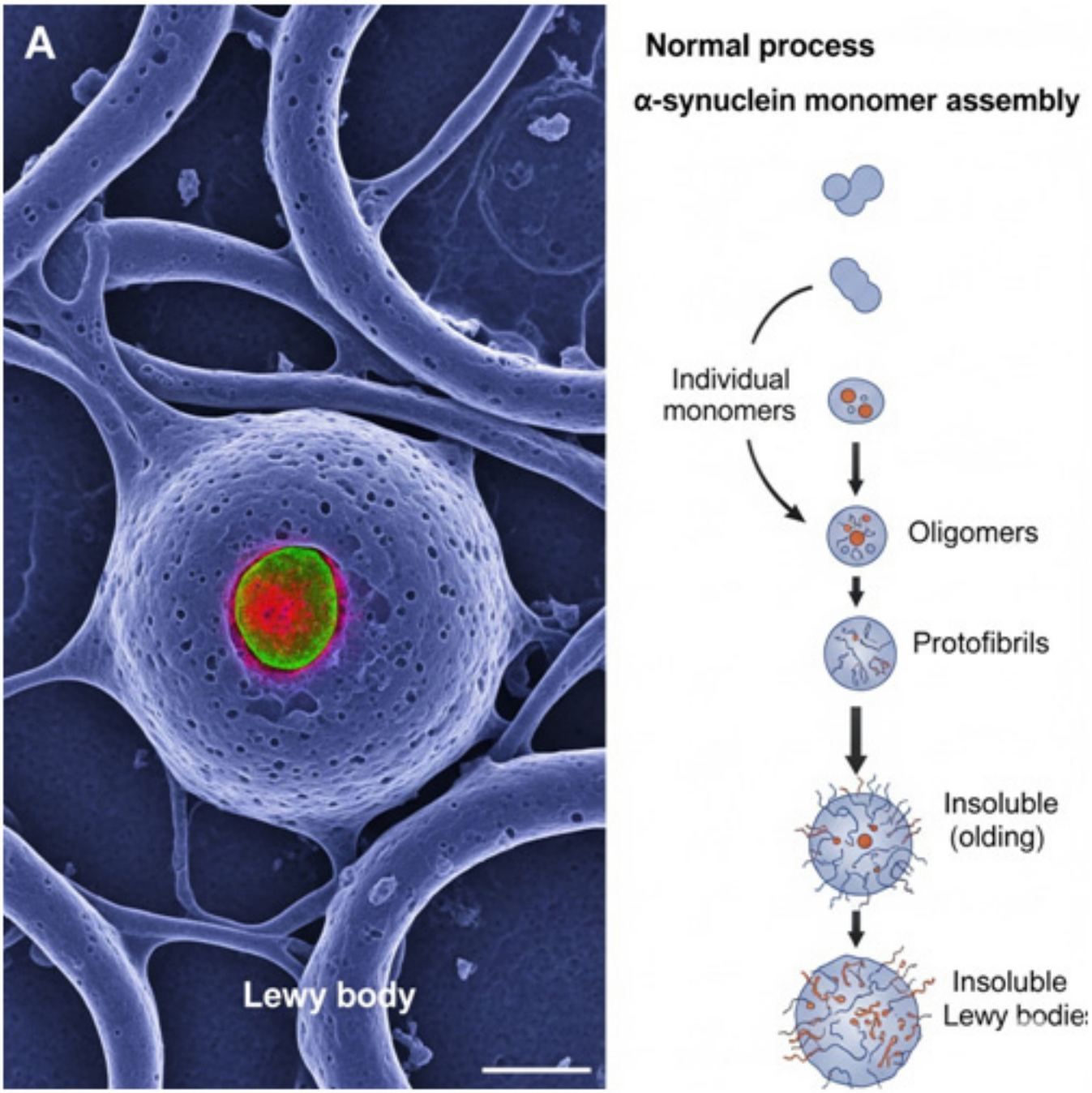

Figure 2.13: A microscopic image of a Lewy body within the cytoplasm of a neuron (e.g., stained with alpha-synuclein antibody). Diagram showing normal alpha-synuclein monomers assembling into oligomers, then protofibrils, and finally forming insoluble Lewy bodies.

Lewy Body Dementia (LBD) is a spectrum of disorders including Dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD), characterized by the abnormal accumulation of alpha-synuclein protein [45].

Lewy Body Distribution

• In DLB, Lewy bodies are prominently found in the cerebral cortex, leading to cognitive fluctuations, visual hallucinations, and spontaneous parkinsonism.

• In PDD, Lewy bodies primarily affect the substantia nigra (a brain region involved in motor control) early in the disease, causing motor symptoms, with cognitive impairment developing later [45].[

Pathogenic Mechanisms

Neurotransmitter Imbalances:

Alpha-synuclein pathology disrupts neurotransmitter systems, particularly dopaminergic pathways (contributing to motor symptoms) and cholinergic pathways (contributing to cognitive and psychiatric symptoms, especially visual hallucinations).

• Disrupts synaptic vesicle trafficking.
• Impairs mitochondrial function and axonal transport.
• Triggers neuroinflammation and oxidative stress [46].

Mitochondrial and Lysosomal Dysfunction:

Similar to other proteinopathies, alpha-synuclein aggregation can impair mitochondrial function and lysosomal degradation pathways, contributing to neuronal toxicity.

Lewy body pathology often overlaps with Alzheimer's pathology. Patients are sensitive to antipsychotic medications and may experience severe extrapyramidal side effects.

Emerging research shows real-time quaking-induced conversion (RT-QuIC) assays are promising for detecting alpha-synuclein aggregates in CSF as potential biomarkers [46].

Comparison of Major Dementia Pathologies

A quick comparison of the key neurobiological features discussed, in the various section is presented in the table below.

Key Neurobiological Features of Major Dementia Types

Feature	Alzheimer's Disease (AD)	Vascular Dementia (VaD)	Lewy Body Dementia (LBD)
Primary Proteinopathy	Amyloid-beta (α\β) plaques and hyperphosphorylated tau (Neurofibrillary Tangles)	Not a proteinopathy; related to vascular injury	Alpha-synuclein (Lewy bodies & Lewy neurites)
Key Brain Regions Affected	Hippocampus, entorhinal cortex, neocortex (progressive)	White matter, basal ganglia, cortex (ischemic lesions)	Brainstem (substantia nigra), cerebral cortex, limbic system
Microscopic Hallmarks	Amyloid plaques (extracellular), Neurofibrillary Tangles (intracellular)	Infarcts (strokes), white matter lesions, microbleeds	Lewy bodies (intracellular), Lewy neurites
Primary Mechanism	Synaptic dysfunction, neuronal death from α\β and tau	Ischemia/hypoxia, blood-brain barrier disruption, loss of l connectivity	Disruption of neurotransmission, mitochondrial/lysosomal dysfunction, neuronal death
Typical Onset Symptoms	Progressive memory loss	Cognitive slowing, executive dysfunction, focal neurological deficits (post-stroke)	Cognitive fluctuations, visual hallucinations, parkinsonism

Conclusion

The neurobiology of dementia reveals a complex interplay of protein misfolding, neuroinflammation, vascular pathology, and network disintegration. Despite distinct pathological hallmarks, considerable overlap exists among different dementias, reflecting shared molecular cascades. A deeper understanding of these mechanisms fuels the development of disease-modifying therapies and precise diagnostic biomarkers, heralding an era of personalized dementia care.

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Review of the importance of using the fracture risk assessment tool (FRAX) by primary health physicians to optimise diagnosis and management of osteoporosis in Qatar

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Abstract

Background: Osteoporosis is an increasing worldwide systemic skeletal disorder leading to fragility fractures, affecting approximately 200 million people globally, with 8.9 million fractures occurring annually (1).

The burden of osteoporotic fractures is significant, encompassing physical, emotional, and financial consequences associated with direct and indirect treatment costs.

In 2021, Qatar pioneered a national FRAX tool which is accessible for use by health care professionals and patients.

Primary care is a better place than many other specialities in providing an holistic approach in patient care. Early detection and management of osteoporosis through the help of primary care physicians is of paramount importance.

Methodology:This is a narrative review of published articles looking at using the FRAX tool in primary care to screen and detect osteoporosis in Qatar, using Google online search engine. I included reviews, clinical trials, systemic reviews concentrating on the most recent articles published in Qatar and neighbouring countries in the last 5 years.

Results: There is still a large treatment gap of osteoporosis, related to a low rate of osteoporosis diagnosis (2).

Most studies and guidelines recommend early detection and management of osteoporosis and the importance of screening postmenopausal and elderly men for osteoporosis.

Studies in Qatar and neighbouring countries demonstrated average levels of knowledge on osteoporosis, lack of knowledge on how to use the FRAX tool and lack of awareness about country-specific calculators of the FRAX tool among primary care physicians as well as difficulty of integrating the assessment in busy clinics (3).

Implications: We need to increase the awareness of osteoporosis and the use of the FRAX tool among primary care physicians in Qatar by providing educational and training sessions. We can also integrate the use of the FRAX tool into routine health check and screening of elderly patients. Further clinical trials and audits will help understand the obstacles in-depth and allow us to overcome them.

Conclusion: In conclusion primary care physicians can have an important role in early detection and management of osteoporosis by using the FRAX tool on a targeted population. There are limitations to the FRAX tool, because of the limited number and details of risk factors included in the assessment. Regional studies found that primary care physicians have difficulties in using the FRAX tool, partly from lack of knowledge of osteoporosis and the use of the FRAX tool, plus the lack of available time in busy clinics.

Keywords: Osteoporosis: FRAX tool: primary health care: Qatar

Introduction

Osteoporosis is a growing global health concern, due to increasing life expectancy. Primary prevention, early detection, and treatment of osteoporosis is of paramount importance in reducing disease burden due to complications and consequences on the individual, community, the healthcare system and the country in general.

In modern healthcare, the need for effective fracture risk assessment is vital, particularly in primary care settings as early intervention can significantly influence patient outcomes.

Osteoporosis treatment is cost-effective with favourable side-effect profile, plus other feasible treatment modalities making screening and early diagnosis of osteoporosis highly beneficial.

The FRAX tool's simplicity allows its use in primary care without bone mineral density (BMD) values, making it an ideal screening tool.

Primary care physicians must be familiar with FRAX tool to integrate it into routine clinical practice, thus enhancing the capacity to identify high-risk individuals. This facilitates patient education and osteoporosis awareness, as it is a screening, educational and counselling opportunity. In addition, it guides treatment decisions which can be initiated in primary care, such as lifestyle advice, prescribing nutritional supplements, exercise programmes or referrals to secondary care for further assessment and/or treatment.

Studies demonstrate FRAX-based screening, with or without BMD, reduces hip fracture rates by 20% in the community. Between the year 2017 and 2019, over 380 osteoporotic hip fractures were diagnosed in Qatar.

Implementing the FRAX tool, will significantly help reduce this number through early detection as patients would be referred for appropriate treatment before the fractures occur. Moreover, it paves the way for further studies and research in this field, and develops advanced versions of the FRAX tool and other calculators to accommodate all possible risk factors; not to mention increased awareness of this increasing underdiagnosed health issue, among health workers and patients. Soon, it may be initiated by nurses or patients themselves before reporting to their medical appointments (4).

