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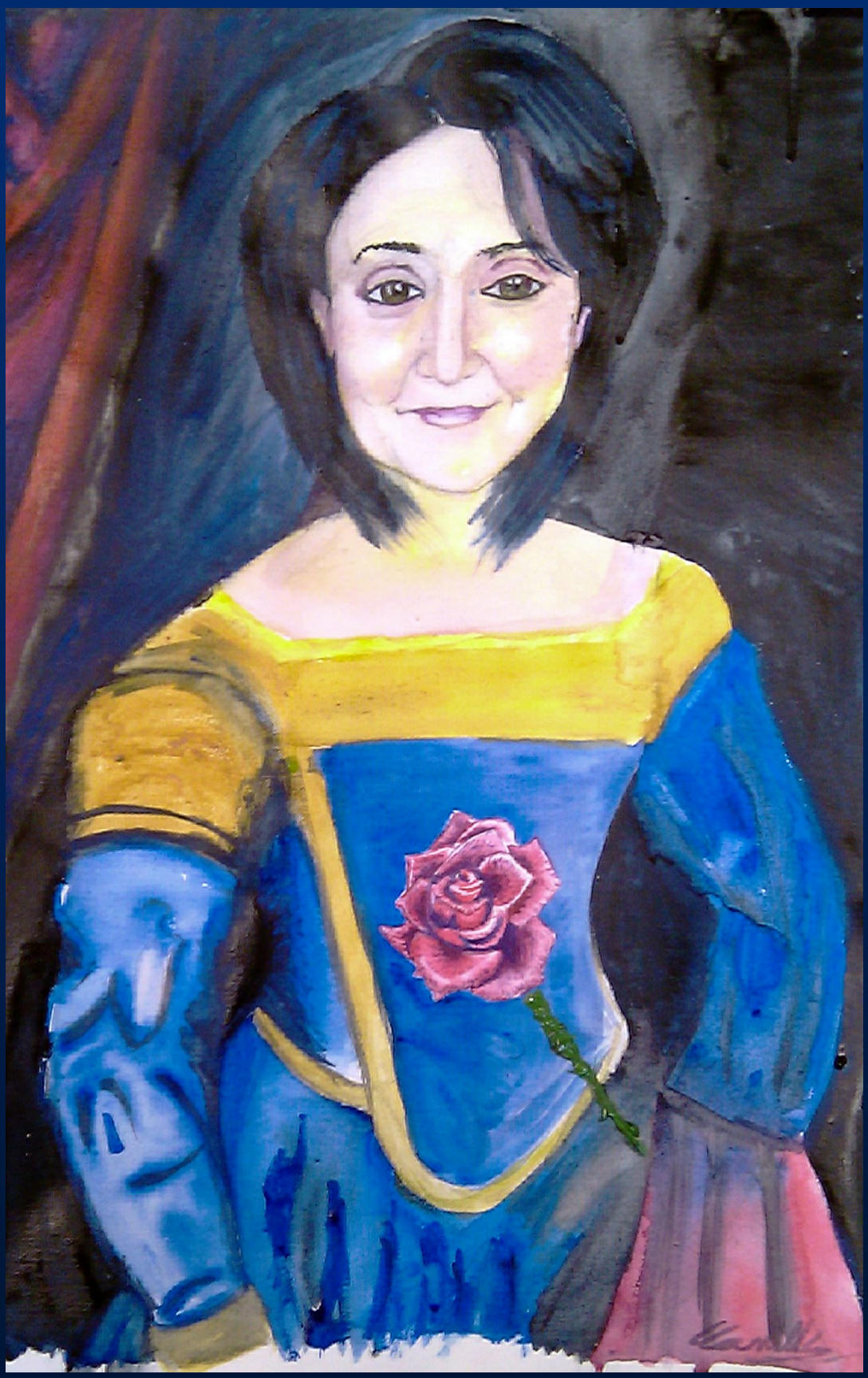

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Editorial

Viruses, Man & Ebola

Christopher Barbara

Have you ever asked yourself how many viruses there are on earth? The answer is 10^{31}, that is about one hundred billion trillion viruses. The majority of these are found in the oceans. 80% of the biomass in the oceans consists of bactiriophages and these are cidal to the biofilims contaminating our seas. Hence the blue green algae are preserved and so is the oxygen supply on our planet.

On the other hand, there are those viruses which are notorious for the diseases they cause. These may infect man directly, or else effect the food we consume such as plants, vegetables and animals.

New and emerging viruses have led to outbreaks, epidemics and even pandemics. When man encountered the virus for the first time he showed no or little immunity against it. This, together with the fact that during the Neolitic period man congregated into communities made the transmission of these viruses much easier. Also man developed farming and agricultural skills and to combat diseases such as potato blight. Also viruses may exhibit the ability of "jumping species", e.g., an avian virus or a swine virus may suddenly infect man or other animals or primates. The newly formed re-assorted virus has the potential to infect us humans as our immune system has no protection against such a new virus. A classical example is the Influenza virus which has led to epidemics and pandemics.

Two of the oldest recorded viruses which led to outbreaks were smallpox and measles. Initially smallpox was thought to infect only rodents, but it 'jumped species' to infect man. Millions of people succumbed to this deadly disease and it was not until the discovery of the smallpox vaccine by Jenner in 1798 that man started to develop ways to protect himself against these infective agents. Today we have quite a large collection of vaccine preventable diseases and with the launch of each novel vaccine, there has been a corresponding dramatic decline in the disease thanks to Jenner and the vaccine, smallpox has today been eradicated globally.

In spite of the protection afforded by vaccines and the number of complications and deaths prevented, many are those who are sceptical of the use of vaccines because of some documented adverse effects or because of some unfounded articles published in the media and on the net. This unwillingness to get vaccinated has unfortunately led to the re-emergence of diseases which had been almost eradicated:- the best example is the recent measles outbreaks. In Europe and the UK "following scares of autism from the MMR (Measles, mumps, rubella) vaccine.

A major development in the 20th century was the onset of the silent epidemic of HIV and AIDS which in sub-Saharan Africa infected over 70 million people, and is today spread globally. Up to the present moment we are still challenged by the hypervariable region of the virus to produce an effective vaccine for it, but even though research results appear promising we are still without an effective HIV vaccine.

At present, many of us are closely following the escalation of the Ebola virus outbreak on the local and international media. Health services all over the world are preparing for a possible scenario in case health care workers need to handle someone infected with Ebola.

Malta is no exception to this and although we have never had a patient with Ebola on our shores the Health Authorities have issued guidelines on practices and algorithyms to be followed just in case there is an imported case.

Sentinels for disease surveillance have been placed at sea ports and at the Malta International Airport and clinicians are being alerted on the symptomatology of the disease. These include headache, sore throat, muscle pain, sudden fever and intense weakness at an early stage. At an advanced stage the patient may present with vomiting and diarrhea, a skin rash, internal and external bleeding and impaired liver and kidney function. The incubation period varies from 1 to 21 days.

These symptoms, together with a history of recent travel to affected countries (Guinea, Sierra Leone, Liberia and Nigeria) should alert the clinician and he should immediately contact the public Health Medial Officers on hotline 21324068.

Blood samples are collected by the Public Health Officer, who is bound to take all the standard precautions necessary in order to eliminate contact with any blood or body fluids. An EDTA bottle is sent to the Molecular Diagnostics Section at Pathology at Mater Dei using the triple packaging systems supplied by the laboratory.

Using molecular techniques (polymerase chain reaction) the virus may be detected within 6 hours from the time the sample arrives at the laboratory.

In the first few days of the incubation period the viral load may still be very low and one may obtain a false negative result. Hence if the clinical suspicions are still high the test should be repeated again within 3-5 days. During this low viral load stage the patient is not or unlikely to be infectious .

If a patient is confirmed positive for Ebola, he is

transported to the new section of the Infectious Disease Unit at Mater Dei Hospital using the newly procured isolator tent. This tent, equipped with high pressure efficiency (HEPA) filters, isolates the patient from health care workers, thus eliminating the risk of contagion. All hospital infection control guidelines will be followed during the patient`s hospital stay.

Treatment includes supportive care with:

- Fluid and electrolyte management
- Haemodynamic monitoring
- Ventilation
- Steroids for adrenal crisis
- Treating secondary bacterial infections.

Anticoagulants, intramascular infections, acetyl salicylic acid and non steroidal anti inflammatory agents are contraindicated.

Also one has to manage severe bleeding complications using:

- Cryoprecipitate
- Platelets
- Heparin for disseminated intravascular coagulation (DIC) and fresh frozen plasma.

Antivirals, such as Ribavirian, have no documented benefit for Ebola Virus disease (EVD). However ZMapp, developed by Mapp Biopharmaceutical Inc., is a product which consists of monoclonal antibodies that bind to the protein of Ebola virus. This has not yet been tested for safety and effectiveness in humans and trials are currently being conducted.

In case the patient succumbs to EVD, arrangements have been made for the transfer of the body to the hospital morgue. Prayers and funeral service will be held at the Morgue and the body will be placed in double body bags with formalin granules filling the space between each bags. The bags will then be place in a zinc lined coffin. Burial will then proceed to a selected site at the Addolorata cemetery.

While we cannot ever avoid to live in the midst of bacteria and viruses it is important for us not to underestimate the potential of virulence exhibited by some of these microorganisms. So I would recommend that we are always prepared for any eventuality. We should prevent disease by advocating vaccination and should keep ourselves and our immune system healthy in order to be able to defend and withstand attack.

Cover Picture:
The Pharmacist
By Christian Camilleri
I was born in Malta in 1989. My passion for art began in my childhood. I was self taught and began drawing scenes of rural areas in Malta in my early teens. In my early twenties I began painting watercolour portraits. I find inspiration in Baroque art. Some of my work has been displayed in the recent MCC exhibition in Summer 2014. I am also a medical doctor, graduated in 2012. Painting is a passion I enjoy during the free time I have left.

Original Article

Epidemics of poliomyelitis in the Maltese island of Gozo: genetic susceptibility

H.V. Wyatt

Abstract

There were fewer epidemics of polio in Gozo than in the much bigger island of Malta, but over many years the proportion of cases was similar. Within Gozo, the attack rate was greater in some villages and this was caused by some extended, related families with genetic susceptibility to polio. In these families, there was considerable consanguinity. Two thirds of the polio cases were related. To understand polio, one must study the disease over many years, not just isolated statistics from unconnected epidemics.

Key words

Consanguinity, genetic susceptibility, Malta, poliomyelitis

Introduction

The smaller island of Gozo lies north-west of Malta (for a map, see[1]) with an area of 67 square kilometres and about one tenth the population. The polio cases on Gozo and their controls form the basis of this study: many of the parents and grand-parents of polios and controls on the island of Malta had migrated from Gozo and have been included. Polio seasons typically began after September and lasted over Christmas to spring with very few cases in May to August. Therefore the annual incidence (Fig. 1) is given for each July to the next June, emphasising the extent of the epidemics. In most years when there were no cases on Gozo, there were some on the bigger island of Malta. The last cases on Malta and Gozo occurred in 1964, after which the Sabin oral polio vaccine (OPV) was used to immunise the population.

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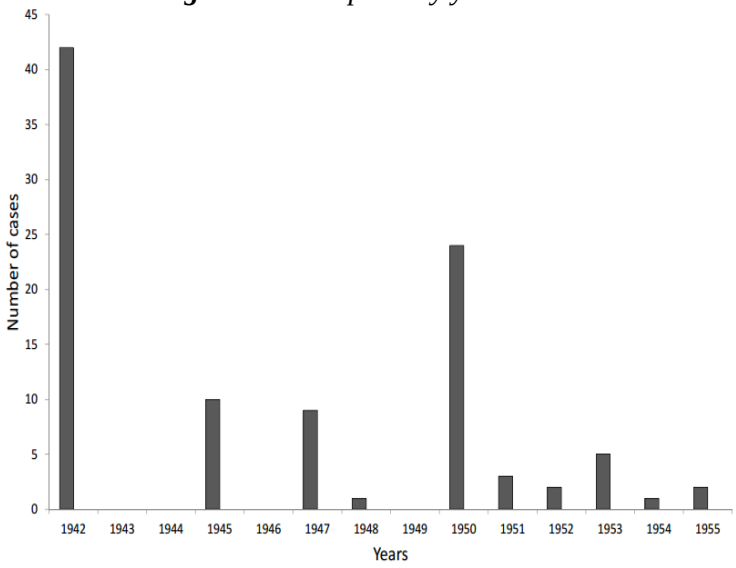
***Figure 1**: Gozo polio by year*



Materials

With the permission and support of the Chief Government Medical Officer, I was able, in 1982-1987, to examine the records of the Infectious Diseases Hospital 1926-1964 (which were later trashed by unknown vandals) and the Physiotherapy notes at Saint Lukes Hospital. With the permission and support of the Archbishop of Malta, the Bishop of Gozo and the Director of the Public Registry (a lawyer) I was able to trace the polios and their controls in the records of baptisms and marriages which, in the parishes, also gave dispensations for consanguinity.

I found details of 1 072 polios in Malta and Gozo and these were traced to their great grandparents. For each polio, a control child (prefixed 'C') was found either five baptisms before or after in the same parish and traced in the same way. The marriages of the great grand-parents were traced in three parishes although this involved more than doubling the work. A register of polio cases in the Gozo Health Department gave details of cases plus another 2 whose parents came from Gozo, but who were paralysed on Malta. I found cases from 1909 to 1940 in the Gozo hospital records when they later received treatment as adults. One teenager, born in Detroit, but paralysed on holiday in Gozo, was traced through his uncommon surname. The father of one polio

child was a UK soldier and 3 fathers of controls were born in the UK.