Development of FRAX tool:
The FRAX tool was developed in 2008 by the University of Sheffield University by the WHO (1).

In 2021, Hamad Medical Corporation's Rheumatology Osteoporosis team collaborated with Sheffield University to create a Qatar-specific FRAX tool, which suits the unique population demography in Qatar. According to the 2020 census the Qatari population was 2.8 million. The majority are expatriates and only 12% are Qatari citizens. Using data from neighbouring countries helped in formulating the Qatar specific tool (5).

The FRAX tool algorithm evaluates seven risk factors, most of which are accessible to primary care physicians: Age, body mass index (BMI), prior fracture, use of glucocorticoids, parental hip fracture, current smoking, alcohol intake and rheumatoid arthritis.

Now the FRAX tool is being developed further. FRAX-Plus calculates additional risk factors as well as more details of the previous risk factors. A second version of the core FRAX risk engine is under development (6,7).

A study found that vertebral fracture risk increases in individuals with type 2 Diabetes Mellitus which in turn increase mortality so type 2 Diabetes Mellitus can be an indicator of frailty; more research is needed in this area (8). Also results of a previous study showed that obese men with waist circumference (WC) over 102 cm had a significantly higher vertebral fracture incidence compared with normal weight (94 cm ≤ WC < 102 cm) and underweight (WC < 94 cm) men. Trunk fat mass, VAT mass, and limb fat mass were negatively associated with vertebral body BMD and geometry in men and women. BMD and geometry are related to vertebral strength, but they may not be directly related to the risk of fractures that are also influenced by other factors including biomechanical factor (9).

Longitudinal studies and regular audit cycles in Qatar are es-sential to assess FRAX's long-term effectiveness in reducing fracture rates, building on current evidence that FRAX-based screening reduces hip fracture rates by 20%. These studies could also aid the development of advanced FRAX versions, ensuring continuous improvement in osteoporosis management and reduction of disease burden.

The use of new and emerging technologies, such as AI-driven algorithms and mobile health applications, could further en-hance FRAX use by enabling patients to self-screen with inte-gration of real-time data, thus making screening more accessi-ble (10).

Limitations of FRAX tool:
Over the years, FRAX has been criticised for several issues. FRAX was designed to be a simple tool, accessible, and easy-to-use in primary care. Therefore, only a yes or no answer is accommodated in most questions in the tool. This means that risk factors that are number- or dose-dependent are not fully captured. Examples include the number of prior fractures, smoking pack-year history, the consumption of alcohol and the dose of glucocorticoids. The age of the parental fracture is also not considered. Recent studies have proposed arithmetic adjustments to the conventional FRAX probabilities to address some of these limitations. Recently, in the absence of a direct question related to falls history in FRAX and suggested potential adjustments, an analysis has provided probability ratios

or multipliers that can be applied according to the number of falls over the last year. The new FRAX plus website will permit modification of FRAX probability to account for a range of additional clinical considerations (1). However, limitations still exist as other risk factors such as Type 1 and 2 Diabetes Mellitus, Vitamin D deficiency, Vitamin K are still under investigation and not yet incorporated.

Other limitations are the lack of knowledge among primary care physicians on osteoporosis management guidelines, and the use of FRAX tool as well as lack of time to implement the screening in busy clinics.

Benefit of FRAX tool in primary care and family practice in Qatar:
The FRAX tool offers significant benefits in primary care by streamlining fracture risk assessment, thereby facilitating informed treatment decisions.

By providing a comprehensive estimate of a patient's 10-year probability of osteoporotic fractures, FRAX helps identify high-risk individuals who may require interventions or further diagnostic testing, optimize resource allocation, and improve patient outcomes.

Local guidelines emphasize the importance of the use of the age-dependent hybrid model of the Qatar fracture risk assess-ment tool for screening osteoporosis and risk categorization. The guideline is provided to all physicians across the country involved in the care of patients with osteoporosis and fragility; it includes screening, risk stratification, investigations, treatment, and monitoring of patients with osteoporosis (4).

Studies have noted positive behavioural changes in patients after the use of FRAX, though awareness still needs to be raised of the value of FRAX in osteoporosis prevention (11).

Furthermore, FRAX supports a personalized medicine approach, tailoring osteoporosis prevention strategies to individual risk profiles, addressing factors such as an increas-ingly aging population, sedentary lifestyles and managing co-morbidities such as diabetes or vitamin deficiencies.

To date, The FRAX tool is the most widely used fracture risk assessment tool throughout the world. It is presently used in many countries comprising about 80% of the world populations. The main objective of using the FRAX tool is to enable medical professionals especially in family practice and in primary care settings, to identify those patients who would benefit from pharmacological therapy in reducing fracture risk. However, like any other scientific tool, FRAX is beset with merits and limitations, as outlined above (12).

There are many studies including a cross-sectional study con-ducted in Jeddah, Saudi Arabia, intended to assess the aware-ness and usage of the FRAX tool among family physicians in Jeddah and to identify gaps in screening knowledge. The re-sults showed moderate awareness (88.20%). Of those aware of FRAX, only 57.20% reported using it in their practice, with the main barriers being a lack of a country-specific model, a busy practice, and not knowing how to use it. Targeted educational interventions and further studies are needed to overcome these barriers and to improve the tool's usage in clinical practice (13).

The FRAX tool also enhances patient education, allowing primary care physicians to use FRAX results to discuss osteo-porosis prevention and promote proactive health behaviours, such as adopting healthier lifestyles and adherence to treat-ment interventions.

Conclusion

In conclusion, the FRAX tool is the leading global tool for assessment of fracture risk, incorporated into over one hundred guidelines worldwide. It is a pivotal asset in primary care for the effective assessment of fracture risk and the guidance of treatment decisions. It not only tailors risk evaluation based on individual clinical factors but also provides a pragmatic approach to screening osteoporosis, especially in populations with limited access to advanced diagnostic methods like DEXA scans.

The new FRAX plus website will permit modification of FRAX probability to account for a range of additional clinical considerations (6).

Research demonstrates that the FRAX tool can successfully categorize patients into varying risk levels, as demonstrated by studies showing significant differences in fracture risk estimates compared to alternatives like CAROC (14), particularly in older adults who are often at higher risk. Moreover, the ability of FRAX to integrate both clinical risk factors and bone mineral density results facilitates comprehensive patient management, thereby optimizing health outcomes and resource allocation in settings facing economic constraints. Therefore, the implementation of FRAX in primary clinical practice in Qatar represents a strategic advancement in preventative healthcare, reducing the incidence of osteoporotic fractures and improving patient quality of life.

We should start educating primary care physicians about oste-oporosis and management guidelines and how to use the FRAX tool and to integrate the screening of osteoporosis for targeted population in routine health check clinics. This will al-low further studies and clinical trials to be conducted with the aim to have better understanding of the obstacles and improv-ing the outcome at different levels.

Conflict of interest:
No conflict of interest.

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A Case Report on Unusual Presentation of Pulmonary Embolism

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Case Presentation

A 39-year-old female, previously healthy, presented to the walk in clinic in our health center with a chief complaint of upper abdominal pain for 4 days radiating to the right shoulder and back and aggravated by spicy and fatty food. There was no specific relieving factor and was associated with nausea and vomiting 4 times daily, with vomit containing food no blood in vomitus, and no change in bowel habits.

Review of systems:

Constitutional: No fever, No chills.

Respiratory: Mild shortness of breath mainly with breathing in, not related to excretion. No cough, No wheezing.

Cardiovascular: No chest pain, No palpitations.

Genitourinary: No dysuria, No urinary frequency, No urinary urgency.

Musculoskeletal: No joint pain, No muscle pain.

Neurologic: Alert and oriented

Last menstrual period: 1 week ago

Past medical history: Not known to have any chronic illness.

Drug history: She was taking OCP for menstrual regulation for last 3 months.

Surgical history: No previous surgeries

Allergies: Mild allergic reaction to amoxicillin

Social and family history: Married, lived with her spouse, not smoker nor alcoholic. No family history of chronic condition

On examination:

Vital signs: Heart rate: 80 beats per minute, Blood pressure: 126/90, Oxygen saturation: 100%. Looks in pain.

Abdominal examination: not distended, soft lax abdomen, no tenderness, no organomegaly, negative Murphy's sign.

Patient given analgesia while waiting for the lab results which showed Normal complete blood count (CBC), mild elevated liver function test with no previous report: AST 76 ALT :100 and elevated C reactive protein (CRP):22, therefore, the patient was then transferred to emergency department as case of acute abdominal pain for further investigation and management.

In the emergency department, the patient's condition deteriorated, developing shortness of breath and desaturation. Further investigations revealed a massive pulmonary embolism with right ventricular strain. The patient was therefore admitted to the ICU for treatment with anticoagulation, stabilized and discharged after 1 week.

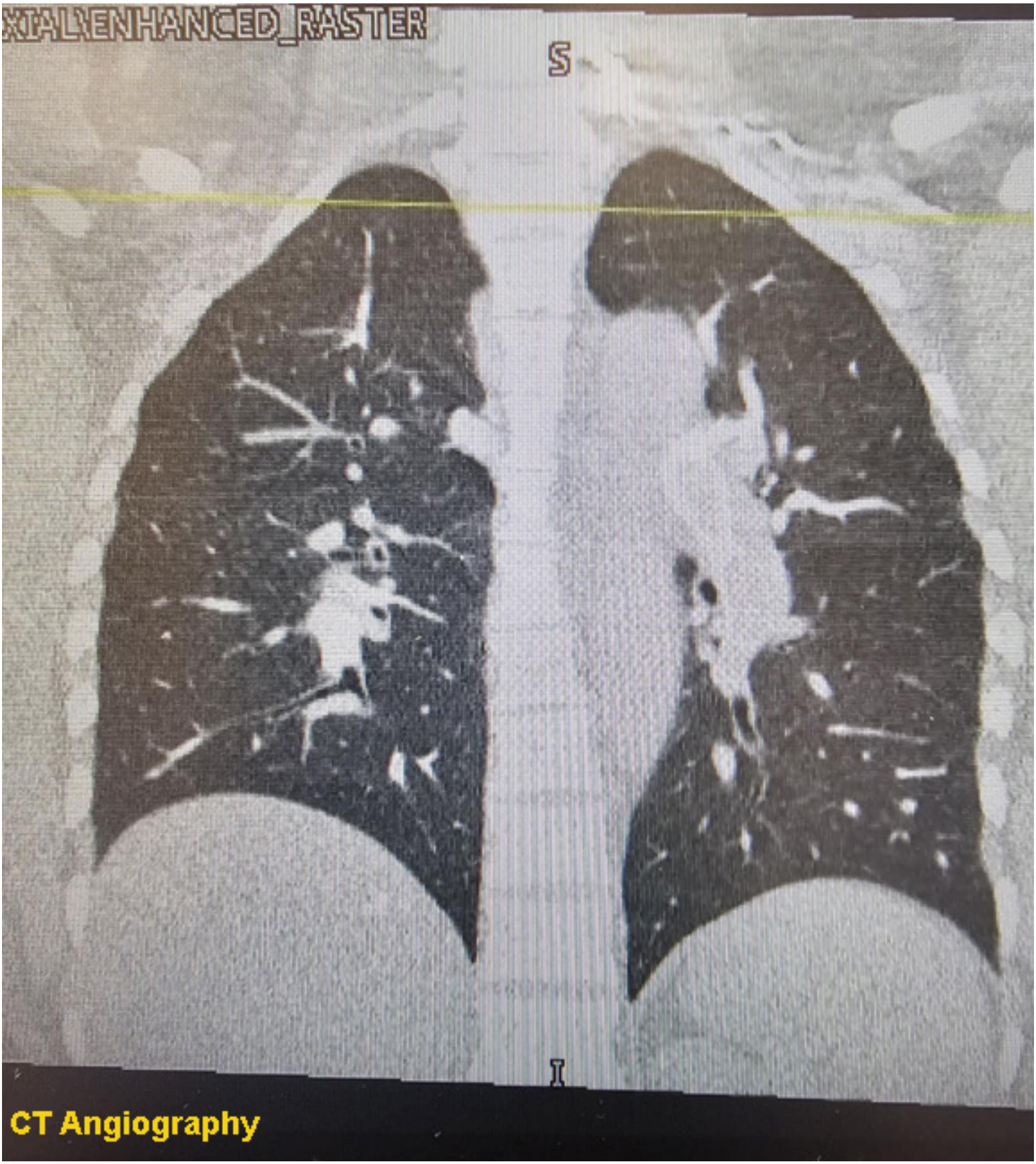
Investigations:

ECG - Sinus rhythm, heart rate-: 99/beat per minute, T inversion II, III, AVF, V3 - V6 D-Dimer: 6.05 mg/L FEU High Troponin-T HS: 44.8 ng/L High

CT pulmonary angiography: features are suggestive of massive pulmonary embolism with features of RV strain.

Ultrasound abdomen:
No obvious sonographic features to suggest cholecystitis or pancreatitis. Common bile duct is not dilated.
Hepatomegaly with moderate liver fatty changes.

Echocardiography:
- Normal global systolic LV function
- The left ventricular ejection fraction M-mode is 61 %.
- Grade 1 diastolic dysfunction (normal left atrial pressure)
- There is mild concentric left ventricular hypertrophy.
- Pulmonary artery pressure is moderately increased


AXIAL ENHANCED_RASTER
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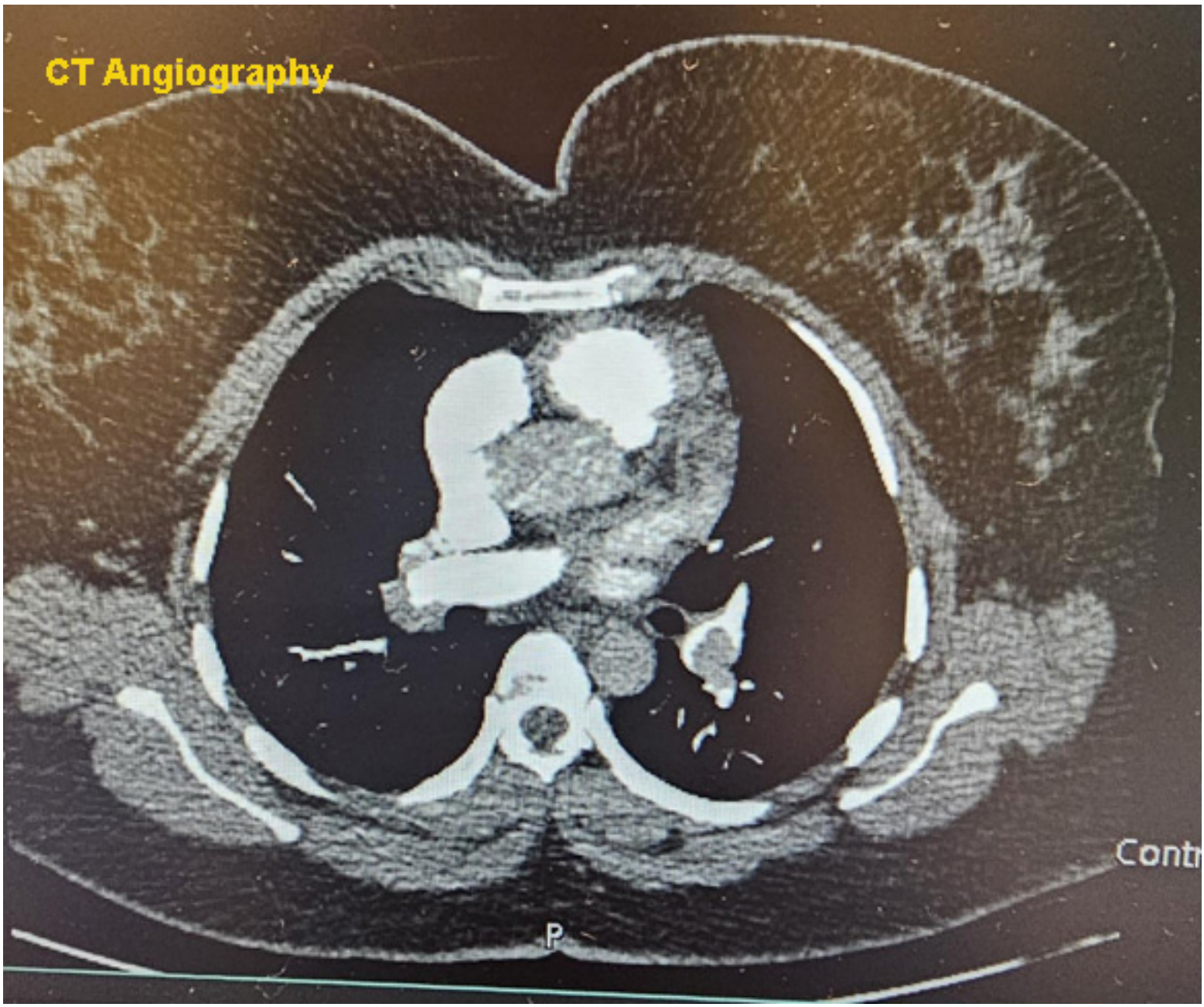
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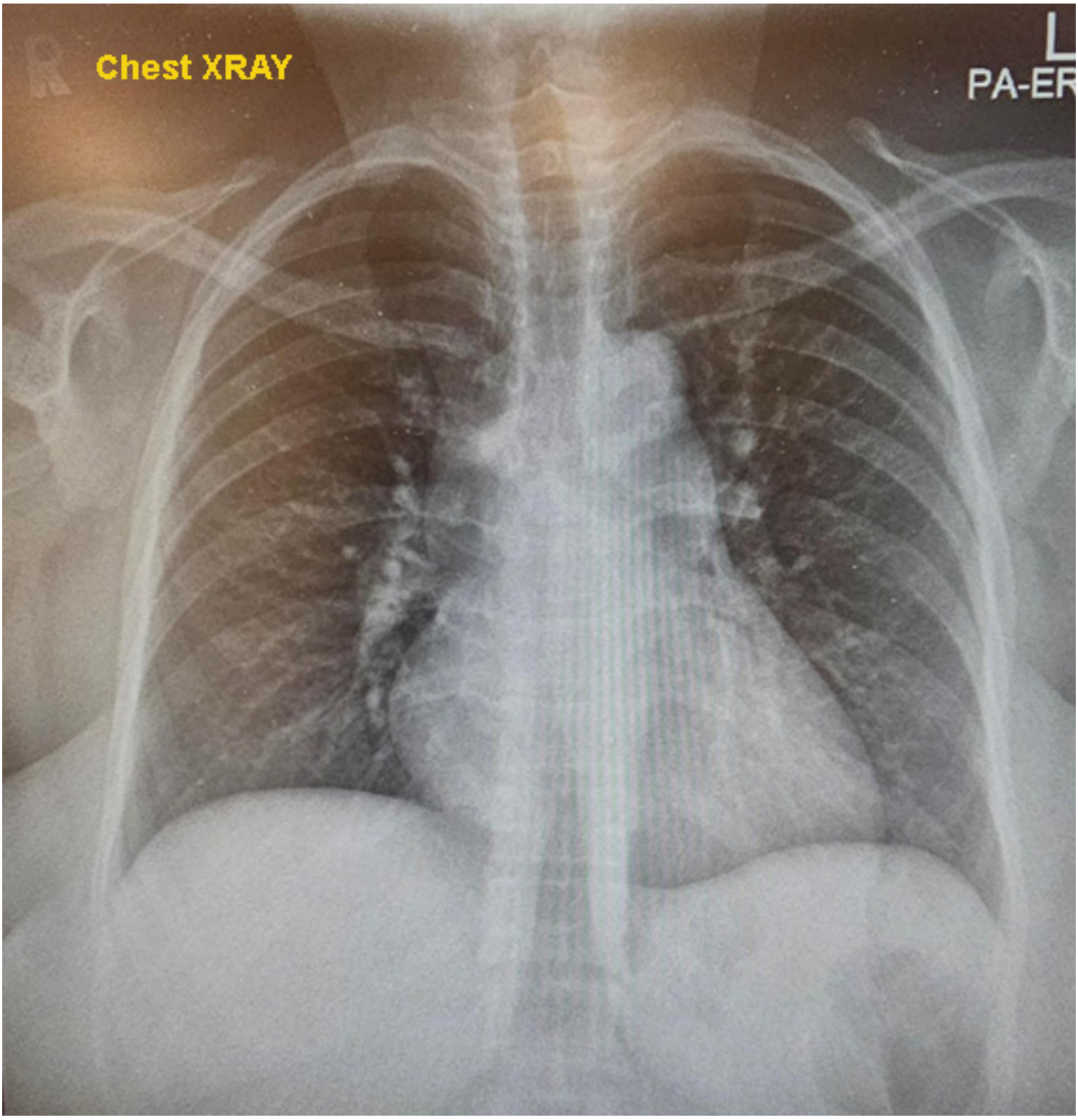
Chest XRAY
PA-ER

Differential diagnosis:
-gall bladder disease
-acute cholecystitis
-acute pancreatitis

Treatment:
Anti-spasmodic and anti-coagulant

Outcome and follow up:
In the emergency department, the patient's condition deteriorated, developing shortness of breath and desaturation. Further investigations revealed a massive pulmonary embolism with right ventricular strain. The patient was therefore admitted to the ICU for treatment with anticoagulation, stabilized and discharged after 1 week.

Discussion

This case illustrates the importance of thorough evaluation and consideration of alternative diagnoses in patients presenting with acute abdominal pain. It emphasizes the need for a comprehensive approach to diagnosis, including interdisciplinary collaboration and appropriate utilization of imaging modalities. This case underscores the importance of maintaining a broad differential diagnosis and considering pulmonary embolism even in the absence of classical respiratory symptoms, to prevent delays in diagnosis and expedite appropriate management.