Results

There were 39 cases with paralysis in the Maltese islands prior to the 1942-1943 epidemic and of these, seven were from Gozo. Although the numbers are small, one might have expected only four from Gozo as the population was about one tenth that of Malta. In the years after 1943, Gozo had fewer outbreaks than Malta suggesting that the virus travelled less frequently to Gozo. Nevertheless, the cases from Gozo were similar to the ratio of the populations of the two islands. Of the 110 polio children born on Gozo, 67% were related. Eight were sibs, 15 were first cousins, (17 were first and second cousins) and 64 were second cousins.

The 1942 epidemic

The first case occurred on 3 December in Victoria and was followed the next day by two sibs in Zebbug and others in Nadur, Victoria and Sannat (part of Victoria).These cases were not at first diagnosed as polio by the local pediatrician (personal interview). For these cases to have occurred almost simultaneously all over the island suggests a common source infecting a number of adults who travelled to the different villages. There were no soldiers on the island and little petrol for transport. Probably a small boat had returned from Marsa or Valletta on the main island of Malta after carrying produce to market – the siege had been lifted, but food was still scarce. There were 35 cases until January, with two unrecognised at the time. The last cases in Zebbug on 12 December and Victoria on 21 December left the virus circulating in Xaghra (11 January) and Nadur (18 January), reappearing in Gheinseilem on 16 April and Xaghra again on 1 May 1943.

The majority of cases, 70%, were under 3 years old when paralysed suggesting that there had been previous silent waves of virus circulating before the isolation of Malta after June 1940 by the Italian navy– there had been single cases in 1937 and 1939. Not everyone had been infected in these earlier waves – the 1937 case was 24 yr old and there was a 7 yr old in Gharb in 1942.

Later epidemics

In later years a few older children were paralysed – a 10 yr old and a 14 yr old in Victoria in 1946 and 1961 respectively and a 9 yr old in Xewkija in 1954, suggesting that although each wave of viruses circulated very widely, there were a very few children who escaped infection.

In 1945-1946 there were 5 cases in Kercem (part of Victoria) starting on 17 December (the only cases ever in Kercem) with 3 other cases in Victoria and 1 each in Xewkja and Xaghra. An even smaller outbreak started in July 1947 with 2 cases in each of Xewkja, Victoria and Nadur and 1 case in Xaghra with the last case in October. Two cases in June 1948 in Xaghra and June 1949 in Zebbug may represent continuing presence of a virtually avirulent strain. In August 1950 another wave of cases continued until July 1951 with 23 cases in all the major villages, including 8 children in Nadur.

The incidence was far from uniform (Table 1) with the highest in Zebbug the smallest and most remote village, and the lowest in the cosmopolitan Victoria and two small remote hamlets. However, there were several cases where a polio in one parish was related to several in another parish e.g. two polios living in Gheinseilem were closely related to at least four, and possibly six others in Xaghra.

***Table 1**: The incidence of polio in Gozo 1942 – 1964.*

Town/ village	No. of children No. of polio cases % cases/children < 4 yr 1931 census[2]	No. of polio cases 1942-1943	No. of polio cases 1945 +	% cases/ children
Zebbug	89	4	4	9
Gheinsielem	145	7	4	7.6
Nadur	296	8	12	6.6
Qala	122	1	6	5.7
Xaghra (Caccia)	297	10	5	5
Xewkja	240	1	10	4.6
Gharb & Ghasri	142	3	3	4.5
Victoria (Rabat)*	673	7	18	3.7

**I have included San Lawrenz, Kercem and Sannat with Victoria (see [1]). There was no census after 1931 because of the war.*

Genetic susceptibility in the villages

Although a US doctor had published many papers citing families with multiple cases, in the 1900's[3], genetic susceptibility had been ignored after 1935, in favour of research for vaccines. The first page of the medical notes of the polio children from 1942-1943 and those from earlier and later years, is blank with no genetic or family information. However, the genealogical data of the grand-parents and great grand-parents has shown many relationships.

In the village of Nadur, I traced further ancestors because the complicated consanguinities suggested further relationships. In the 1948 census the village had a population of more than 3,000, most of whom had been born in the parish. There were 29 cases of polio in

the parish, of which 23 were related in a convoluted, tightly knit group of families linked by many consanguinities (Table 1), with two cases now living in other villages. Of the 39 cases in Malta and Gozo prior to the 1942-1943 epidemic, two were from this group from Nadur (cases #20 and #32 in 1909 and 1921). There were five cases and one in another parish in the 1942-1943 epidemic and others in 1947, 1952, 1956 and 1958 with nine in 1950-1951 and two, with one in another parish, in 1953.

The 23 polios were related with 33 links to each other and to 12 controls in the same family complex. There was one pair of polio sibs, and another mixed pair of a polio and a control. There were more consanguinous marriages among the polio ancestors than among those of the controls (Table 2).

***Table 2**: Consanguinity among parents and grand-parents on Gozo: marriages of Parents ranged from 1908 to 1957 and grand-parents from 1871 to 1922. (Details of dispensations from the parish registers)*

	Parents						**Grand-parents**					
	No.	**II**	**II/III**	**III**	**III/IV**	**IV**	**No.**	**II**	**II/III**	**III**	**III/IV**	**IV**
Polis	103	6	2	9	0	0	249	4	7	15	14	33
Sibs										1		2
Shared										1	5	6
Controls	111	5	0	8	0	1	251	7	1	10	7	22

Three pairs of mixed sibs, each with one polio and one control shared grand-parent marriages: these and other shared grand-parents have been included in both totals. Dispensations for IV have not been required since 1917.

The small, straggling village of Zebbug is isolated in the North West corner of the island and had eight polios, seven of whom were closely related with many consanguinities (Table 3). The seven polios were related with ten links to each other and to a control in the same family complex. There were two cases and a pair of sibs in the 1942-1943 epidemic. The eighth case, #1243, was related to case #154 at another village through a great grand-parent. The father of case #443 from a smaller parish nearby was married to a lady from the village, whose sister was married to case #459 from another village. The mother of case #494 from Nadur was from here: her parents were II/III plus IV and her maternal grand-parents were related to case #865. In the 1948 census[4] there were more than 1,000 inhabitants most of whom had been born in the village, although many left for other villages. There were many more children since the previous census.

The large parish of Xaghra lies between Zebbug to the north-east and Nadur to the east with four 1942 polios related in a family group with two others living in Gheinseilem and a third who was living in Germany. Two cousins (one was 8 yr old) had unusual surnames and were almost certainly related to three of the family group. A pair of sibs had a paternal grand-parent IV and another polio had one who was III/IV.

Xewkija lies just south of the main road from the port of Mgarr (Gozo) to Victoria and suffered ten polios in the last years of the epidemics - one of whom was 9 yr old. There were three pairs of polios who were second cousins with several consanguinities and a pair of cousins, one of whom was brother to a possible polio who had a limp.

Gharb is an isolated parish to the east of the island where a 24 yr old with parents III suffered polio in the inter war years. There were two pairs of second cousins and one polio a cousin to two second cousins in St. Julian and Cospicua on Malta. One polio whose parents were III, had maternal grand-parents who were II/III.

Gharb is an isolated parish to the east of the island where a 24 yr old with parents III suffered polio in the inter war years. There were two pairs of second cousins and one polio a cousin to two second cousins in St. Julian and Cospicua on Malta. One polio whose parents were III, had maternal grand-parents who were II/III.

The large town of Victoria had the smallest proportion of cases, of which 15 and a pair of sibs were not related to others. The 13 yr old from Detroit, was a second cousin to a case in Mellieha on Malta. One polio was a second cousin to another polio and to two step-brothers. A 10 yr old polio whose parents were cousins, II, was a second cousin to a 14 yr old whose grand-parents were II/III. Four second cousins were from Sannat (parents II/III), Victoria (grand-parents IV) and two (second-cousins) from Xaghra (one with grand-parents IV, the other with parents III and grand-parents IV). One polio

with grand-parents IV was cousin/second cousin to a polio in Zurrieq (Malta) with parents III and grand-parents IV.

Isonymy

There was little difference in the number of isonymous marriages between the polios and the controls. The number of isonymous marriages was highest in Nadur and was low in Victoria, similar to consanguinity. Five of the 12 parent and 13 of the 26 grand-parent isonymous marriages were consanguineous.

Surnames of polios

Some uncommon surnames were associated with polios and their great grand-parents also showed that they were less common among the controls (Table 4).

Table 3*: Consanguineous marriages in villages in Gozo. (Details from the parish registers)*

	Polios						**Control**					
	Parents			**Grand Parents**			**Parents**			**Grand Parents**		
	Consanguineous						**Consanguineous**					
Village	**No**	**Percentage**		**No**	**Percentage**		**No**	**Percentage**		**No**	**Percentage**	
Nadur	28	4		53	19[a]		23	10		61	14[b]	
Xaghra	14	1		39	16		14	1		37	7	
Xewkija	11	1		24	7[a]		13	0		32	7[a]	
Gheinsielem	6	1		21	3		11	1		16	4	
Qala	6	2		16	7		7	0		12	4	
Gharb	8	2		17	4		6	0		16	4	
Zebbug	7	2		13	8		9	1		19	4	
Total	**80**	**13**	**16%**	**183**	**63**	**34%**	**83**	**13**	**16%**	**193**	**44**	**23%**
Nadur	23	3	13%	65	4	6%	28	1	3%	58	3	5%

Notes: [a] *of which one was a double consanguinity:*
[b] *of which four were double, eg II + IV).*

Table 4*: Surnames of great grand-parents associated with polios or controls*

Surname	**Parish**	**No.**		**Totals on Gozo**	
		Polios	**Controls**	**Polios**	**Controls**
X	Gharb	17	0	31	14
Y	Victoria	10	2	35	15
Z	Xaghra	10	2	11	7
U	Victoria	8	3	11	4
Q	Victoria	7	1		
	Gharb	7	2	16	3
O	Xaghra	41	29	57	41

Sibs

There were eight pairs of sibs in my sample – three with both polio sibs, four where only one had polio, and one pair of both controls. Of those with both polios, two had grand-parents III/IV and IV and there were also two pairs of polio sibs on Malta for each of which one grand-parent came from Gozo. Of the four with mixed polio and control, two had only one Gozitan parent and another pair were step-children (a control Gozitan and a polio child on Malta): another had IV grand-parents. A mixed pair in Cospicua (Malta) had one grand-parent from Gozo. The parents of the pair of control sibs were isonymous with one pair of III/IV grand-parents and grand-parents of a polio.

Discussion

At the beginning of this study there was no suggestion among the published papers and the archives that the distribution of polios was other than random in the various villages. The unexpected concentration of polios in some villages has meant that the controls are also more frequent in those villages and are not a reflection of the entire population. I chose the baptism of a control four distant from the polio to avoid baptisms of twins and cousins: I did not know that the priest in those times would hurry to baptise a new-born infant in case it died or was still born.

In general, there were more consanguineous marriages among the parents of polios and many more among the grand-parents (Table 2). The large village of Nadur had the greatest proportion of consanguineous marriages and, surprisingly, Zebbug had few (Table 3). There have been fewer consanguineous marriages in recent years so there are far fewer among parents than among the grand-parents. As in Malta, some families showed multiple consanguinities in both parent and grand-parent marriages (Table 5). Consanguineous marriages over several generations were common in a few families, probably due to the limitations on meeting other suitable teenagers. Family events, marriages, fiesta celebrations and birthdays provided the unsupervised meeting of teenagers. Within a village, there would be a hierarchy of respectability. At the top would be someone wealthy, the president of the church laity, president of the band club and the leading political party. His family would not normally marry beneath them. During epidemics, meetings between children would have been avoided.

It was said of Zebbug that 'intra-village marriages up to the war [1940] were 80%' and 'new households set up in the village as close to the core as possible'.[5] Vella[6] reporting a high incidence of thalassemia minor, said 'Zebbug was described by a prominent educated villager as one large family'. Vassallo[7] had reported on consanguinity in Gozo. In small communities, counts of isonymous marriages from marriage registers may include some which are related. However, although an isonymous marriage with a rare surname may well indicate common sharing of genes, this may not apply with more common surnames. There may well be many non-intermarrying groups for instance among e.g. Buttigieg, which may include both rich and poor. The Maltese surnames of Catania and Messina were possibly given to immigrants from those towns in Sicily, but immigrants with these same Maltese surnames may be unrelated and came at different times. Marriages from two villages may be between a couple from adjacent farms in the two parishes.

Conclusion

There is much evidence of genetic susceptibility to poliomyelitis.

Acknowledgements

I am deeply grateful for travel grants from the Peel Medical Research Trust in 1982 and the Royal Society in 1985, to all the doctors, kappillans and other clergy who helped me, but especially to Professors H.M.Gilles and A. Sclicuna-Spiteri. I thank many others who have helped me.

***Table 5**: Multiple consanguinities in Gozitan villages*

Village	Polio	Family of		
		Parent	Grand-parents respectively	Great Grand-parents
Zebbug	483	III	III + IV	
Gheinsielem	1241	II	IV	
Nadur	1220	III	II/IV & II/III + III	III + IV & II + III
	1222		II + IV & II/III + III	III + IV & II + III
	1227		III & IV	IV & III
	1228	II/III	III + IV & IV	III + IV
	1223		III/IV	III
Qala	1248	II	III	III
Xaghra	1204	III	IV	
	1203		IV	IV
Gharb, Ghasri	1252	III		II/III

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Original Article

Outcome of Nephrectomies in Malta since 2000

Gerald Busuttil, Simon Bugeja, Patrick Zammit, Stephen Mattocks, Karl German

Abstract

Aim: To audit the oncological results and perioperative surgical outcome of nephrectomies performed in Malta since year 2000.

Method: A retrospective index case list of all nephrectomies carried out by three urological surgeons at St Luke's and Mater Dei Hospitals from 1st September 2000 to 31st March 2012 was compiled from departmental data. Clinical, radiological and histological data were compiled from the case notes and hospital intranet computerised investigation results. Clinical staging of all patients was revised using the *Union Internationale Contre le Cancer* TNM staging 2009. All the patients who underwent nephrectomy for clear cell renal cell carcinoma were stratified according to individual predicted prognosis based on the SSIGN score developed by the Mayo clinic.

Results: Between September 2000 and March 2012, 319 nephrectomies were carried out at the Urology Unit, of these 288 were carried out for malignancy, 218 of which were clear cell renal cell carcinoma (RCC). 112 complications were recorded for the whole cohort; two patients died from perioperative complications. 80 patients passed away, 51 of these as a direct consequence of their renal cell cancer. Median duration of follow up was 42.7 months. A Cox model reveals that a SSIGN score greater than 6 significantly worsens survival rate for RCC ($p<<0.001$).

Conclusion: Morbidity following surgery, mortality rates, and oncological results in our single centre study are acceptable when compared to larger series.

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Keywords

Nephrectomy, Renal Cancer, Cancer Specific Survival, Crude Survival, Morbidity

Introduction

Despite the progress made in recent decades with the elucidation of various molecular pathways involved in the carcinogenesis of renal cell carcinoma of the kidney[1-4] which has paved the way for the development and introduction of systemic targeted therapies, the treatment of renal cell cancer remains predominantly surgical, with a paucity of alternative or adjunctive oncological options available to patients suffering from this aggressive disease.

The indication for surgical treatment has also widened with the consolidation of cytoreductive nephrectomy in metastatic disease[5-6] and establishment of laparoscopic techniques outside of centres of excellence.[7-8]

Nephrectomy is also sometimes indicated in severe benign diseases of the kidney making it a commonly performed operation in most urological units worldwide.

Cancer of the kidney and ureter was seventh most commonly diagnosed cancer in Maltese males in 2012 with an age standardised incidence of 15.0/100,000 [9] and represents a significant proportion of the patients seen at our institution's Urology Unit.

The increasing use of cross sectional imaging for investigation of various medical complaints has also resulted in an increasing incidence of incidental asymptomatic renal tumours, a phenomenon common to most urology units in the developed world. [10]

Method

A retrospective index case list of all nephrectomies carried out by three urological surgeons at St Luke's and Mater Dei Hospitals from 1st September 2000 to 31st March 2012 was compiled from departmental data. Operative data relating to procedures carried out within our Urology Unit is compiled in a prospective manner using a Microsoft Access®-based database, allowing accurate and reliable retrieval of the index case list.

Clinical presentation, prognostic factors, histology, radiological characteristics, surgical technique, post-operative morbidity and mortality, length of hospital stay and vital status were compiled from the case notes and hospital intranet radiological and clinical databases.

Survival data was corroborated with death certificates obtained from the Department of Health Information.

Staging of all patients was revised using the TNM staging *Union Internationale Contre le Cancer* TNM staging 2009, which has been externally validated in 2011.[11,12] Information from preoperative CT scans and histopathological report of the resected specimen were combined to restage all the patients in the cohort.

All the patients who underwent nephrectomy for clear cell renal cell carcinoma were stratified according to individual prognosis based on the Stage, Size, Grade, Necrosis Score Algorithm (SSIGN) developed by the Mayo clinic [13] and recently externally validated in a European study. [15] As the SSIGN score is validated for use only in clear cell renal cell carcinoma, patients whose pathology was not clear cell renal cell carcinoma were excluded from survival analysis, although these records were included in other analyses. 35 patients who developed a second malignancy (excluding squamous cell carcinoma or basal cell carcinoma of the skin) during the study period were excluded from this analysis.

Results

Patient and tumour characteristics are shown in Table 1. 319 patients underwent nephrectomy between September 2000 and March 2012. 288 patients underwent nephrectomy for tumour, of these tumours 218 were clear cell renal cell carcinomas. Other indications for nephrectomy included inflammatory or infective pathologies (26), benign masses (36), polycystic kidney disease (4) and vesico-ureteral reflux with dysplastic kidney (1). 75% (*n*=241) of the patient cohort were diabetic, other risk factors for renal malignancy included current smoking at time of surgery (16.9%, *n*=54), smoking history (14.4%, *n*=46) and positive family history (1.5%, *n*=5).

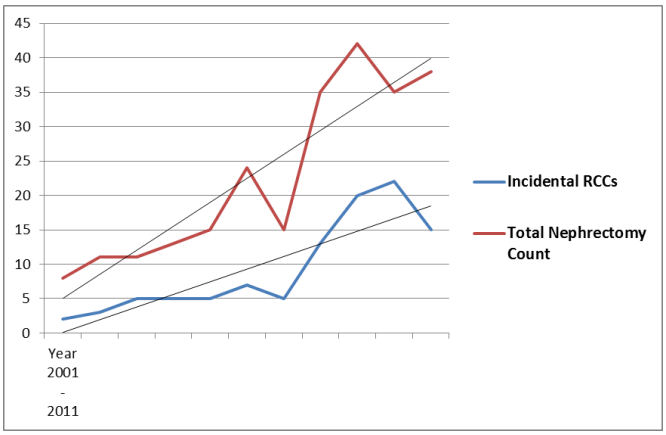
The local incidence of incidentally detected kidney tumours has been rising over the last decade (35%, *n*=115) (Figure 1). The total number of nephrectomies performed per year has also been increasing in parallel over the study period. Loin pain was the presenting symptom in 24% (*n*=82), gross haematuria in 23% (*n*=79), pyrexia of unknown origin in 3% (*n*=11), anaemia in 2% (*n*=8) and abdominal mass in another 2% (*n*=6). 11 patients (3%) presented with uncommon symptoms, such as nasal congestion from posterior nasal space metastasis, visual deterioration from occipital lobe metastasis and skull metastasis. Information on clinical presentation is not available in 26 patients (8%).

The majority of the patients underwent open radical nephrectomy (70%), followed by open partial nephrectomy (Table 1). One patient underwent joint procedure with cardiothoracic surgeons with radical nephrectomy, inferior vena cava exploration and removal of right atrial tumour thrombus under cardio-pulmonary bypass.

***Table 1**: Patient and Tumour Characteristics*

Total number of patients	**319**
Nephrectomy for tumour	**288**
Males (%)	191 (60)
Females (%)	128 (40)
Age (years) mean (range) ± SD	58.7 (22 - 90) 11.85
Radiological Size (cm) mean (range)	6.3 (1 -20)
Tumour location	
Upper pole	92
Central	90
Lower pole	77
Complete renal infiltration	10
Renal pelvis	11
Ureter	4
Not available	4
TNM Distribution	
Localised at presentation	
T1a N0 M0	71
T1b N0 M0	51
T2a N0 M0	15
T2b N0 M0	19
T3a N0 M0	29
T3b N0 M0	7
T3c N0 M0	2
T4 N0 M0	0
Metastatic at presentation	
T2a N1 M0	1
T3a N1 M0	1
T3b N1 M0	1
T4 N1 M0	1
T1b N0 M1	1
T2b N0 M1	4
T3a N0 M1	4
T3b N0 M1	1
T3a N1 M1	1
T3b N1 M1	1
T3c N1 M1	2
T4 N1 M1	1
Surgical Procedure	
Open Radical Nephrectomy	225
Open Partial Nephrectomy	34
Nephroureterectomy	15
Simple Nephrectomy	15
Laparoscopic Partial	13
No Data	11
Laparoscopic Radical	5
Open Radical and Sternotomy	1
Fuhrman grade (mean)	2.33

***Figure 1**: Incidence of incidental tumours and total nephrectomy surgeries over study period*



Morbidity and mortality data are shown in Table 2. A total of 62 patients (20%) suffered from a post-operative complication. 46 patients suffered one complication, 12 patients suffered two events and four patients suffered three complications.

After excluding post-operative transfusion (9.7%), important complications included pneumonia (15 patients), deterioration in renal function requiring temporary dialysis (8 patients), wound complications (16 patients) and intestinal obstruction requiring laparotomy (3 patients). Two patients were rendered anephric by surgery in the context of adult polycystic kidney disease, and the need for permanent dialysis was determined by pre-existing end-stage renal failure.

Two patients died within 30 days of surgery from complications related to the nephrectomy, one patient sustained a myocardial infarct followed by cardiac arrest and a second patient developed DIC after severe haemorrhage and multiple blood transfusions.

Oncological results are shown in Table 3. 288 patients who had histologically proven renal cancer were included for analysis of oncological outcome. Patients whose final histological diagnosis was clear cell renal cancer (n=218) were stratified and analysed according to the SSIGN score. This scoring system is based on the pathological tumour stage, tumour size, tumour necrosis, nodal status and presence of distant metastasis. Every patient with known clear cell renal cell carcinoma was included in one of five risk groups. Crude survival and cancer specific survival for each group was calculated and showed using the Kaplan Meier method. (Figures 2 and 3).

The same cohort of patients was then divided into two risk groups using a cut off of SSIGN score 6, with the group having a score of > 6 having a statistically significant survival disadvantage (p<0.001). (Figures 4 and 5).

***Table 2**: Summary of Complications*

Haematological		Renal/urological	
Transfusion	28	Temporary Dialysis	8
DVT	2	Perinephric/retroperitoneal haematoma	3
Febrile reaction to transfusion	1	Permanent dialysis (anephric)	2
DIC	1	Renal dysfunction - no dialysis	1
		UTI	1
Respiratory		Clot colic with obstruction	1
Pneumonia	15	Calculous obstruction single kidney	1
Intraoperative desaturation	1	Urocutaneous fistula	1
Pleural effusion	1		
Cardiovascular		Drug related	
MI/cardiac arrest	1	Opiate overdose	3
Arrhythmia (cardioversion)	1	Drug rash	1
Arrhythmia (pharmacological rx)	2	Hand and Foot Syndrome (TKIs)	1
Angina	2		
Cerebrovascular event	1		
GIT/Intrabdominal		Body Wall	
Bowel obstruction (conservative)	3	Wound infection	7
Bowel obstruction (laparotomy)	3	Incisional hernia	7
GI bleed	2	Wound haematoma	2
Psoas abscess (surgical drainage)	1		
Systemic		Perioperative death	
Sepsis	3	DIC	1
Hyperglycaemia	2	MI	1
Acute confusion	1		

***Table 3**: Follow up data*

Follow up (days) mean (range)	1282 (13 - 4246)
Adjuvant Oncological Treatment	
Systemic chemotherapy	8
External beam radiotherapy	15
Interferon	2
Tyrosine kinase inhibitor	7
Local Recurrence n (%)	10 (3.4)
Distant Metastasis n (%)	43 (14.9)
Metastasis free survival (metastatic pts only) (days) mean (range)	566 (8 - 3186)
Local recurrence free survival (recurring pts only) (days) mean (range)	280 (103 - 645)
Metastasis sites n of pts, (%)	
Lung	21 (30)
Bone	12 (17)
Liver	9 (13)
Retroperitoneal LNs	7 (10)
Adrenal	6 (8)
Brain	3 (4)
Pancreas	2 (3)
Other	11 (15)
Second Primary Tumours n of pts, (%)	35, (12%)
Site of second primaries, n of pts	
Bladder	8
Prostate	6
Colon	6
Breast	5
Lung	3
Other	7