The consequences of missing pulmonary embolism (PE) can be catastrophic. It is believed to be responsible for 50,000-200,000 deaths yearly. Overall mortality for PEs without treatment is estimated to be 30%. The diagnosis can be elusive since there is no pathognomonic sign or symptom for PE2.

Clinicians often take solace in clinical decision rules in patients without any clear risk factors.

We present a case report on a patient with abdominal pain who was diagnosed with a large PE, highlighting the importance of considering pulmonary embolism early in the differential diagnosis of acute abdominal pain.

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Misleading Symptoms in Testicular Torsion: Two Cases of Diagnostic Delay in Two Months

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Abstract

We present two clinical cases of testicular torsion which attended our primary healthcare center within a short period of 2 months. These were a 14-year-old teenage boy, and a 36-year-old male. Both cases had rather atypical features and unfortunately, both had to undergo orchiectomy due to delayed presentation. We will also review relevant literature to elucidate the findings of our cases in light of available evidence. Our aim is to highlight the utmost significance of clinician's alertness to this urgent diagnosis in patients presenting with acute scrotum and swift surgical intervention in an attempt to salvage a functioning testis.

Key words. Testicular, Torsion, bell clapper deformity, orchidectomy

Introduction

Acute scrotum is defined as a sudden painful swelling of the scrotum and/or its contents, accompanied by local signs or systemic symptoms [1]. Testicular torsion is the most important and potentially serious of the acute processes affecting the scrotal contents because, without prompt evaluation and surgical exploration, it may result in the loss of the testicle which can lead to subfertility or infertility, and psychological trauma in men [2]. Surgical exploration is the only definitive management option and should be performed without delay, preferably within 6 hours of the onset of symptoms, in order to have the highest chance of saving the affected testicle.

Case Presentations

Case No. 1:
In October 2024, a 14 year old male patient presented to a walk-in clinic in our primary care health center with a history of left sided testicular pain and swelling for 24 hours. There was no history of vomiting or fever. The patient was otherwise fit and well with no significant past medical history. There was no recent history of trauma or fever. The patient was up to date with immunizations.

Physical examination showed a grossly swollen and very tender left testis. The overlying scrotal skin was inflamed. The cremasteric reflex was absent. The rest of the examination of the abdomen and hernial orifices was normal.

It is worth noting that 2 days prior to this presentation, the patient was seen in the pediatric emergency department with complaint of left sided lower abdominal pain without diarrhea or vomiting or urinary symptoms. There was no fever. At that time, the patient had not complained of any scrotal symptoms. The patient was assessed and no obvious cause was found for the abdominal pain. Constipation was suspected. Patient was discharged with safety netting advice. However, records do not show any mention of genital/scrotal examination.

The possibility of testicular torsion was discussed with the patient and guardian, and the patient was transferred to the pediatric emergency department straightaway via ambulance for further evaluation. An urgent Doppler ultrasound was carried out and the following findings were noted:

“The left testis appears heterogeneous, with no detectable parenchymal flow and multiple hypoechoic areas, probably representing necrosis. No central perfusion on color Doppler. Epididymis is bulky and heterogeneous exhibiting no vascular flow. The spermatic cord is twisted and markedly thickened. Conclusion: left testicular torsion with potential necrotic changes.

Urgent surgical exploration was performed. The left testis was found dark with 270-degree clockwise torsion. Detorsion was done, warm compresses applied. The color remained the same after about 15 min. Left orchidectomy was performed. Right orchiopexy was also carried out.
Histopathology report showed a congested and hemorrhagic cut surface of testicular parenchyma and epididymis consistent with hemorrhagic infarction due to torsion.

Case No. 2:
In December 2024, a 36-year-old male patient presented to a routine family medicine clinic complaining of sudden onset of pain in left sided scrotum 2 days ago. The pain was present all the time and it was associated with swelling of the left hemi-scrotum but no vomiting or diarrhea. There was no history of injury. The patient did not complain of any fever and there was no dysuria or urethral discharge. The patient had no other significant past medical history. He was married and had one child. There is no history of past sexually transmitted infections.

Physical examination revealed tense and swollen left testis without any significant overlying inflammation. The testis appeared to be higher in the scrotal sac and lying transversely. The rest of abdominal examination was normal, and no groin hernia was present.

The Patient was admitted straightaway under urology for further evaluation, with suspected testicular torsion. A doppler ultrasound was carried out on an urgent basis.

The following findings were noted on ultrasound:
LT Testis: Edematous, hypoechoic with spots of calcifications, and no vascularity [Figure 1.] The left spermatic cord is bulky, heterogenous with whirlpool appearance, and peripheral vascularity but devoid of central vascularity [Figure. 2]. Conclusion: Left testicular total infarction likely due to neglected torsion.

Urgent surgical exploration of scrotum was carried out. The following findings were noted during surgery:

Left testicular torsion two and half complete twists. Testis was blue in color, left epididymis was black and gangrenous. Detorsion done. Vascularity was NOT regained even after 15 minutes of warm gauze application. Left orchiectomy was performed and Right orchiopexy carried out. The histopathology report confirmed the findings of necrotic left testis and epididymis due to infarction.

Figure 1: Doppler Ultrasound of both testes. Edematous, hyperechoic left testicle (white arrow) with spots of calcifications and no vascularity.

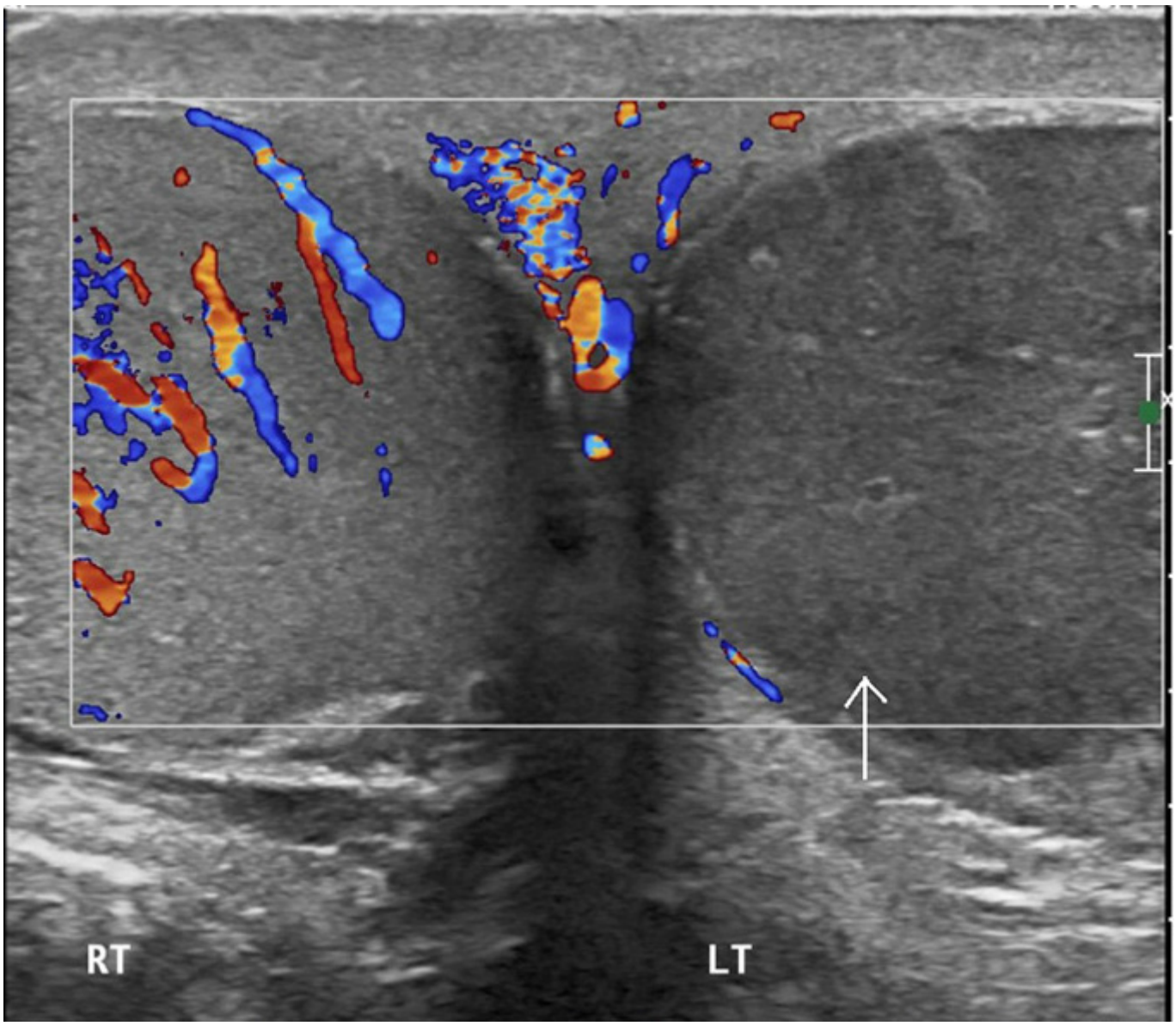
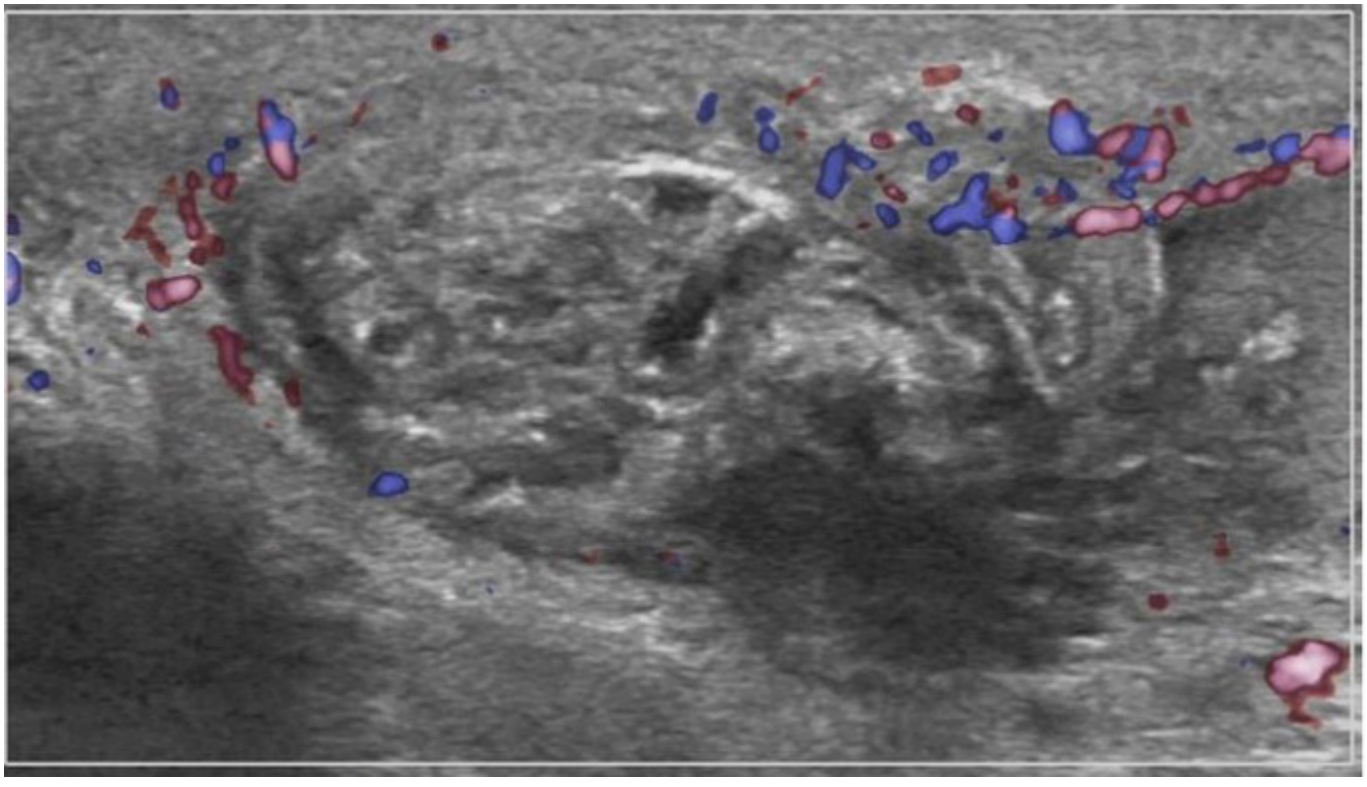


Figure 2: The left spermatic cord is bulky, heterogenous with peripheral vascularity but lacking central vascularity



Discussion

The differential diagnosis of the acute scrotum is broad and the proportion of patients present¬ing with each of these conditions varies [3]. The most common causes of acute scrotal pain in children and adolescents include testicular torsion, torsion of the appendix testis, and epididymitis. A 2-year retrospective review of 238 cases of acute scrotal pain encountered in a children's hospital emergency department revealed the incidences of testicular torsion, torsion of a testicular appendage, and epididymitis as 16%, 46%, and 35%, respectively (making up 97% of all causes) [4]. Because testicular parenchyma cannot tolerate ischemia for more than a short time, testicular torsion must be ruled out rapidly as the cause [5].

Various countries have reported similar incidence rates with some variation. In USA, the incidence of testicular torsion has been reported as 4.5 cases per 100,000 in 1-25 years of age in male subjects per year [6]. Two peaks of incidence have been reported when plotted by age group. A small peak happens during the neonatal period, but the majority of cases occur around the average age of puberty [7]. Although, the incidence decreases after 25 years of age, testicular torsion can happen in older adults. Therefore, age is not useful in discriminating between patients with testicular torsion from other patients with scrotal pain [8]. Thus, one of our cases presented at 36 years of age where an infective cause would normally be suspected in most cases.

The typical symptoms of testicular torsion include sudden onset of severe unilateral testicular pain associated with nausea and vomiting [1,9,10].

On examination, the ipsilateral scrotal skin may be indurated, erythematous, and warm, although changes in the overlying skin reflect the degree of inflammation and may change over time [10]. The spermatic cord shortens as it twists, so the testis may appear higher in the affected scrotum. This is a very specific finding and, when present, is strong evidence of testicular torsion. Because of venous congestion, the affected testis also may appear larger than the unaffected testis [11]. The affected testicle can also have an abnormal horizontal orientation. The presence of the cremasteric reflex suggests, but does not confirm, the absence of testicular torsion [10]. The well-known TWIST score (Testicular Workup for Ischemia and Suspected Torsion) which is based mainly on the above features is a useful tool for testicular torsion diagnosis. Meta-analyses revealed that the TWIST score achieves high sensitivity and high specificity [12].

Unfortunately, not every patient with testicular torsion presents with straightforward testicular pain. A significant minority of males with testicular torsion may present with vague abdominal or groin pain and not initially report testicular pain [13]. The lower abdominal pain or inguinal pain may move to the scrotum a few hours after the onset of the initial abdominal presentation [13].

Similarly, in our first case the presentation was atypical. In the case of the 14-year-old patient, he initially presented to emergency department with flank/abdominal pain without any scrotal symptoms. After 2 days, he presented to our clinic with 24 hours history of left sided scrotal swelling and pain. It can be assumed that his symptoms were initially abdominal but later shifted to scrotum, thus resulting in significant delay in diagnosis and, sadly, loss of one testicle. This presentation emphasizes the importance of a complete genitourinary examination in all males who present with abdominal pain. In particular, the external genital organs should be examined in every child or adolescent with acute abdominal pain.

Ultrasound is an effective diagnostic tool for testicular torsion. Studies have found that the diagnostic sensitivity of color doppler ultrasound for testicular torsion can reach 80% to 98%, and the specificity can reach almost 99% [14]. However, as discussed later, the window of opportunity for achieving the highest rates of salvaging testis is very brief (6 hours) with the chances falling drastically with every passing hour. Some researchers argue that the delay associated with performing imaging can extend the time of testicular ischemia, thereby decreasing testicular salvage rates [8]. Both our patients underwent immediate pre-operative Doppler ultrasound which confirmed testicular torsion.

Surgical exploration is the only definitive management option and should be performed without delay. Prompt restoration of blood flow to the ischemic testicle is critical in cases of testicular torsion [15]. The viability of the testicle in cases of torsion is difficult to predict; hence, emergent surgical treatment is indicated despite many patients presenting beyond the four- to eight-hour time frame [16]. Reported testicular salvage rates are 90% to 100% if surgical exploration is performed within six hours of symptom onset, decrease to 50% if symptoms are present for more than 12 hours, and are typically less than 10% if symptom duration is 24 hours or more [11,17]. Systematic review of the literature demonstrates that survival percentages are significant even past 24 hours of torsion (25 to 48 hours, 24.4%; and greater than 48 hours, 7.4%) [17]. Hence, these percentages should be considered approximate rather than absolute for the purpose of counseling patients or making clinical decisions [3].
Orchiectomy is performed if the affected testicle appears grossly necrotic or nonviable [3]. If the affected testicle is deemed viable, orchiopexy with permanent suture should be performed to permanently fix the testicle within the scrotum [18]. Contralateral orchiopexy should be performed regardless of the viability of the affected testicle [19]. The bell clapper deformity that increases testicular mobility and, therefore, the risk of torsion, is bilateral in up to 80% of patients [20]. It is assumed to be present contralaterally in all patients with testicular torsion [11].

The absence of a testicle has been shown to be a psychologically traumatic experience for males of all ages. This is more likely in patients who have lost a testis

(e.g. due to testicular torsion) compared to those born with an absent testis. Testicular prosthesis have been shown to reduce the psychological impact resulting from loss or absence of a testicle. Therefore, prosthesis insertion should be offered to all patients undergoing orchidectomy either at the same time, or as future procedure [2].

Conclusion

Testicular torsion is the most urgent of all the acute processes affecting the scrotal contents because it can very quickly result in the loss of the testicle which can lead to subfertility or infertility, and psychological trauma in men. It can occur in older adults although the incidence decreases after 25 years of age. A significant minority of males with testicular torsion may present with vague abdominal or groin pain rather than typical testicular/scrotal pain. Therefore, a low threshold of suspicion for possible testicular torsion and complete genitourinary examination is crucial because surgical exploration is the only definitive management option and should be performed without delay, preferably within 6 hours of the onset of symptoms in order to have the highest chance of saving the affected testicle.

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Knowledge and Management of Ocular Chemical Injury among Family Physicians and Emergency Medicine Physicians in the Kingdom of Saudi Arabia

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Abstract

Background: A chemical injury is the outcome of exposure of the eyes to a chemical substance that exceeds the protective mechanisms of the eyes. An ocular involvement constitutes a third of burn patients. The majority of them are due to chemical exposure. The high prevalence of chemical injuries and such injuries being a true emergency, they require proper evaluation and management.

Method: An observational descriptive cross-sectional institutional–based study was conducted from May 2023 to July 2023. A total of 355 participants were included in this study from PHC centers and hospitals in Saudi Arabia. Data was collected using data collecting sheets and self-administered questionnaires. The data was entered and analyzed using SPSS version 23.

Results: In our study, knowledge regarding signs of severe injury was assessed. Only 53 and 51 emergency medicine and family medicine physicians, respectively, answered correctly about the most common early symptoms of chemical injury (P=0.011). However, there was a significant difference (P= 0.001) regarding the most important sign that indicates the urgency of treatment as 52 respondents recognized the warning sign; 28 of them were emergency medicine doctors. Regarding the practice of emergency, no significant difference was found between the respondents of the two specialties. The level of knowledge regarding ocular chemical injury showed that ER consultant (19.05%), ER specialist (19.25%), family medicine consultant (26.45%), family medicine specialist (18.75%), R1 ER (21.45%), R1 family medicine (16.65%), R2 ER (25%), R2 family medicine (15.20%), R3 ER (36.65%), R3 family medicine (25%) R4 ER (30.80%), and R4 family medicine (21.05%) respectively, have different levels of knowledge. The highest level of knowledge was R3 ER residents while the lowest level was R2 family medicine residents. While the level of practice regarding ocular chemical injury showed that ER consultant (35.70%), ER specialist (37.17%), family medicine consultant (37.27%), family medicine specialist (25.53%), R1 ER (28.58%), R1 family medicine (28.90%), R2 ER (33.98%), R2 family medicine (28.98%), R3 ER (31.10%), R3 family medicine (29.63%) R4 ER (34.63%), R4 family medicine (36.83%) respectively, know the correct practice towards ocular chemical injury. The highest percentage was family consultants while the lowest percentage was family medicine specialists.

Conclusion: The study reveals a lack of knowledge and practice in family and emergency medicine physicians regarding ophthalmic chemical injuries, suggesting the need for guidelines and training to minimize complications and improve outcomes.

Key words: ocular injury, chemical, family physician, knowledge, ER physician, Saudi Arabia

Background

A chemical injury is the result of exposure of the eyes to a chemical substance that exceeds the ability of the protective mechanisms of the eyes (1). Ocular involvement constitutes a third of the burn patients. The majority are due to chemical exposure (2). The high prevalence of chemical injuries, and being a true emergency, requires proper evaluation and management (3). A frequent association that makes it hard to examine, leading to treatment delay and bad sequelae, is massive lid ecchymoses (4). Sequelae include dry eyes, ectropion, entropion, lagophthalmos, symblepharon, limbal stem cell deficiency, corneal opacity, non-healing corneal ulcer, intractable glaucoma, cataract, retinal detachment, and even phthisis bulbi. The sequalae is determined by how severe the injury was and when the treatment was initiated (5). About 7% of eye injuries are managed in hospital emergency departments. In addition to that, more than 60% of chemical injuries occur in workplace accidents, 30% occur at home and 10% are the result of an accident. Visual rehabilitation after an advanced eye injury occurs in less than 15% of the affected individuals. Men are threefold more likely to experience injuries than women; furthermore, individuals aged 16–45 years are most likely to be affected (13). A chemical injury of the eye is an acute, genuine emergency situation which requires immediate evaluation and management. Despite that, the most devastating sequelae of chemical injuries, corneal melt, limbal stem cell deficiency, and glaucoma, tend to occur over the long term. Early effective diagnosis and treatment often dictate the clinical course and can prevent tragic consequences. The goals of therapy are to restore corneal clarity, normalize the ocular surface, and prevent glaucomatous optic nerve damage (14). Therefore, proper knowledge about the injury and how to evaluate and manage such cases is essential for all medical practitioners especially those working at emergency departments or paramedics being first responders to such cases, and it is favorable for the general population to have knowledge about it, as it will lead to better management and less need for ocular surface reconstruction.