***Figure 2**: 10 year crude survival stratified per SSIGN groups A—E*

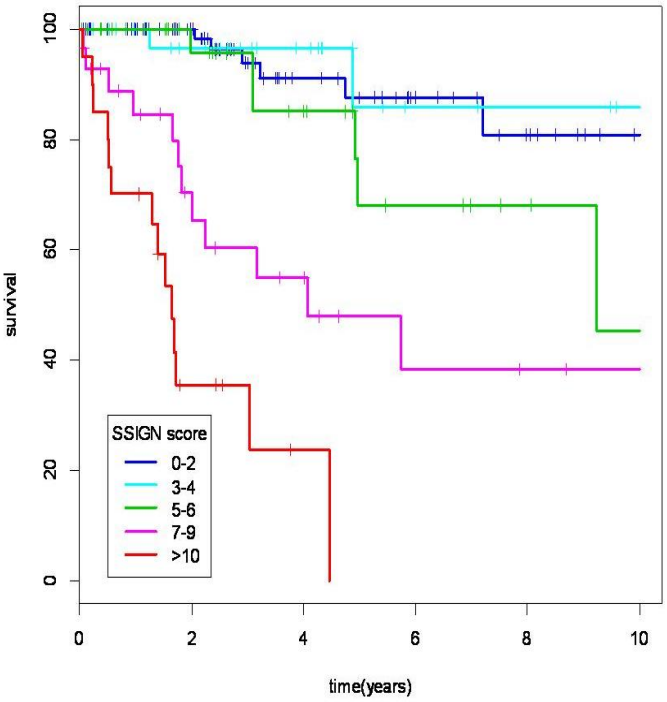


***Figure 3**: 10 year cancer specific survival stratified per SSIGN groups*

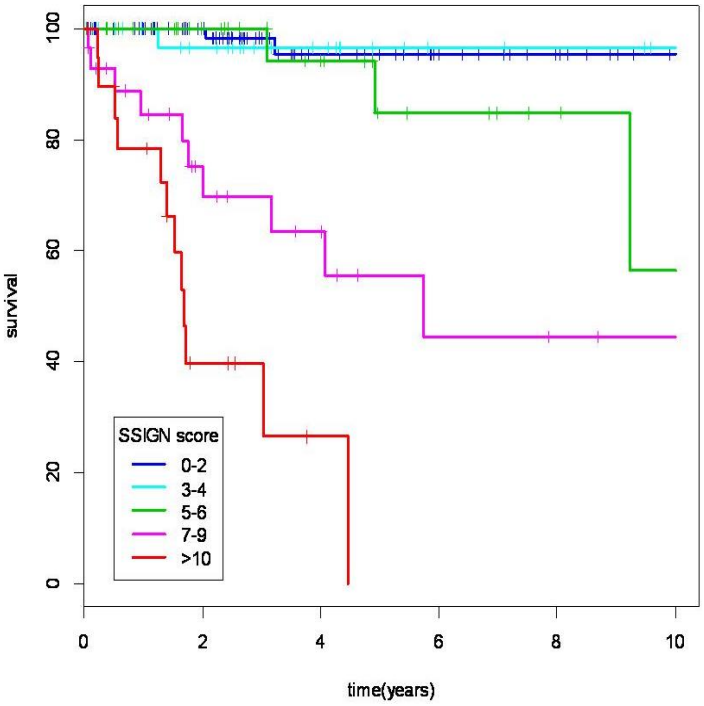


***Figure 4**: 10 year crude survival stratified per low/ high risk groups*

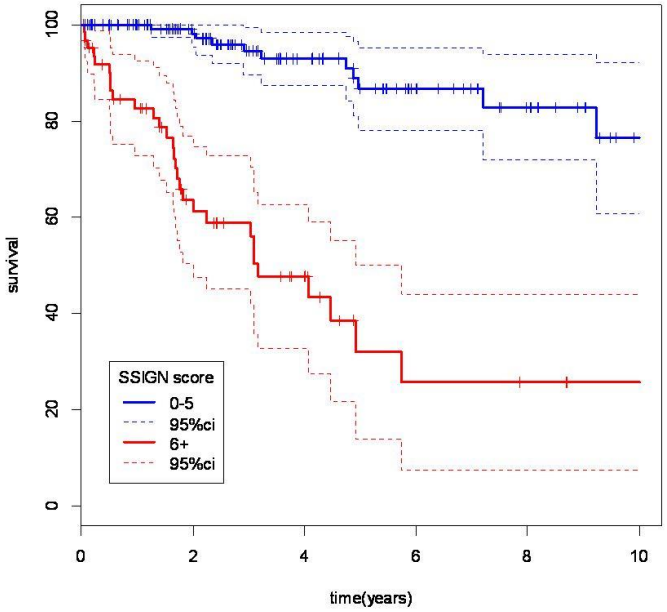
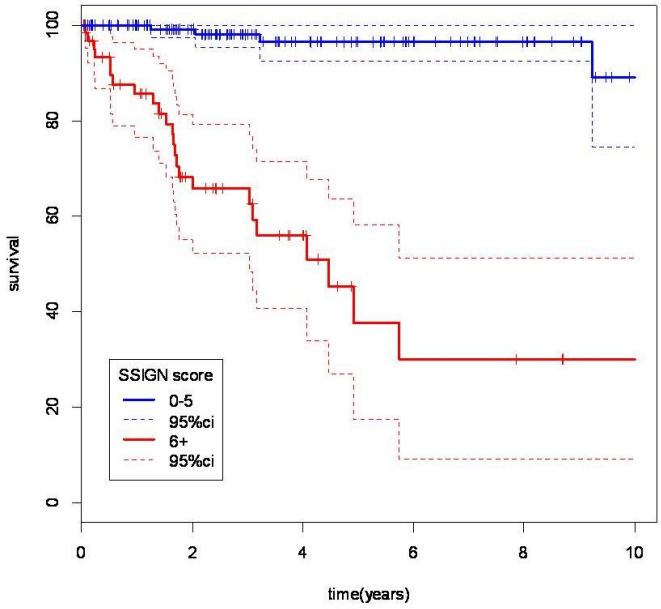


***Figure 5**: 10 year cancer specific survival stratified per low/ high risk groups*



Discussion

In this series, nephrectomy resulted in acceptable morbidity rates. The post-operative 30 day surgical mortality rate of 0.62 % compares well with published figures ranging from 0.77 to 2.3%. [16] Post-operative complication rates are also in line with other published series with a total morbidity rate of 20% (with studies quoting complication rates between 2 and 35%). [17, 18]

Oncological results in the clear cell carcinoma group also compare favourably with larger series published by tertiary high volume centres (Table 4). Our results in the very poor prognosis group are significantly worse, however these patients were mostly (19 out of 20) patients who presented with metastatic disease and had cytoreductive or palliative nephrectomy to alleviate symptoms. These metastatic patients were not included in the series by Frank *et al* [13] or Zigeuner *et al* [14] and this may explain the differences in outcomes observed. In our series the SSIGN score was confirmed to be a good indicator of predicted survival in clear cell carcinoma patients undergoing radical or partial nephrectomy.

***Table 4**: 10 year Cancer Specific Survival stratified by SSIGN score groups*

SSIGN Score (0 - 16)	Number of pts per group (Local Series)	Local Series (*n* = 201)	(Mayo Clinic) Frank I *et al* – 10 yr survival (*n* = 1801)	Zigeuner *et al* - 10 yr survival (*n* = 2333)
0 - 2	85	95%	97%	93%
3 - 4	33	96%	78%	72%
5 - 6	35	56%	57%	46%
7 - 9	28	23%	30%	22%
≥10	20	0%	19%	5%

This series also outlines local trends in kidney cancer surgery, with partial nephrectomy slowly taking over radical nephrectomy as the technique of choice, [19, 20] in accordance with European Association of Urology guidelines.[21] Partial nephrectomy, although being a complex and challenging procedure, affords preservation of renal function which translates lower long term cardiovascular mortality and better overall survival, compared to radical nephrectomy.[22-24] The introduction of laparoscopic techniques into local practice over the last few years is also translating in lower patient morbidity.

Our study has some limitations and numerous strong points. Being the only urology unit in the country, follow up is mostly complete with no patients lost to follow up because of migration. Duration of follow ups is adequate with 10 year survival being presented rather than the traditional 5 year survival rates. Patients readmitted with post-operative complications are cared for by the same unit, so recording morbidity is an easier task. Mortality data was corroborated by death certification data obtained from the National Cancer Registry to minimise inaccuracy.

Limitations include those inherent to a retrospective audit, including incomplete data, reliance on potentially inaccurate medical notes and bias. Recorded complications were not graded according to a validated severity score because of scant clinical details which precluded accurate stratification. The performance status, co-morbidity and ASA score were not recorded, factors which would be expected to influence post-operative complications rates.

Data regarding BMI and blood pressure were not recorded, both obesity and hypertension now being considered as risk factors for kidney cancer carcinogenesis. The issue of obesity and metabolic syndrome could have significant local importance, as shown by the high incidence of diabetics in our cohort.

Lastly, cancer specific survival rather than overall survival was considered as the hard oncological end point, whilst overall survival might represent oncological outcomes in a more clinically meaningful way.

Conclusion

Surgical morbidity and mortality rates and oncological results in our single centre study compare well to larger series. Over the study period changes in international guidelines and progress in surgical techniques have been adapted to our local practice with good effect.

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Original Article

Barriers to implement a smoke free hospital. What action should be taken?

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Abstract

Objective: Tobacco is leading to increased morbidity and mortality. Hospitals have a key role to play in the effective control of tobacco. The aim of this survey was to identify the barriers in implementing a smoke free hospital.

Methods: The tool used was a modified Fagerstrom questionnaire. These questionnaires were distributed to all employees at the main state hospital. The data obtained was analysed using SPSS software using frequency tables, univariate and multivariate analysis.

Results: The response rate was 55.1%. The findings showed that 27.1% of male staff and 24.8% of female staff are active smokers. 22.2% of smokers refrain from smoking in hospital. The highest percentage of smokers was in the youngest age group (18-25 years). The highest prevalence of smoking was found in nurses (23.6%), followed by doctors (10.4%). A positive finding was that 25.7% of current non-smokers were ex-smokers with the greatest incentive to quit being for health reasons. Most members of staff were aware of the adverse effects of smoking and a number had symptoms suggestive of smoking-related pathology.

Conclusion: Hospital staff mirror the general population with respect to smoking prevalence, habits and co morbidities. This indicates that further initiatives are required to decrease the number of health professionals who smoke, as these should ideally be role models for patients, and hence be able to effectively support patients in quitting smoking.

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Key words

tobacco, hospital, health professionals

Introduction

It is a known fact that tobacco affects every organ of the body and contributes to a number of major modern-day diseases, not least of which, lung cancer and cardiovascular disease. If current consumption continues, estimates for the numbers of worldwide deaths attributable to smoking will reach ten million by 2020 with 30% of these occurring in the developed countries.[1] The World Health Organisation estimates that globally over one billion people currently smoke tobacco.[2] In the major part of Europe, tobacco is the leading risk factor for non-communicable diseases.[3] Hence tobacco needs to be a priority area for action in all countries due to the fact that consumption rates continue to rise despite the number of effective ways for quitting. These measures include government action

plans, strategies and legislation on marketing and access, price increases, counter-advertising, treatment for dependence and smoking cessation programmes.

The Preamble of the WHO Framework Convention on Tobacco Control (WHO FCTC) recognizes the role that health professional organizations have in curbing tobacco abuse by reaching a wide spectrum of the population. Such organisations also have the opportunity to help individuals change their behaviour by providing advice, guidance and answers to questions related to the consequences of tobacco use. They also use preventative strategies to forewarn children and adolescents about the dangers of tobacco.

Taking into consideration that smoking prevalence in health care professionals remains high in many countries, ranging from 18-50%,[4-18] one wonders to what extent, if any, such health care workers include tobacco control in their agenda. Coupled with this is the policy proposed by the WHO to implement a 100% smoke free environment to reduce harm from tobacco.[19] Smoking behaviour among health professionals has been shown to influence smoking cessation advice to patients in practice.[20-22] Hospitals should thus play an exemplary role in implementing smoke-free policies and enforcing them, whilst developing a culture of well-being. Many European hospitals have already implemented smoke-free hospital policies and have seen a reduction in the prevalence of smoking among hospital staff and a positive change in attitude to smoking.[23-31]

In Malta, health-promoting initiatives in tobacco control are an on-going process and the introduction of a 2004 legislation banning smoking in public places in Malta was a step further in the right direction. There exist a substantial number of smokers who may be willing to stop smoking if adequate help and support is available. However it is evident that one major group of people who have a great influence on tobacco control, namely health care professionals, are still smoking. Although the legislation banned smoking in public places since 2004, the ban was not proven to be as effective in the main state hospital. Hence the need for implementation of a completely smoke-free zone for the hospital had long been felt. At the time the study was carried out, smoking was permitted in a number of designated outside spaces within the hospital, but in the interim, these locations have been reduced to merely three areas located outside the hospital building and away from the public eye. The aim is to eventually ban these smoking zones altogether and thus render the hospital and its outside spaces completely smoke-free.

As part of the planning towards this initiative, the need for more information on the smoking habits of hospital staff and the perceived impact this has on their health and working practice was required. Hence the main aims of the study were to:

Estimate the smoking prevalance among workers in hospital

Evaluate their knowledge and attitides to tobacco
Assess their willingness to quit and seek assistance
Discern attituides to the smoke-free hospital initiative

Methods

A cross sectional survey among staff working at the main state hospital was conducted.

Population sample

It was estimated that there are 3600 people working in the main state hospital. Since the number is relativey small, it was decided that all these people will be included in the population sample. All personnel working regularly within the hospital regardless of employer and job were included as part of the study.

Study instrument

A literature review and analysis of existing questionnaires used for similar studies abroad, was conducted. A questionnare was then structured having 31 closed-ended questions. The questions included:

- Demographic data on gender, age, type of employment, professional qualification, department and work hours.
- Questions on smoking habits and pattern.
- Questions on symptoms related to smoking.
- Questions on attitudes to quitting.
- Attitides to the smoke-free policy for hospital.

The questionnaire was set up in English and translated into Maltese. Participants were offered a choice of language. A pilot study was conducted in order to validate the questionnaire.

Approvals

Ethics committee, Data Protection and hospital administration approval were all obtained once the questionnaire was ready and the target population identified.

Fieldwork

Questionnaires were distributed by hospital volunteers and health-care professionals. Help in filling in questionnaires was given when required. More so, a key person within the respective department or ward was identified and queries were dealt with accordingly.

Data input and statistical analysis

Data was inputted electronically onto a database, set up by the health information directorate office and analysed using SPSS 13.0 software for Windows. Descriptive analysis was done using frequency and percentage tables. Pearson Chi-Square Test was used for univariate analysis, and a logistic regression model for

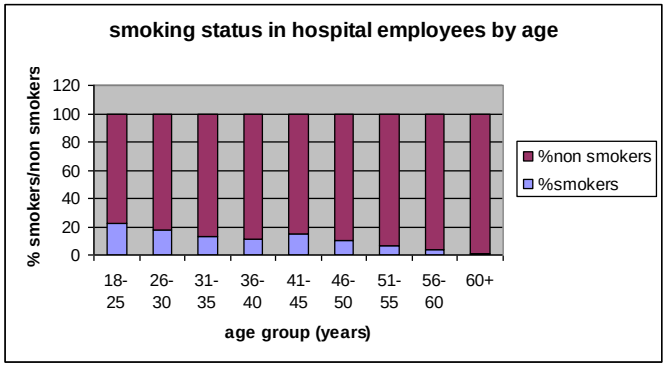
multivariate analysis. The dependent variable referred to the current smoker while other variables referred to covariates. Confidence interval was taken at 95% and significance testing was set at $p \leq 0.05$.

Results

Sociodemographic characteristics

The population studied involved all employees at Mater Dei Hospital, the main state hospital, which included both government and non-government employees. Of the 3600 questionnaires distributed, 1,984 were completed, resulting in a response rate of 55.1%. 17% of these were nurses and 8% doctors. The remaining 75% comprised all other groups of workers within the hospital. There was a predominance of female workers (54%) in the sample population which was reflected in the greater number of female respondents (58.8%) out of the total repondents. The majority of employees belonged to the younger age group (18-25 years), and the numbers in each group decreased with increasing age (Figure 1).

***Figure 1**: Smoking status in hospital employees by age*



Questionnaire reliaibility/validity

The internal consistency of the questionnaire was within the satifactory range with overall Cronbach alpha of 0.93 which is much higher than the threshold of 0.7 indicating high validity.

Smoking prevalence

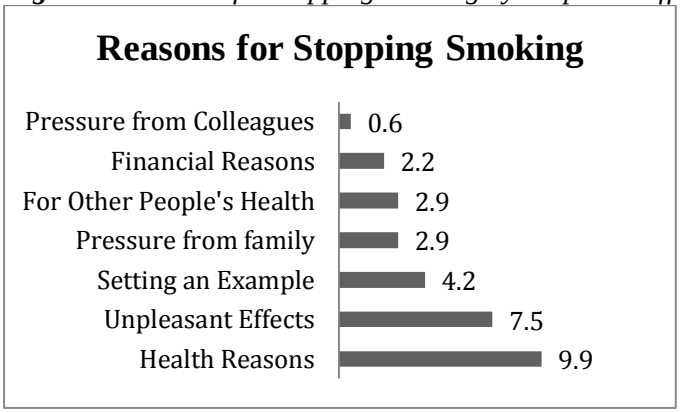
The prevalence of active smokers in this population was 25.4% (95% CI 23.4-27.3) with the greater majority of smokers being male (27.1% v. 24.8%) (95% CI 23.7-30.5%; 22.3-27.3%).

The youngest age group contributed to the highest percentage of smokers at 29.9% (Figure 1). Furthermore, 10.4% of doctors, 23.6% of nurses and 31.2% of the other subgroups were active smokers.

There was no significant change in the number of smokers with increasing seniority, across the board for both doctors and nurses (p=0.85; p=0.43). Night shifts done regularly by 40.5% of the staff population responding the questionnaire did not represent a significant factor in the smoking or non-smoking populations.

It was found that 25.7% (95% CI 23.4-28.0%) of the current non-smokers had previously smoked. The majority of these had successfully stopped more than ten years prior to the study date, the greatest incentive being for health reasons (Figure 2). Male ex-smokers were more likely to have stopped for health reasons, however this was not statistically significant. The majority (24.6%) were successful in quitting without any help, 4.3% used nicotine replacement methods and 1.1% attended smoking cessation classes.

***Figure 2**: Reasons for stopping smoking by hospital staff*



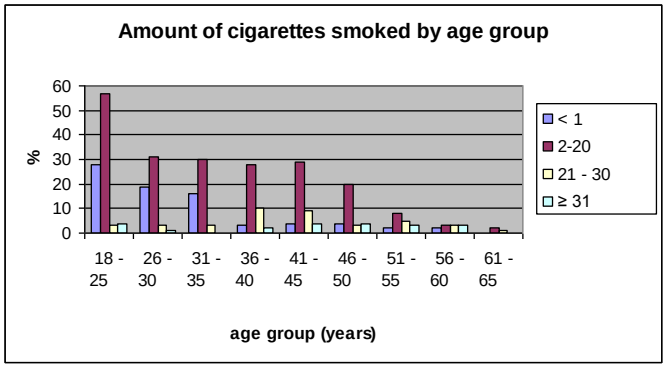
The study also looked at age of starting smoking, with 50.2% of the active smokers having started smoking in the ages between 16 and 20 years, a further 30.2% had started in their early teens. Males were significantly more likely to have started smoking at a younger age (p=0.001) than females. Although not statistically significant, the study showed that the earlier one started smoking, the less likely one was to quit. The most common reason given for initiating smoking was curiosity (20.9%), followed by stress relief (15.5%), peer pressure (10.0%) and family influence (3.4%).

The actual numer of cigarettes smoked per day varied acording to age group. The most commonly smoked number of cigarettes across all age groups was 1-20 cigarettes, followed by less than one cigarette per day (Figure 3).

Attitudes to smoke-free hopsital proposal

Almost half (43.8%) of the surveyed population find difficulty in refraining from smoking in forbidden areas and a further 43.3% would find it most difficult to give up their first cigarette of the day. A near quarter of these smokers (23.6%) require their initial cigarette in the first fifteen minutes after waking up. However, 71.2% will refrain from smoking if unwell in bed. No relationship was found between the degree of addiction, as expressed from the need to smoke soon after waking up, and any of the following: smoking if unwell, number of cigarettes smoked, difficulty in omitting the first cigarette of the day, and age at starting smoking.

***Figure 3**: Number of cigarettes smoked per day by age groups*



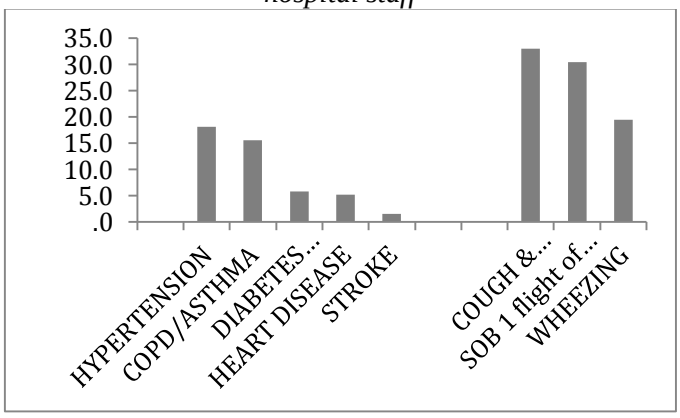
Attitudes to quitting

Willingess to quit smoking appears to be high at 46.2% of the total smoker population, 30.2% having attempted to quit at least once, closely followed by 32.6% who have had two to five attempts. 7.4% have tried to quit more than five times. No significant difference was found between the number of attempts to quit and gender.

Awareness of effects of tobacco

Most members of staff are aware of the potential adverse effects of smoking and a good percentage suffer from chronic illnesses or have symptoms suggestive of smoking-related pathology (Figure 4).

***Figure 4**: Comorbidities and symptoms in the smoking hospital staff*



Only 22.2% of smokers refrain from smoking at the workplace. However, despite the fact that more than three quarters of smokers admitted to smoking at work, only 21.4% disclosed where they smoke on hospital grounds. Discrepancy was also shown in the time allocated to smoking: 14.7% in official breaks, 9.9% in unofficial cigarette breaks, while the rest (75.4%) did not reply.

As an incentive, it was asked if forbidding smoking on hospital premises would encourage smokers to stop - for 74.1% this would not make any difference. When offered smoking cessation classes, 41.1% were willing to attend if these were available (41.6% males, 38.0% females).

91.8% of the whole study population agreed that the hospital has a role to play in promoting a healthy lifestyle, with 35% believing that no one should be allowed to smoke within the hospital building. This is confirmed further by 22.8% of members of staff who are bothered by cigarette smoke in hospital - this is highly significant for non-smokers ($p<0.001$). Ex-smokers were equally as likely to be bothered by this as non-smokers.

Discussion

Despite the ideals held by those who have received medical training and are directly or indirectly exposed to smoking-related illness, the number of hospital staff who are smokers is not dissimilar to that of the general population. In fact, in the European Health Interview Survey[32] carried out on the general population in 2008, 25.9% admitted to being daily or occasional smokers. We notice that this is close to the prevalence of 25.4% obtained in our hospital survey. The only difference is that males exceed female smokers by 10% in the general population while in hospital, female smokers only lag behind males by 2.3%. When compared to EU member states however, the rate of daily smoking in Malta is comparatively low, with Malta having the 5th lowest rate after Portugal, Sweden, Finland and Slovakia respectively.[33]

This high prevalence rate of smokers in health care workers is also reflected in students. In a study carried out on student health professionals at the University of Malta, 27.1% were regular (daily) smokers.[34]

Smoking prevalence among health professionals varies between member states. In Italy, the rate of smokers in health professionals is twice the rate of smoking in the general population (44%).[12] A high prevalence rate was also estimated in workers in a Portugese hospital (40.5%) which contrasts with the low population prevalence of 20.9%.[35]

This survey revealed that a higher percentage of nurses (23%) were identifed as smokers as compared to doctors (10.4%). This pattern is also seen in other countries.[12,36]

However there was no significant difference in smoking habits among grades of nurses, as well as between the different medical specialties that doctors belonged to. The fact that the highest percentage of smokers belonged to the youngest age group (18-25 years) is of some concern, as this is the generation most exposed to anti-smoking campaigns in schools and tertiary education.

After analysing willingness to attend Smoking Cessation Classes by age group, the older age group (61-65) scored highest at 67%. This could represent a bias in view of the small numbers found in this age group; however, it can also represent more willingness to quit

smoking due to health problems which are likely to be present at this age.

The survey attempted to address the degree of smoking addiction by incorporating some questions from the Fagerström Nicotine Dependence Scale . The fact that almost half find it hard to refrain from smoking in forbidden places or to give up their first cigarette of the day reveals that addiction is certainly present. However we did not find this to correlate with number of cigarettes smoked and age at which smoking was initiated.

The fact that smokers are often granted unofficial cigarette breaks may serve as a deterrent to smoking cessation, in that smokers have more breaks from work than do their non-smoking counterpart. This issue certainly needs to be addressed so as to avoid 'awarding' smokers. Superiors need to be stricter with their smoking staff and abolish unofficial smoking breaks altogether.

With only three available areas for smoking within the hospital grounds, this implies that a not insignificant number of smokers congregate to smoke. There may be a psychological element involved in this practice, in that smokers may view themselves as a rebel clan who may appear to be defying hospital authorities that are attempting to decrease the number of smokers within the hospital.

There were some limitations to this study. The response rate obtained was lower than expected considering that questionnaires were delivered individually by hand, and that respondents were offered help with filling in questionnaires. Besides, collection of data was met with refusals; questionnaires were returned blank, incompletely or incorrectly filled. A postulated theory for this is the unwillingness to have implementation of smoke-free regulations within the hospital, hence presenting bias on the part of smokers. We also felt there may have been suspicion of possible identification of the respondent despite reassurance of anonymity. Another confounding factor was that staff working solely night shifts and especially on reliever basis may not have all been reached since questionnaires could not always be distributed during their shift hours. A web-based survey might have increased the response rate by reaching more workers whilst cutting costs involved in the use of paper questionnaires.

Another possible bias may be due to the fact that smoking status was self-reported. Respondents may have found it difficult to declare their smoking habits as questionnaires may have been distributed by healthcare professionals working in the same area.

This study is the first representative study done to estimate the prevalence of smoking at the main state hospital. The fact that the rate is similar to that of the general population indicates the need for targetted interventions to these particular groups. It is well known that health professionals who smoke may not be as effective in counselling patients on quitting compared to their non smoking colleagues. Consequently, their own smoking behaviour may impact negatively upon that of their patients. This is of great concern as health professionals are of key importance in tobacco control at population level. With the introduction of the smoke-free hospital policy for the main state hospital, it is expected that health care professionals will take alternative measures. Needless to say, a number of these will continue to smoke during their breaks by exiting the hospital premises. It is hoped that a good proportion of the current smokers will take up the recently set up smoking cessation programmes being provided during working hours in the main state hospital itself.

It is essential to take initiatives to instil a non smoking culture amongst health professionals who ought to serve as role models and a source of encouragement to smoking patients.

What this paper adds

- The smoking prevalence amongst health professionals in Malta is equivalent to that of the general population hence further intiatives are needed to assist them to stop smoking, apart from general prevention measures.
- Training at undergraduate and as CPD on tobacco needs to be ongoing.
- The majority of health professionals are supportive of the main state hospital being smoke free and health-promoting. Hence this opens a window of opportunity to further tobacco control measures to ensure implementation.

Aknowledgments

We thank all the hospital staff who participated in this study and the hospital managment for coordinating the fieldwork.

Competing interests

Non declared.

Funding

None

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Original Article

An Overview of Suspected and Acute Poisoning in Mater Dei Hospital

Robert Camilleri

Abstract

An observational study was carried out to give a descriptive overview of acute poisoning in Mater Dei Hospital**.** The aim of the study was to investigate characteristics of patients with suspected acute poisoning by creating a database combining clinical and laboratory data**.** Clinical and laboratory data of 677 patients aged 14 years and over, presenting with suspected acute poisoning, over a nine month period in 2010 were gathered for analysis and graphical presentation.