Problem statement:
Eye injury is a leading cause of monocular blindness and is second only to cataract as the commonest cause of visual impairment. Injury is the commonest reason for eye-related emergency department visits.

Justification:
Chemical injuries are considered as one of the true ocular emergencies where timely management can save vision and years of visual rehabilitation. Thus, knowledge of the injury and its management is very important for medical professionals as well as the general population.

Objectives

General objectives:
• To assess the knowledge of health practitioners from Saudi Arabia about ocular chemical injuries.

Specific Objectives:
1. To study the socio-demographic characteristics of participants.
2. To assess the knowledge regarding signs of severe ocular injuries.
3. To assess the knowledge regarding management of chemical ocular injuries.
4. To assess the practice of participants regarding chemical ocular injuries.
5. To determine if there's a correlation between knowledge and different departments.
6. To compare the knowledge regarding chemical injuries, to different medical positions.

Literature Review

A study was conducted in Saudi Arabia in the year 2021 to assess population awareness regarding eye injuries first aid in Asser region, Saudi Arabia. 1,213 individuals participated in this study. 69% had constant eye pain, 68.3% had Foreign Body (FB) in the eye, 66.9% had torn eye lid. When asked about signs of scratched eye, 64.2% reported feeling a foreign body inside, 58% said eye pain and 55.2% complained of blurred vision. 25.7% of participants said they should blink several times in case of getting eye scratch, while 77.8% said they should rub the eye to try to remove any foreign body, 36.3% said to use soothing eye drop (13).

Another study was done in India in the year 2020 to assess the knowledge, attitude, and practices of respondents from across the population, about ocular chemical injuries. 60 individuals were divided into two groups. Residents, casualty medical officers, and paramedical staff formed the first group, while the second group included those of site supervisors from the workplace and family members of patients. Participants answered a pre-formed questionnaire. Knowledge about causative agents was better in the first group, while both groups had a similar attitude towards the signs and symptoms of injury and the practice pattern of emergency management was better in the first group (15).

In addition, another cross-sectional study was conducted in Saudi Arabia in the year 2020 to assess knowledge of Saudi Arabian residents regarding steps to be taken in cases of chemical eye injury. 888 individuals were included in this study from the Saudi community. (8.3%) had a history of chemical eye injury. Regarding the first step taken in case of chemical eye injury, (78.5%) participants indicated washing with water, (18.5%) indicated visiting the emergency department, (1.2%) indicated using eye drops, and (0.6%) indicated covering the eye immediately. (8.4%) of respondents agreed that an eye injured with an acidic material should be washed with an alkaline solution (16).

Meanwhile in the UK, a retrospective study was conducted in the year 2020 to understand the incidence, causes, management and outcomes of intentional (assault) and unintentional severe ocular chemical injuries (SOCI). Between 2011-2012, (50%), three out of six cases were due to assault. Between 2012-2013, (87.5%), seven out of eight, were due to assault, and between 2013-2014, (54.4%) six out of eleven, were due to assault. Assault was responsible for (64%) cases overall, while (32%) cases were work related. The causative agent was known to be alkali in 64% cases, while 40% did not complete the follow-up. Surgical intervention occurred in one case out of 25. The final best-corrected visual acuity was 6/12 or worse in 11/25 (44%) and was counting fingers or worse in 4/25 (16%) (17).

Lastly, a study was done in India in the year 2019 to study the incidence, pattern and management of chemical injuries of the eye in a tertiary health care center of Western Odisha. Chemical injuries of eye were encountered in 13.04% of cases. Males (73.5%) were more affected and 31-40 years age group was the most vulnerable one. Most of the cases (59.8%) presented with unilateral involvement of eye and 72 cases (70.59%) of chemical injury were caused by alkalis. Grade II injury (35.6%) was the most common finding and some post-operative complications were also encountered during the follow-up (18).

Methodology

Study Design
The study was conducted as an observational descriptive cross sectional institutional– based study.

Study Area
The study was conducted in different primary healthcare (PHC) centers and emergency departments in hospitals across the Kingdom of Saudi Arabia.

Study Population
Family medicine residents, family medicine consultants, emergency medicine residents and emergency medicine consultants who worked in PHC centers and hospitals in Saudi Arabia.

Inclusive Criteria
Family medicine residents, family medicine consultants, emergency medicine residents and emergency medicine consultants who were present at the time of data collection and who were willing to participate in this study.

Exclusive Criteria
- Non-practicing physicians.
- Physicians who refused to participate in this study.

Period of Study
The study was conducted during the period from May 2023 to July 2023.

Sample size:
Simple random sampling including 355 participants who were available and eligible during the study period.

Data collection:
Data was collected using standardized self-administered questionnaires.

Data collection tools:
A structured and self-administered electronic questionnaire was used in the study for data collection. The questionnaire had been validated and approved by an ophthalmologist, and a pilot study was done. The questionnaire consisted of three main sections; sociodemographic characteristics, physicians' attitude regarding ocular injury and the practice in PHC centers and hospitals regarding ocular chemical injury.

Plan for data analysis:
Data collected was computerized through Microsoft Excel. The data was analyzed through SPSS Version 21. The data was presented graphically (frequency tables, graphs).

Ethical consideration:
It was sought from the research technical and ethical committee at the Faculty of Medicine. Informed ethical consent was taken from the participants. No personal data or information was included in the questionnaire to ensure the participants' privacy and confidentiality.

Results

Our study included 355 participants from all regions of Saudi Arabia; 171 physicians from emergency medicine and 184 from family medicine (Figure 1). The majority of our participants were from the middle region (31.3%) and the western region (27.3%), while only 9.3% were from the southern region (Figure 2). The greatest number of respondents were level 1 residents in both specialties, as shown in Figure 3. Table 1 reveals the participants' sociodemographic characteristics.