The peak age for males and females with acute poisoning was 20-29 years whilst another peak was observed for females in the 50-59 years group. Males predominated in the younger age groups (below 50 years). Out of 677 patients with suspected acute poisoning, 350/677 (52%) were diagnosed with acute poisoning and 327/677 (48%) were found to have an alternative diagnosis. The most common poison agents were prescription drugs, of which benzodiazepines and tricyclic antidepressants were the most common (43% and 20% respectively). Opiates were the most commonly detected (59%) drug of abuse and paracetamol was the most commonly ingested analgesic (36.6%). None of the patients died in the hospital. 21% (73/350) and 5% (19/350) of patients with confirmed poisoning required a monitored bed and intensive care respectively.

The study demonstrated trends in patient characteristics, commonly used agents and outcomes of patients with acute poisoning in the local setting.

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Keywords

Acute poisoning, descriptive study, clinical scores, Poison Severity Score.

Introduction

Suspected acute poisoning is a common condition presenting to the emergency department. Management depends on an accurate diagnosis based on history, physical examination and toxicological analysis. An observational study was carried out to give a descriptive overview of acute poisoning in Mater Dei Hospital**.**

Aim and objective

The aim of the study was to investigate characteristics of patients with suspected acute poisoning by creating a database combining clinical and laboratory data.

Methods and materials

Mater Dei Hospital is an acute general hospital with an emergency department that registers more than 100,000 patients per year. After obtaining approval from the University Research and Ethics Council, a database including 677 patients was created from data extracted from clinical notes, discharge summaries and laboratory results. Subjects included consecutive patients aged 14 years and over requiring toxicology investigations over a nine month period in 2010. Cases with insufficient information or unclear diagnosis were excluded.

The collected data were organized into fields and grouped as follows:

a. Patient age, gender and past medical, psychiatric and drug history including history of drug abuse.
b. Information related to the suspected poisoning event.
c. Clinical presentation.
d. Glasgow Coma Scale (GCS) and Modified early Warning Score (MEWS).
e. Toxicology analysis results.
f. Final diagnosis.
g. Outcomes (level of care and Poison Severity Score).

The Modified Early Warning Score (MEWS) is a composite clinical score (Table 1) based on physiological parameters and has been validated as a prognostic tool in observation and medical wards.[1-4]

***Table 1**: An example of a Modified Early Warning Score.*[4]

Physiological parameters	3	2	1	0	1	2	3
Respiration Rate		≤8		9-14	15-20	21-29	≥29
Heart Rate		≤40	41-50	51-100	101-110	111-129	≥129
Systolic BP	≤70	71-80	81-100	101-199		≥200	
Temperature		≤35	35.1-36	36.1-38	38.1-38.5	≥38.6	
Level of Consciousness				Alert	Voice	Pain	Unresponsive

Outcomes were defined by the level of care and the Poison Severity Score (PSS).[5] The PSS is a composite score based on graded abnormalities of physiological systems and is expressed as 5 grades of organ injury: grade 0 - no injury, grade 1 - mild injury, grade 2 - moderate injury, grade 3 - severe injury and grade 4 - death and has been validated in acute poisoning.[5-12] Symptoms and signs are graded for each physiological system in increasing severity.

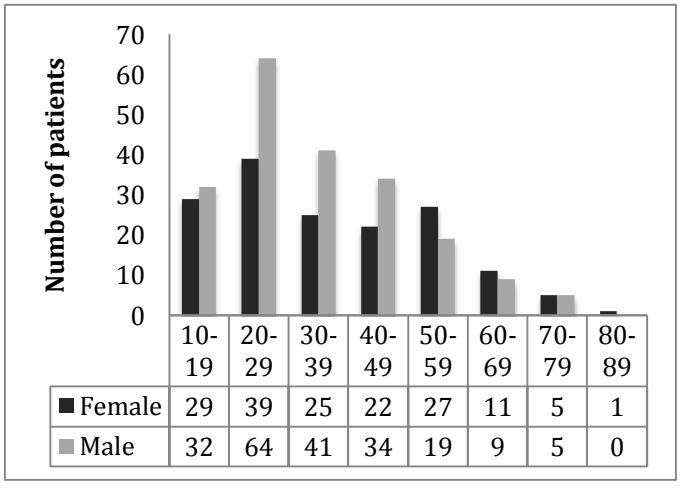
The data were inputted into a MS Access database which was modified to calculate the MEWS and PSS values automatically. The data were transferred to a MS Excel spreadsheet for analysis and graphical display.

Results

Age and gender distribution

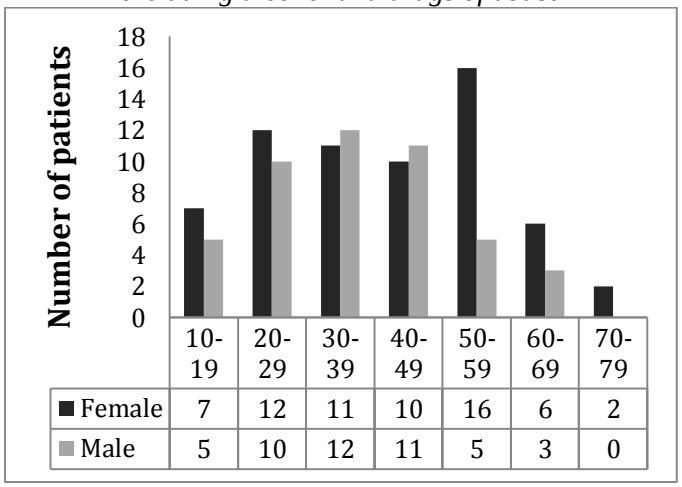
The distribution for age and gender for patients with acute poisoning is shown in Figure 1.

***Figure 1**: Age /gender distribution for all cases diagnosed with acute poisoning*



The peak age for males and females was 20-29 years whilst another peak was observed for females in the 50-59 years group. Males predominated in the younger age groups (below 50 years) whilst females predominated in the 50-69 age groups. There were no gender differences in the 70-79 years group. Figure 2 shows a predominance of females in the 10-29 and over 50 years age groups in a subgroup of patients excluding alcohol and drugs of abuse.

***Figure 2**: Age/gender distribution for drug overdose excluding alcohol and drugs of abuse*



Source of report of poisoning and reason given for poisoning

The source of the report of poisoning is often the patients themselves or the relatives as shown in Table 2. When available, the reason for the poisoning event was recorded for all drugs, analgesics and street drugs as shown in Table 3. Suicidal intent was admitted in 40% of patients with acute poisoning whilst self-harm was the intention in 3%.

***Table 2**: Source of report of suspected poisoning*

Source of Report	Number (%)
Patient	144 (41%)
Relative	24 (7%)
Friend	8 (2%)
Police/Guard	4 (1%)
Other	6 (2%)
None	164 (47%)

***Table 3**: Stated intent for acute poisoning for all drugs, analgesics and street drugs*

Intent	All Drugs	Analgesics	Street Drugs
Accidental			
Suicide	59 (40%)	8 (80%)	4 (25%)
Substance abuse	21 (14%)		10 (63%)
Self harm	5 (3%)		
To forget	16 (11%)		
To sleep	8 (5%)	1 (10%)	
Domestic fight	19 (13%)	1 (10%)	1 (6%)
Alcohol abuse	12 (8%)		
Call for help	2 (1%)		
Pain relief	1 (1%)		

Other reasons given for acute self poisoning included 'to forget' (11%), 'to sleep' (5%), pain relief (1%), and following a domestic fight (13%). Alcohol and substance abuse constituted 8% and 14% of cases respectively. Only 1% admitted to a call for help and 2% were accidental.

Differential diagnosis of suspected acute poisoning

The differential diagnosis of patients with suspected acute poisoning is shown in Table **4**. Out of 677 patients with suspected acute poisoning, 350/677 (52%) patients were diagnosed as acute poisoning of which 35% were further classified as acute drug overdose, 15% as alcohol intoxication, 1% as acute drug toxicity and 1% as chemical ingestion. 327/677 (48%) patients had an alternative diagnosis which was further classified into acute medical condition (19%), chronic drug toxicity (2%), epilepsy (5%), acute psychiatric episode (6%) and trauma (16%).

***Table 4**: Final diagnosis of patients with suspected acute poisoning*

Diagnosis	Number (%)
Acute medical condition	126 (19%)
Epilepsy	37 (5%)
Drug toxicity	14 (2%)
Acute psychiatric condition	44 (6%)
Trauma	106 (16%)
Alcohol intoxication	99 (15%)
Drug overdose	235 (35%)
Acute drug toxicity	9 (1%)
Chemical ingestion	6 (1%)
Fume inhalation	1 (0.1%)
TOTAL	**677**

Poison agents

Major classes of poison agents that were used are shown in Figure 3. The largest group included prescription drugs, of which benzodiazepines (43%) and tricyclic antidepressants (20%) were the most frequently used (Table 5). Opiates (59%) were the most commonly used drugs of abuse (Table 6). whilst paracetamol (36.6%) was the most commonly ingested analgesic (Table 7).

***Figure 3**: Distribution of major poison agents*

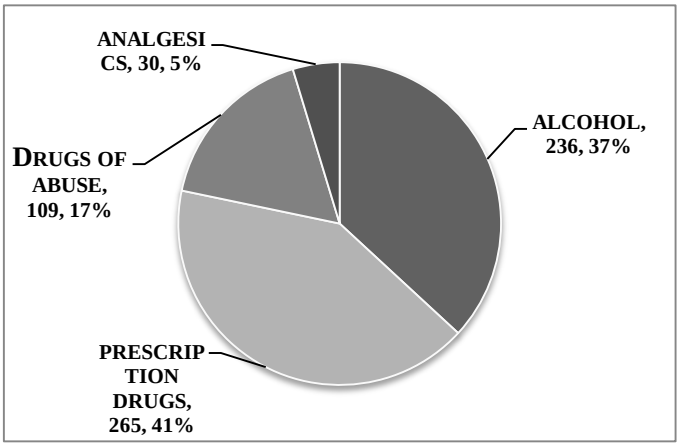


***Table 5**: Distribution of prescription drugs*

Prescription Drugs	Number (%)
Anticholinergic	7 (3%)
Anti-Epileptic Drugs	13 (5%)
Antihistamine	11 (4%)
Atypical Antipsychotic	13 (5%)
Benzodiazepine	113 (43%)
Methadone	12 (5%)
Phenothiazine	3 (1%)
SNRI	6 (2%)
SSRI	21 (8%)
TCA	53 (20%)
Tetracyclic	3 (1%)
Misc	10 (4%)

***Table 6**: Distribution of street drugs*

Street Drugs	Number (%)
Opiate	64 (59%)
Cocaine	24 (22%)
Amphetamine	8 (7%)
Ecstasy	6 (6%)
Cannabis	4 (4%)
Mephedrone	3 (3%)

***Table 7**: Distribution of analgesics*

Analgesics	Number (%)
NSAID	9 (30%)
Paracetamol	11 (36.6%)
Opiate Analgesic	8 (26.6%)
Opioid Analgesic	2 (6.6%)

Disposition and level of care

Disposition of patients with confirmed poisoning is presented in table 8. None of the patients died in the hospital, whilst 21% (73/350) and 5% (19/350) of patients with confirmed poisoning required a monitored bed and intensive care respectively.

***Table 8**: Distribution of disposition of patients with acute poisoning*

Outcome	Number (%)
Ward	196 (56%)
Monitored bed	73 (21%)
ITU	19 (5%)
Discharged	42 (12%)
Self-discharged	20 (6%)
Total	**350**

Clinical scores

Table 9 and Figure 4 show the distribution of the Glasgow Coma Scale (GCS) and the Modified Early Warning Score (MEWS) in patients with acute poisoning. The distribution of the Poison Severity Score (PSS) is shown in Figure 5 whilst the percentage of moderate to severe poisoning (PSS grade of 2 or more) was higher in the age groups greater than 50 years as shown in Table 10.

***Table 9**: Distribution of GCS in patients with acute poisoning*

Glasgow Coma Scale	15	14	13	12	11	10	9	8	7	6	3
Number of patients	68	16	10	1	2	1	2	3	1	1	9

***Figure 4**: Distribution of Modified early Warning Score (MEWS) in patients with acute poisoning*

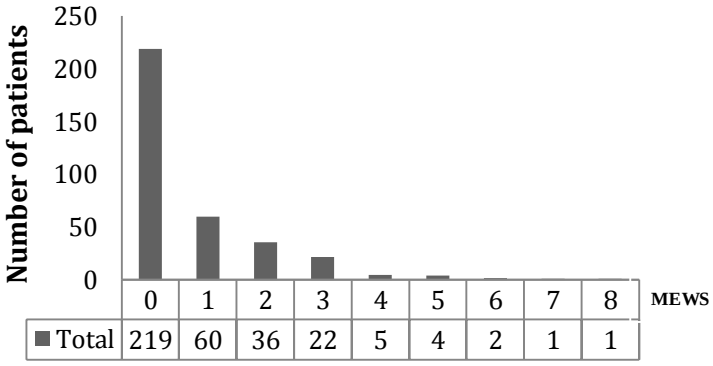


***Figure 5**: Distribution of Poison Severity Score (PSS) in patients with acute poisoning*

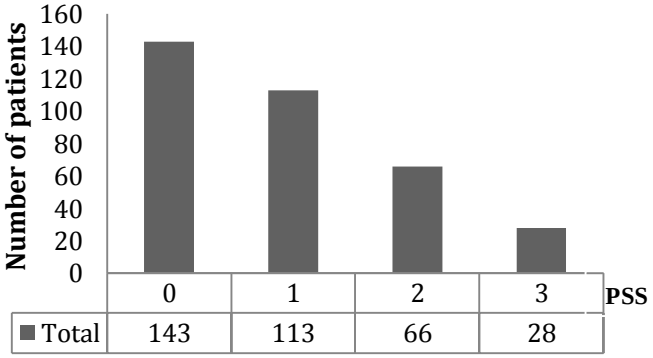


***Table 10**: Age distribution of acute poisoning comparing mild organ injury (PSS≤1) with moderate/severe organ injury (PSS>1)*

Age	No or mild organ injury (PSS≤1)	Moderate to severe organ injury (PSS>1)
10-19	75%	25%
20-29	73%	27%
30-39	80%	20%
40-49	76%	24%
50-59	61%	39%
60-69	67%	33%
70-79	70%	30%
80-89	100%	0%

Discussion

Age and gender distribution

The male preponderance of patients with confirmed acute poisoning in patients <50 years old and the reversal of the gender ratio in the 50-69 age groups contrasts with other studies showing a prevalence of females in the younger age group.[13-15] However the male predominance is likely to be due to the inclusion of alcohol intoxication and street drug abuse as shown in

the female predominance in the subgroup that excluded these cases (Figure 2).

Source of report of poisoning and reason given for poisoning

The study showed that patients and relatives were the main source of a history of acute poisoning. Most cases of acute poisoning were self induced with the most common reasons being suicide/self-harm and recreational, whilst only 2% were accidental.

Differential diagnosis

Only 51.7% (350/677) of patients requiring toxicology investigations had a diagnosis of acute poisoning. A significant proportion of this group (15%) was diagnosed as primary alcohol intoxication and only 35% had a confirmed drug overdose. The relatively low rate of positive laboratory diagnosis of a drug overdose reflects the low threshold for requesting toxicology investigations.

Poison agents

The common use of benzodiazepines and tricylic antidepressants in prescription drug poisoning reflects underlying psychological mechanisms and trends in psychotropic medication use. The preponderance of opiate poisoning among drugs of abuse is likely due to widespread regular use in the community and also the tendency to necessitate hospitalization because of respiratory depression when compared to occasional recreational/party use of stimulant drugs. The availability of paracetamol as an over the counter analgesic may explain its preponderance.

Disposition and level of care

A significant number of patients with confirmed acute poisoning (12%) were discharged. There were no deaths and only 5% required intensive care. This contrasts with a study of 226 patients with acute poisoning that whilst similarly reporting no deaths, 84/226 (37%) patients were admitted to intensive care.[2] It is however difficult to compare hospital practices since indications for intensive care and monitored areas may vary.

In Mater Dei Hospital, patients with actual or potential cardiovascular complications but without respiratory compromise are admitted to a monitored area. This would compare with the combination of patients (26%) in the local study admitted to either ITU (5%) or a monitored area (21%).

Clinical scores and the Poison Severity Score

The distribution of the GCS and MEWS shows that the majority of patients with acute poisoning are alert and stable. The higher rates of moderate to severe injury in the elderly groups is similar to a study which showed that severe poisoning was more common in males aged over 45 years.[14]

Limitations

Possible sources of bias include the retrospective design of the study, the limitation of subject inclusion to patients requiring toxicology analysis and missing clinical data. Although the final diagnosis in each case was extracted from discharge notes and laboratory results, the interpretation was made by a single author.

Conclusion

The study demonstrated trends in patient characteristics, commonly used agents and outcomes of patients with acute poisoning in the local setting.

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Original Article

Malta: Mediterranean Diabetes hub – a journey through the years

Sarah Cuschieri, Julian Mamo

Abstract

Introduction: Diabetes mellitus in Malta has been an established major health problem for years. It has been linked with cultural, geographical, historical, genetic as well and a change from a Mediterranean diet to a Westernized diet. This diabetes burden has lead to establishment of diabetes clinics both in the central general hospital, as well as in the community. Over the past 50 years, there have been two major epidemiological diabetes studies conducted to evaluate diabetes in the Maltese population.

Diabetes in Malta: To date, there is no established national diabetes plan or diabetes register in Malta, although there has been the formation of a governmental diabetes focus group. The time is right for an updated prevalence study to look at the current Maltese generation and their changing determinants including diabetes risk factors and genetics, followed by the development of preventative strategies and policies.

Conclusion: Over the years, diabetes burden has increased and become a public health and national financial concern. It is of utmost importance to address this national disease. An updated prevalence study would provide the evidence-based backbone for the development of diabetes preventive strategies and policies. The combination of which will enable the Maltese health services to be improved and better equipped to come to grips with this epidemic.

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Keywords

Diabetes Mellitus; Policy; Malta; Diet, Mediterranean

Introduction

Diabetes mellitus type 2 (T2DM) is a growing epidemic globally. By 2013 it was affecting 382 million people worldwide with an estimated 135 million currently unaware of their disease status.[1] Those suffering from T2DM are known to have a significant reduction in life quality as well as life expectancy, directly caused by this disease.[2] Moreover, in 2013 diabetes was estimated to be responsible for 5.1 million deaths worldwide.[1]

As in other European countries, diabetes mellitus is a major health problem in the Mediterranean island of Malta. T2DM is not a recent occurrence in Malta and it is known that by the eighteenth century, diabetes was already documented in medical literature. [3] Diabetes has been documented to have a negative impact on the lives of many Maltese since 1886, where diabetes was noted to be responsible for 2.1 per 10,000 deaths of the population. Diabetes related mortality rate continued to increase to 4.5 per 10,000 of population in 1900 and 8.7 per 10,000 in 1942. By 1955, Malta had the leading recorded diabetes mortality rate in the world with 26.1 deaths per 100,000 population followed by Belgium with 23.9, the USA with 15.5 and Italy with 11.1. [4]

The scope of the present paper is to review diabetes mellitus type 2 in Malta over the years along with the various local factors contributing to the high prevalence of diabetes in Malta and the current diabetic epidemiological situation.

Predisposing factors for Diabetes Mellitus in Malta

Malta is a small island in the center of the Mediterranean Sea, positioned at the crossroads between Europe and North Africa. Over the years, Malta sustained different cultural changes as one dominating empire took over from another, leaving an ethnic mixture, substantial socio-diversity and varied genetic imprints on the Maltese population. [5] In 2008, as part of his PhD studies Al-Ashtar A. reports that both the Maltese and the Libyan populations had similar genetic

diabetic and metabolic profiles. [6] In a recent PhD study, Pace N. found as many as ten candidate genes significantly associated with type 2 diabetes mellitus and the metabolic syndrome among adult Maltese newly diagnosed diabetic persons. [7] In Malta, a strong family history of diabetes among Diabetics was already established with a statistical significant relationship between Diabetes and both maternal and paternal diabetes history.[8-9]

Having a restricted irrigated agricultural land has meant that Malta had to import most of its food supplies from overseas. The dependence on imports and their inconsistent supply had led to a tendency for chronic food deprivation in years gone by, especially during the period of world war II (1937 – 1949) affecting all of the population including pregnant women and their unborn children. [10] This most probably led to the development of the *Thrifty Diet Phenotype*. This phenotype is a protective mechanism developed to adapt for periods of starvation and food deprivation.[11]

It was suggested that a strong link between Malta and Diabetes contributed to a change from a Mediterranean diet to a more British type of diet in the late 19th to early 20th century, which may have led to this increase in T2DM prevalence. The theory suggests that an increased intake of fat and refined carbohydrates led to an overload of the *Thrifty Diet Physiology* which is in turn responsible for the increase in peripheral insulin resistance as well as to an increase in the prevalence of obesity.[3] This forms the *Baker's hypothesis* whereby those children originally adapted to surviving in a starved situation, now faced rich foods predisposing towards childhood and adulthood obesity and adult T2DM.[12] This link was found to be present in the Maltese population when the 2001-02 Health Behaviour in School children Study (HSBC) showed that 33.3% of the Maltese population was either overweight or obese.[13]

In more recent times, pregnant women in Malta have been found to be overfeeding their unborn child while in utero. This predisposes the child to foetal obesity or macrosomia. This is the basis of the *Pedersen's hypothesis*, which suggests that such a situation leads to the foetal pancreas and hypothalamus being adapted to this nutritional state with a predisposition to obesity and T2DM later on in their lives.[14]

Past epidemiological studies in Malta

A high diabetes occurrence in the Maltese population was first documented in 1927, and in his book, Debono JE. describes the prevalence estimated to be 4.5% of the population and the disease firmly linked with obesity.[15]

The increasing disease burden over the years led to the establishment of a special Diabetes Clinic in 1939 at the only general hospital in the island. By the 1950s, T2DM was considered to be of major public health concern, during which time there was an extension of diabetic clinics in the community.[3, 16] This heightened the keen interest of local academia and by 1964, the first epidemiological diabetes 'pilot study' was conducted by Prof. J. Zammit Maemple. Table 1. Summaries the study design, results and outcomes of this study.[17]

***Table 1**: Summaries the first epidemiological study (1964) design and outcome*

		JV Zammit Maempel - 1964
Population Sample		5757 subjects
Population demographics		All ages
Study Design		All households in Urban area of Floriana & Rurar area of Gharghur, Madliena and Bahar ic-Caghaq
Screening methods		
	Phase I	Urine dipstick for glucose, reducing substance, ketone bodies & albumin
	Phase II	Glycosurics (from phase I) undergone a 50g OGTT, questionnaire and physical examination, along with an equal number of age-matched non-glycosuria individuals
	Phase III	Statistical Study of the findings
Results	Phase I	Glycosuria - 8.9% (9% males; 8.8% females); Albuminuria - 23%
	Phase II	Of the glycosuric - 70.1% had DM; 7.4% lag storage curve; 7.4% had renal glycosuria; remaining had normal OGTT.
		Of the non-glycosurics - 15% had DM, 15.7% lag storage curve; 1.5% had renal glycosuria; 67.8% had normal OGTT
Risk factors		Obesity (60 out of 100 diabetics)
Complications		Peripheral Vascular disease, Coronary disease, Cerebrovascular disease, Hypertension
T2DM prevalence		19.9%
Newly Diagnosed T2DM		1 out of every 10 inhabitants

T2DM – Type 2 Diabetes Mellitus; DM – Diabetes Mellitus; OGTT – Oral Glucose Tolerance Test

In 1981, the World Health Organization (WHO) performed the second prevalence study on Diabetes in Malta. During the same year, the Maltese Diabetes Association was set up and a year later (1982) became part of the International Diabetes Federation (IDF). Table 2. Summaries the study design, results and outcomes of this study.[18]

***Table 2**: Summaries the 1981 WHO epidemiological study design and outcomes*

		World Health Organization Study - 1981
Population Sample		2945 subjects
Population demographics		> 15 years
Study Design		Randomized from electoral list, stratified according to age, gender, occupation & education
Screening methods		If not previously diagnosed with DM:
	Phase I	Fasting blood capillary sample from ear lobe, Fasting urine sample (glucose, proteins, blood & ketones), 75g OGTT, questionnaire, blood pressure, weight, height, and skinfold thickness.
	Phase II	Repeat of OGTT in those with abnormal or indeterminate result in phase I. Blood for Insulin, C-peptide, HLA-type, blood groups, Renal profile, Uric acid, lipid profile,
	Phase III	Clinical follow up of complications
Risk factors		Obesity linked with high calorie intake. Hypertension
Complications		DM patients showed: Higher mortality rate; Blindness more common; Acute MI more common; Left Ventricular failure more common; Neuropathy in lower limbs more
T2DM prevalence		7.7% (5.9% previously know, 1.8% newly diagnosed)
Newly Diagnosed T2DM		1.8%
IGT		5.6%

T2DM – Type 2 Diabetes Mellitus; DM – Diabetes Mellitus; OGTT – Oral Glucose Tolerance Test; IGT- Impaired Glucose Tolerance; MI- Myocardial Infarction.

The *pilot study* conducted by Prof. Zammit Maempel in 1964 could today be critically appraised for its design, whereby the sample population studied was non-randomized and not a representative sample of the Maltese population. There was no stratification for the different social factors and age, making it more difficult to differentiate the different types of diabetes. One can appreciate however, that as a first attempt to establish diabetes prevalence, it gave a clear idea of the relatively high diabetes burden among the Maltese population and of the poor control of the disease among sufferers at the time as well as of the strong local link of the disease with obesity.

The measurement tools used comprising seeking out glycosuria and subsequently confirming with an oral glucose tolerance test (OGTT) was also quite unique.

When considering the study conducted by WHO in 1981, one appreciates the improved epidemiological approach and the use of a randomized stratified sample of the population selected from the electoral list.

The screening method used by the WHO was the 75g OGTT - the gold standard screening tool, unlike the 50g OGTT used in the Zammit Maempel study earlier. The WHO study gave a more reliable and comparable diabetes profile, with appropriate distribution by age and gender.