Figure 1: Participants' specialty percentages

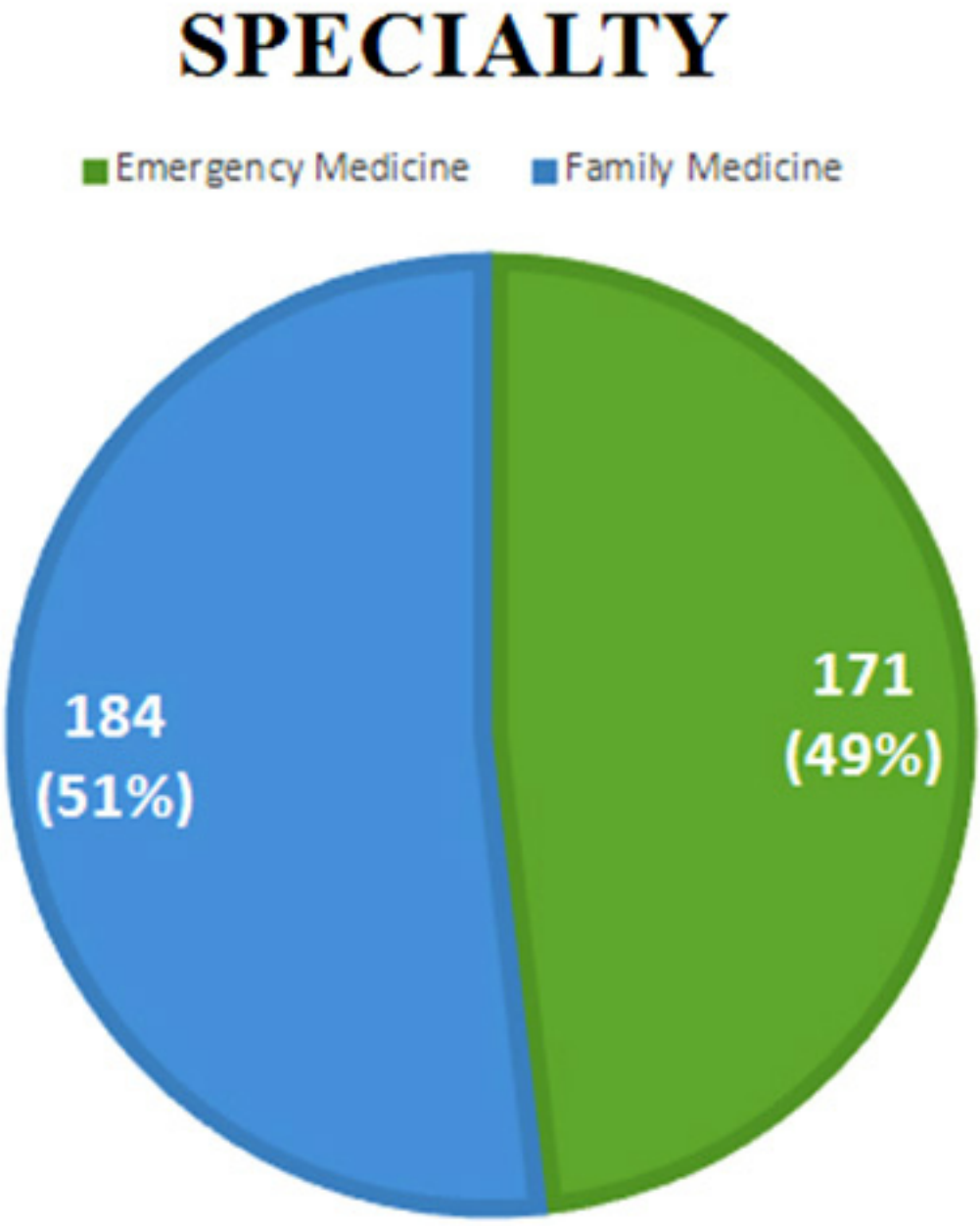


Figure 2: Participants' regions

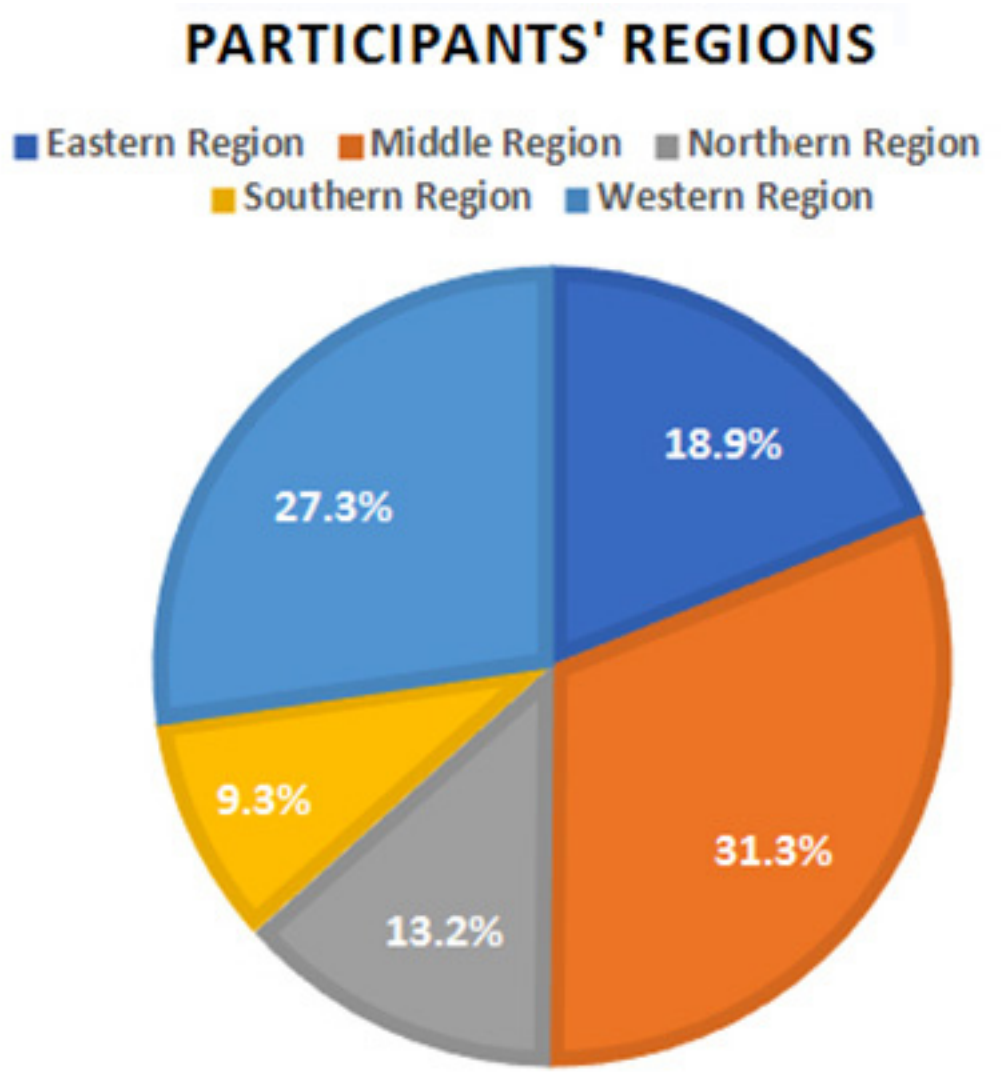


Figure 3: Participants' SCFHS classification

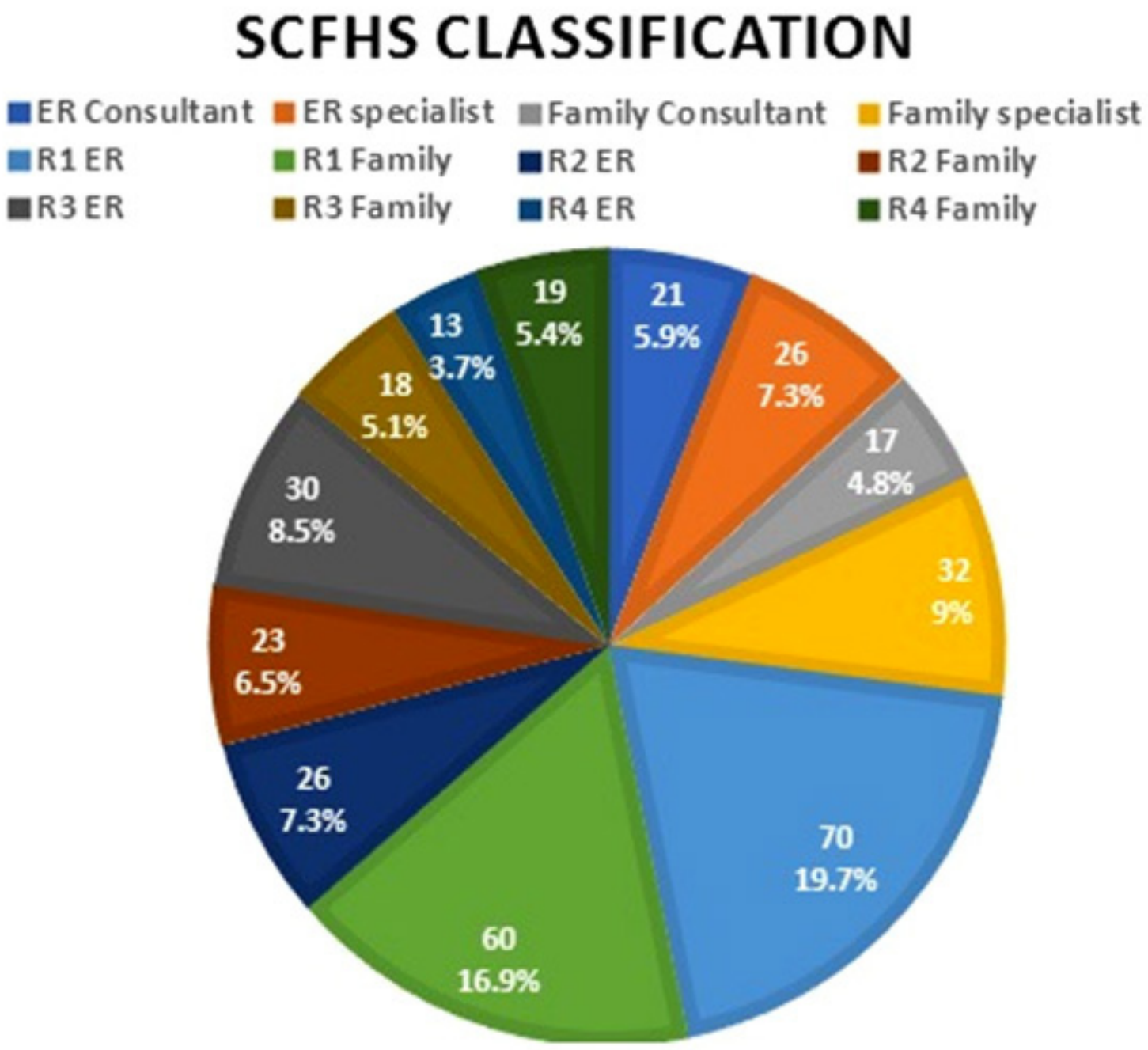


Table 1: Participants' Characteristics

Participants Characteristics	Frequency	Percent
Age		
25 - 30	241	67.9
31 - 35	53	14.9
36 - 40	31	8.7
41 - 45	13	3.7
46 - 50	10	2.8
51 - 55	5	1.4
61 - 65	2	.6
Gender		
Female	183	51.5
Male	172	48.5
Marital Status		
Divorced	12	3.4
Married	174	49.0
Single	167	47.0
Widow	2	.6

Table 2 shows the knowledge regarding signs of severe injury, which only 53 and 51 of emergency medicine and family medicine physicians respectively answered correctly about the most common early symptoms of chemical injury (P=0.011). However, there was a significant difference (P=0.001) regarding the most important sign that indicates the urgency of treatment as 52 of respondents recognized the warning sign, 28 of them were emergency medicine doctors.

Table 2: Participants responses regarding the knowledge of ocular chemical injury

Knowledge regarding signs of severe injuring			
	Emergency Medicine	Family Medicine	P value
What are the most common early symptoms of chemical injury?			0.011
A. Redness of eye	53	51	
B. Burning sensation of the eye	83	81	
C. Pain in the eye	34	38	
D. Don't know	1	14	
What are the most important signs to indicate the urgency of treatment?			0.001
A. Whitish opacity of cornea	76	89	
B. Whitish opacity of the conjunctiva	28	24	
C. Reddish conjunctiva	54	34	
D. Don't know	13	37	

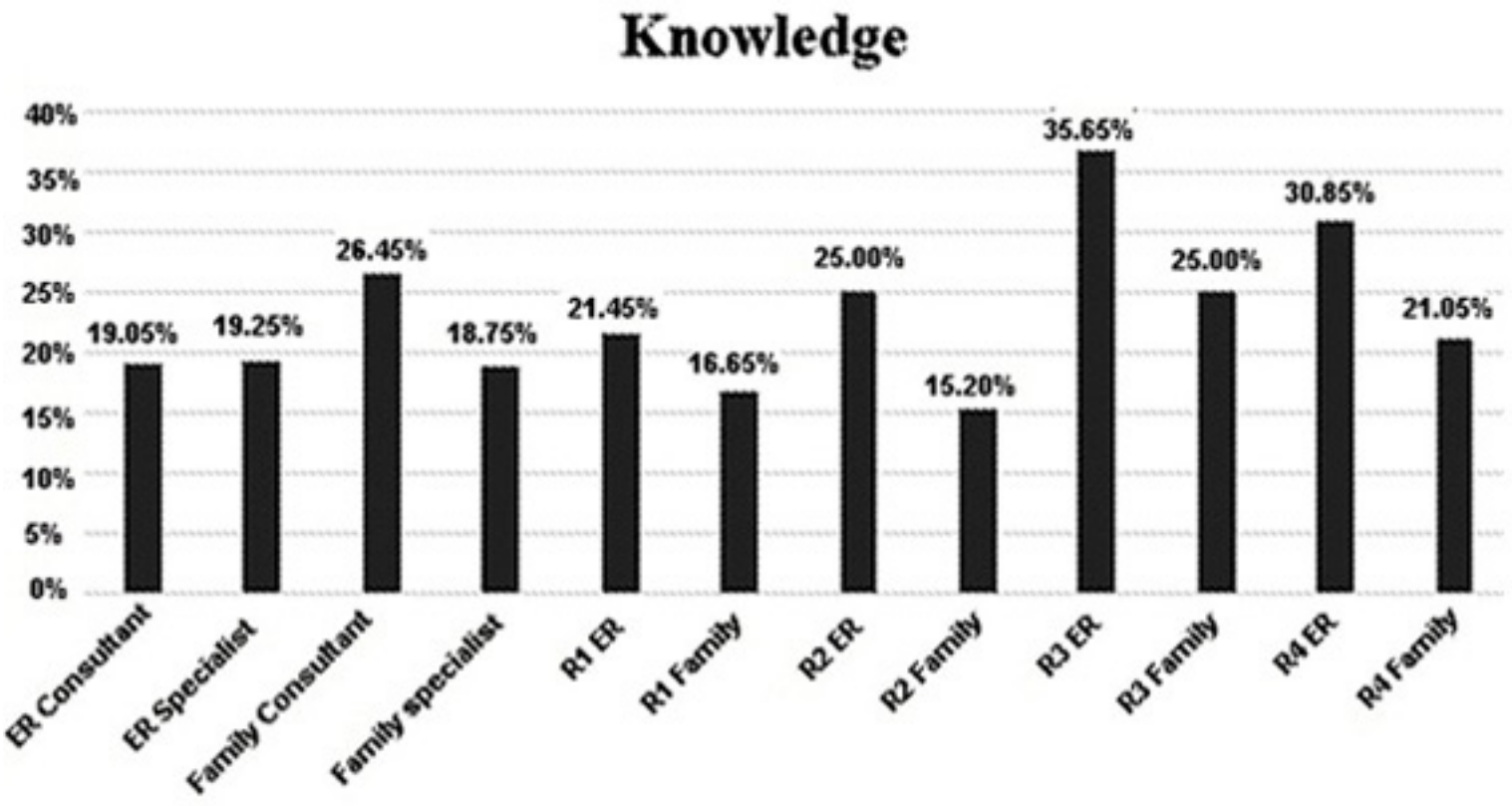
Regarding the practice of emergency management (Table 3), there was no significant difference between the respondents of the two specialties in regard to: the first step in the management (P=0.218), does the emergency management differ in cases of different categories of etiological agents (P=0.424) and the irrigating liquid that can be used to irrigate the eye (P=0.122). On the other hand, there was a significant difference in regard to how to neutralize the chemical injury (P=0.009), the minimum amount of fluid (P=0.000), and duration to irrigate the eye (P=0.005). Only 45 physicians from emergency medicine chose to dilute the chemical to neutralize the injury, while 51 of family medicine physicians responded correctly to the same question. 71 emergency medicine physicians knew the correct amount of fluid needed to irrigate the eye but only 65 of them responded correctly to the minimum duration of irrigation compared to 43 and 79 of family medicine physicians who chose the correct amount and duration.

Table 3: Participants' responses regarding emergency management of ocular chemical injury

The practice of emergency management			
	Emergency Medicine	Family Medicine	p - value
What is the first step in the management of chemical injury			
A. History taking	31	42	0.218
B. Primary ocular survey	23	14	
C. **Start irrigation**	110	123	
D. don't know	7	5	
Does the emergency management differ in cases of different categories of etiological agents?			0.424
A. Yes	67	81	
B. No	28	21	
C. Depends on the situation	60	60	
D. Don't know	16	22	
How will you neutralize the chemical after the injury has occurred?			
A. Balance the pH	61	39	0.009
B. **Dilute the chemical**	45	51	
C. Depends on the situation	54	70	
D. Don't know	11	24	
What is the irrigating liquid can be used to irrigate the eye post chemical exposure?			
A. Ringer lactate / BSS	49	48	
B. Tap water	89	99	0.122
C. Any non – toxic liquid	18	10	
D. Don't know	15	27	
How much minimum fluid is needed to irrigate?			
A. 100 ml	33	29	0.000
B. 500 ml	35	46	
C. 1000 ml	71	43	
D. Don't know	32	66	
What is the minimum duration of irrigation?			
A. 5 min.	25	28	0.005
B. 15 min.	65	79	
C. 30 min.	63	40	
D. don't know	18	37	

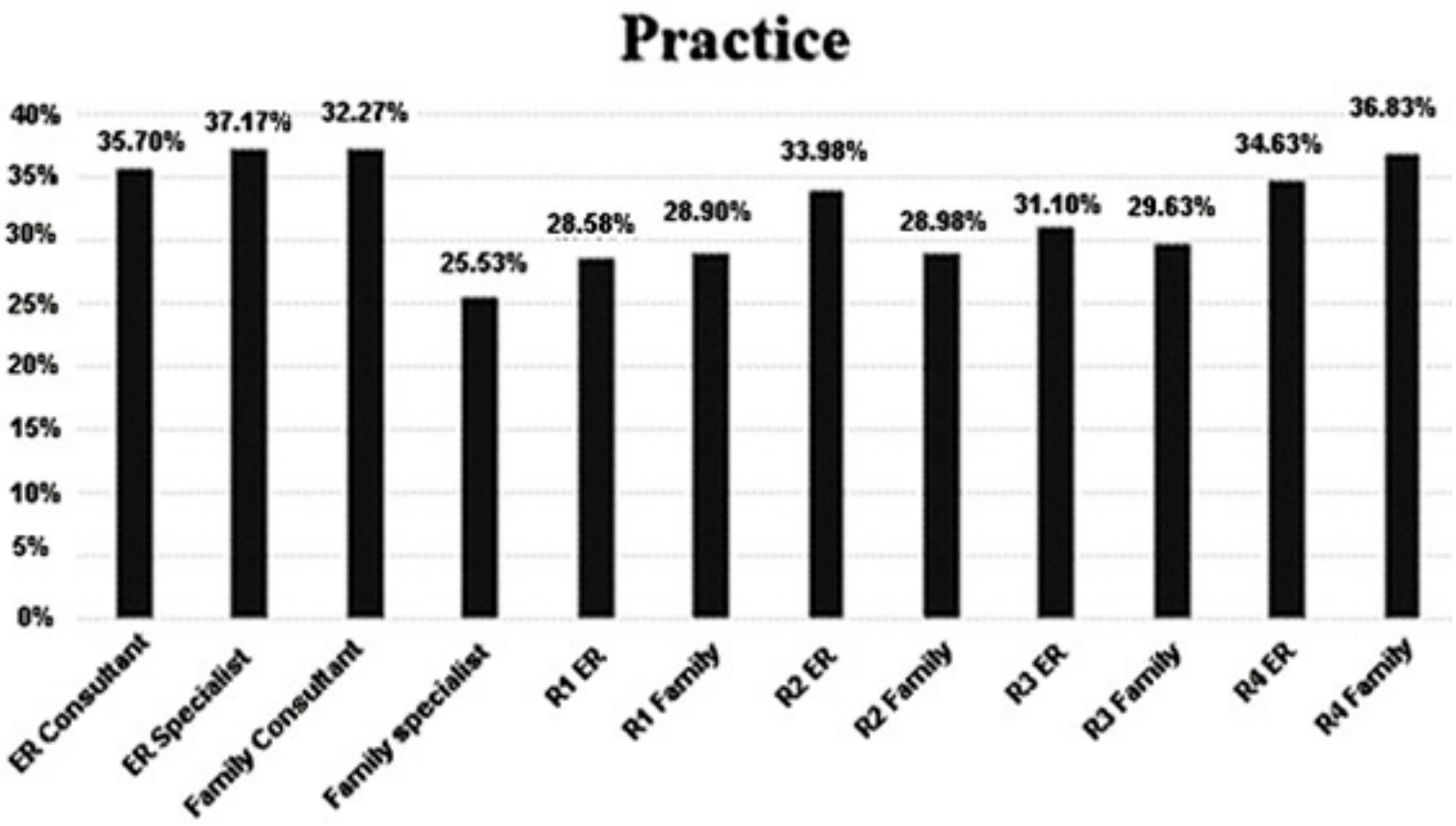
The level of knowledge regarding ocular chemical injury is shown in Figure 4. The figure shows that ER consultant (19.05%), ER specialist (19.25%), family medicine consultant (26.45%), family medicine specialist (18.75%), R1 ER (21.45%), R1 family medicine (16.65%), R2 ER (25%), R2 family medicine (15.20%), R3 ER (36.65%), R3 family medicine (25%) R4 ER (30.80%), R4 family medicine (21.05%) respectively have different levels of knowledge. The highest level was R3 ER residents while the lowest level was R2 family medicine residents.

Figure 4: Level of knowledge of ocular chemical injury



The level of practice regarding ocular chemical injury is shown in Figure 5. The figure shows that ER consultant (35.70%), ER specialist (37.17%), family medicine consultant (37.27%), family medicine specialist (25.53%), R1 ER (28.58%), R1 family medicine (28.90%), R2 ER (33.98%), R2 family medicine (28.98%), R3 ER (31.10%), R3 family medicine (29.63%) R4 ER (34.63%), R4 family medicine (36.83%) respectively know the correct practice towards ocular chemical injury. The highest percentage was family consultants while the lowest percentage was family medicine specialists.

Figure 5: The correct practice towards ocular chemical injury



Discussion

Twenty-five thousand chemical compounds have the ability to cause burns out of 150 million catalogued chemical compounds according to American Chemical Society (ACS) (6,7). In the industrial environment, acids have been reported to be the superior of substances to cause chemical insult by Colby, in which Sulphuric acid is the commonest etiology to cause this insult (8,9). Redness of the eye indicates serious ophthalmic insult which is the earliest sign to appear after the chemical injury. About 29% of emergency medicine and family medicine physicians answered this correctly. Paleness of the conjunctiva is the symptom that suggests the severity of ophthalmic injury in which the urgency of treatment is indicated (3,4,8,10). There was a lack of knowledge about the most important sign that indicates urgency of treatment as 85% of the respondents were wrong. The majority of chemical harm is treated by society's habit of washing the eye as soon as something goes into it (11). 65.6% of both specialties have chosen irrigation of the eye as the first step in management. No significant differences between the respondents of the two specialties in regard to the first step in the management were identified (P=0.218). In regard to the management of different categories of etiological agents 13.8% were correct. Exothermic reaction could be caused by chemical correction of pH. Correction by a huge amount of irrigation is the method of choice to neutralize pH to prevent the consequence of the chemical method (11,12). 27% of the participants were aware of the right method of the pH neutralization. A total of 92% of the physicians were wrong about the irrigating liquid that can be used to irrigate the eye post chemical exposure. Any nontoxic fluid could be used as there are no differences between them (5). Irrigation with 1000 ml of fluid for about 15 minutes is the minimal accepted strategy to eliminate the chemical insult from the eyes, while the recommended method is to irrigate by two litres of liquid over half an hour (1). 41.5% of emergency medicine physicians knew the correct amount of fluid needed to irrigate the eye but only 38% of them responded correctly to the minimum duration of irrigation compared to 23% and 43% of family medicine physicians who chose the correct amount and duration respectively.

The study was done on 355 physicians which showed that the level of knowledge regarding ocular chemical injury was the highest among all participants in R3 ER residents (36.65%) followed by R4 ER residents (30.80%) while the lowest level of knowledge was in R2 Family residents (15.20%). Meanwhile the level of practice regarding ocular chemical injury among the participants, Family consultants were on top (37.27%) and the lowest percentage was in Family medicine specialists (25.53%).
This study aimed to explore the knowledge and management of ocular chemical injury and to compare the competency of managing ocular injury between family physicians and ER physicians. This study could be the first step towards better understanding of knowledge and management between these two groups. The authors acknowledge that the current study is not without its limitations. The study is limited to the knowledge and management and did not consider the awareness of long-term complications such as corneal opacity, phthisis, and glaucoma, which have a tremendous effect on the quality of life.

Conclusion

The study has shown that there is a lack of knowledge regarding ophthalmic chemical injuries in both family physicians and emergency medicine physicians, as well as some insufficiency in their practice and attitude regarding the appropriate management of chemical injuries. The authors suggest that guidelines should be formulated on how to handle such cases, and the physicians have to be trained and well informed of these guidelines in order to minimize the complications and improve the outcomes of ophthalmic chemical injuries.

Recommendations:
• Knowledge regarding chemical ocular injuries should be raised.
• Practice and management regarding chemical ocular injuries should be assessed and improved among physicians in order to improve the quality of life,
• More studies regarding this topic should be conducted in order to assess the situation.

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