No further population based studies have since elaborated on the changing Diabetes picture and burden in Malta until 2010, when the local centre of the European Health Examination Survey pilot study examined 400 randomized adult participants (18+ years) and, on the basis this time of a fasting glucose level, obtained a diabetes prevalence of 9.8% for this population. Females (10.7%) had a higher blood glucose average as compared to males (9%). This study, in common with the previous 2 studies, reported that those already diagnosed with diabetes had a generally poor diabetic management; with 38.5% of the known diabetics having an elevated blood glucose level.[19] This study utilised a relatively small population sample size and consequently, results exhibited wide confidence intervals. The results must therefore be considered with caution.

During the same year, the Department of Health Promotion and Disease Prevention issued "A Strategy for the Prevention and Control of Non-communicable Disease in Malta", which recommended local diabetes targets for 2020. [20]

Diabetes burden in Malta - Nowadays

To date, there is no national diabetes plan or diabetes register in Malta. Similarly, there is a lack of established preventative or screening protocols for diabetes. The lack of any updated diabetes prevalence data for the Maltese population is a clear hindrance to the formulation of any such plans and protocols.

A recent survey conducted on the attitudes and habits of Malta's general practitioners (GPs) reported that there is a lack of consistency in their diabetic preventative and management practices. The screening methods used by GPs studied were varied, with a large percentage using capillary blood glucose as the screening test for diabetes. A correlation was found between the different generations of GPs and the screening tests used. Thus, older GPs (21years+ since graduation) tended to use the HbA1C test more as a screening method when compared to younger GPs.[21]

Diabetes action plan

With the recent establishment of a governmental diabetes focus group and the first national diabetes plan being in the pipeline, the time is right to update the situation on the prevalence of diabetes type 2 and stop basing pharmacological and therapeutic plans on estimates of prevalence that are now no longer viable due to the time and changes in the population in terms of aging and changing risk factor profiles. [22]

A prevalence study at this point in time would be an opportunity to look at current generation of Maltese and their changing determinants and diabetes risk factors. Among these are the growing problems of obesity, the earlier onset of insulin resistance as seen globally.[2] It is also an opportunity to engage hitherto unavailable technology to study the underlying genetic predisposition among the Maltese population.

It is also a critical point in which to study the Maltese pre-diabetic population by linking prevalence to predisposition and risk factors - which may ultimately lead to eventual type 2 diabetes. Acquiring knowledge on the local precursor situation of diabetes (pre-diabetes) among a representative sample of adult Maltese today would be of great public health importance. Such a cross-sectional prevalence study has been proposed and is set to start at the end of 2014.[23] This epidemiological study aims to study a representative 1% of the adult Maltese population. The aim is to come up with valid and reliable updated diabetes type 2 prevalence figures as well as to have the first obesity, hypertension, smoking and alcohol consumption prevalence study with the power to give reliable figures. It is also set to understand the current Maltese dietary lifestyle and identify the risk factors predisposing the Maltese population to pre-diabetes and diabetes. This data can in turn be used to establish a diabetes risk score by age, gender and other factors for persons living in Malta.

With reliable updated diabetes prevalence figures as well as the establishment of the frequency of Diabetes risk factors in the Maltese Islands, a prevention strategy, a Diabetes policy and achievable population targets can then be accurately established to enable an evidence basis for Diabetes control plans.

Of the two broad strategies for the prevention of any disease –high risk and population strategies, none can yet be said to be underway in the Maltese Islands, historical hub of Diabetes in the Mediterranean. Both can, however, be employed side by side.

Employing the high-risk strategy for which screening is essential would enable the identification of high-risk individuals so that early action can be taken for them and ensure effective therapy. On the positive side, this tends to be an acceptable way forward for patients and health professionals while efficiently reducing disease and risk. The negative side is that this is not really a radically effective prevention strategy and is more geared at secondary prevention. The 1968 Wilson and Jungner criteria, universally accepted for any screening programme, are all satisfied in the case of Diabetes and its impact on the Maltese population: Diabetes is an important disease; there is an acceptable and an effective screening tool which can be performed regularly - one which is acceptable to patients and health professionals alike; there is a recognizable early detectable stage and the natural history of the disease is well known; there exist facilities to bring about effective investigation and control of the disease and the costs should be balanced relative to other health costs.[25]

The other option - the population strategy, involves the broad action needed to prevent the primary causes of the disease (lack of exercise, poor diet, obesity) for all individuals in the Maltese population, irrespective of their current risk status. This would involve a multi-sectoral approach including targeted taxation, aimed this time at high fat, high calorie foods and coupled with initiatives in the environment. It would also involve influencing the access to a healthier lifestyle - restrictions on importation and on the food manufacturing industry, an educational drive and action in other related areas for a concerted action. [24]

Given the sustained negative impact of Diabetes on health and the prospect of an ever greater impact of the disease on the lives of adults in Malta with each passing year, there is no reason why both strategies should not be initiated and combined for the prevention and control of Diabetes in the coming years

Conclusion

Diabetes Mellitus type 2 has been a sustained health burden among the Maltese population probably for a long time, but certainly, over the past century with more accurate measures gauging the problem in the 1960s and 1980s. Over the last 33 years estimates were used to gauge the diabetes burden in Malta. Today, we do not really know how many diabetics and pre-diabetics reside in the Maltese islands and whether their needs are being largely met. A national plan and an accurate age-gender disease profile are essential for the planning of control measures for Diabetes among adults in Malta, especially given the high impact of this disease locally.

A proposed diabetes prevalence study now getting underway aims to provide the evidence basis for updated health policies and to furnish health care workers with validated information about this disease.

Establishing profiles of the different risk groups (for pre-diabetes and diabetes) and their associated anthropometric, biochemical markers and genetic factors is another achievable key goal.

Preventive strategies can combine the benefits of screening high-risk controls with pan-population initiatives; bring healthy food and regular exercise within easier access of every Maltese.[26]

The development of a predictive tool such as an "app" for mobile phones and computers could help individuals measure their risk of developing or having a disease such as diabetes. This could be incorporated into primary care practice by patients, health insurers and health professionals. Identifying those in the population with highest predisposing pre-diabetes risk factors and formulating a pre-diabetic risk score would help pick up susceptible subjects at an early stage. Such risk scores reduce the cost and inconvenience of unnecessary screening.[27]

This information, placed within a national diabetes plan, would enable the Maltese health services to be better equipped to come to grips with this ever growing epidemic while aiding to improve the quality of life of those affected by the disease.

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Review Article

Ebola: too far or so close?

Paul Torpiano, David Pace

Abstract

The year 2014 has witnessed the escalation of the largest ever Ebola outbreak which started in Guinea, and later spread to other countries in West Africa. The associated disease burden has already exceeded the total number of cases in all the sporadic outbreaks that occurred since the first description of Ebola in 1976. The threat of further spread across Africa, and possibly beyond through international travel, is of concern and has led several countries around the world to implement preparedness measures against Ebola. In an attempt to contain the spread of Ebola, WHO and other non-governmental humanitarian organisations have pooled their resources to fuel efforts at improving patient care, isolation facilities, healthcare worker training, and availability of personal protective equipment in the affected countries. The outbreak has brought to light the lack of past investment in research into treatment or potential vaccine development against the Ebola virus, with the only hope of expediting a cure that can be used in the current outbreak being through the launch of clinical trials investigating experimental drugs in the affected countries.

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Key words

Ebola virus, Ebola Virus Disease, West African outbreak, Ebola treatment and prevention

Introduction

The Ebola virus (EBOV) is one of the aetiologies of Viral Haemorrhagic Fever (VHF), a syndrome complex characterised by fever, capillary leak, bleeding and shock. This zoonotic RNA virus was first discovered in 1976, following the first documented outbreak near the Ebola River in Zaire (now the Democratic Republic of Congo) which occurred simultaneously with another outbreak in Sudan.[1] Several outbreaks have occurred since its discovery, almost all of which have occurred in sub-Saharan Africa.[2] The current ongoing outbreak in West Africa is the largest ever to be reported and the associated high mortality as well as its potential for international spread are a real concern. The statement on the Ebola virus disease (EVD) released on the 31st of July, 2014 by Margaret Chan, the Director General of the World Health Organization (WHO): "If the situation continues to deteriorate, the consequences can be catastrophic in terms of lost lives but also severe socioeconomic disruption and increased risk of spread to other countries"[3] has led several countries to implement public health preparedness measures to immediately contain imported cases of EVD.

Ebola virus

The most likely vector of the EBOV is the fruit bat, specifically *Hypsignathus monstrosus* (the hammer-headed fruit bat), *Epomops franqueti* (Franquet's epaulettes fruit bat), and *Myonycteris torquata* (the little-collared bat).[4] The means of transmission within bat populations remains unknown.[5] Little is known of the life cycle of the EBOV, and why it only appears during intermittent outbreaks. Human disease is thought to result from consumption of poorly-cooked infected animals, such as bats or chimpanzees (which are known to feed on bats).[4, 6] However unlike other zoonoses Ebola has the potential of spreading from human to human from exposure of mucous membranes or broken skin to infected body fluids including large aerosol droplets that can be produced during coughing. There are 5 known strains of the EBOV as described in table 1.[7]

Table 1: The 5 known strains of the Ebola virus[7]

Strain	Acronym	Description
Bundibugyo	BDBV	First discovered in 2007 during an outbreak in Uganda
Zaire	EBOV	Causative strain in the current outbreak. Commonest cause of human disease
Reston	RESTV	Cause of outbreaks in monkeys and pigs. Not known to cause clinically apparent human illness or death
Sudan	SUDV	Associated with large outbreaks, mostly centred in Sudan and Uganda
Taï Forest	TAFV	Emerged in Taï Forest, Ivory Coast in 1994, causing infection in a single individual

Clinical manifestations

EVD is a severe acute viral illness characterised by the sudden onset of fever, intense weakness, muscle pain, headache and sore throat followed by vomiting, diarrhoea, rash and impaired renal and liver function. Disease progression may lead to disseminated intravascular coagulation, causing the characteristic terminal haemorrhagic phase that manifests as internal and external bleeding[7] including epistaxis, haematemesis, melaena, petechiae, ecchymosis and bleeding at venepuncture sites.[8] These signs are manifest in around 50% of patients.[9] The incubation period is estimated to be between 2 and 21 days, with patients remaining infectious as long as their blood and secretions (including semen) contain the virus, which can persist in semen for up to 61 days after the onset of illness.[7] Patients do not transmit Ebola during the incubation period but become infectious once they develop clinical features of EVD.[7] A diagnosis of EVD can be confirmed by means of several laboratory methods such as an antibody-capture enzyme-linked immunosorbent assay, antigen detection tests, a serum neutralisation test, reverse transcriptase polymerase chain reaction (RT-PCR) assay, electron microscopy, or virus isolation by cell culture.[7] During the current outbreak, RT-PCR kits have proven the most useful, accurate, and popular diagnostic investigation.[7]

Ebola outbreaks

Since the first outbreak in 1976, several Ebola outbreaks have been reported in humans and livestock within Africa over the last four decades (Table 2). The only unrelated handful of isolated cases occurring in Europe, Russia and the USA were in research laboratory workers. The Ebola subtype which is responsible for the current outbreak is the EBOV (or Zaire) virus, a 19.0kb non-segmented genome encoding 8 proteins, which last appeared in DRC in 2008.[2] The total estimated case fatality rate from 1976 to 2008 is estimated at 79%.[2]

Spread of the current Ebola strain: 2014

West Africa

Ebola is spread in the community through human-to-human transmission, with infection resulting from direct contact (through broken skin or mucous membranes) with the blood, secretions, organs or other body fluids of infected people, and indirect contact through contaminated fomites. Burial ceremonies in which mourners have direct contact with the body of the deceased person have been reported to play a role in the transmission of Ebola.[7]

The onset of the latest outbreak which began in Guinea, on the West African coast (Figure 1) has been traced back to late 2013. Contact tracing has successfully identified the index case for the 2014 outbreak to be a 2-year old child inhabiting the Meliandou village in the Gueckedou prefecture of Guinea. This child died on the 6th December, 2013. By February 2014, it had been transmitted to two other locations in Guinea: Macenta and Kissidougou, and by March it had spread to 5 other locations in Gueckedou.[11] The first death in Guinea's capital, Conakry, occurred on 18th March 2014. The patient was a businessman who travelled from Dabola, in central Guinea, having allegedly contracted the virus there through contact with a visitor from Gueckedou (who later also died from the disease). The body of the businessman was taken to Watagala, his village of origin, and following this, 4 of his siblings, along with 4 mourners at his funeral have tested positive for EBOV.[12]

Since then, the virus has spread to involve three other West African countries: Liberia, Sierra Leone and Nigeria. Several suspected cases from Mali all tested negative for EBOV. Four foci for infection have emerged in Liberia, only 1 of which has been explained by contact tracing: a woman arriving from Guinea gave the disease to her sister in Foya, 24km from the outbreak's main focus in Gueckedou). Her sister then travelled to Monrovia, Liberia's capital city, and onwards to visit her husband at the Firestone Rubber Plantation Camp northeast of the city. She died on the 2nd April, 2014.[13, 14]

Table 2: All outbreak and isolated cases of Ebola Viral Disease (1976 to date)[10]

Year(s)	Country	Ebola Subtype	Reported No. of human cases	Reported number (%) of deaths among cases	Description
1976	Zaire (DRC)	Ebola	318	280 (88%)	Disease spread by close personal contact and use of contaminated needles and syringes in hospitals/clinics.
1976	Sudan	Sudan	284	151 (53%)	Occurred simultaneously with outbreak in Zaire. Disease spread mainly through close personal contact within hospitals. Many medical care personnel infected.
1976	England	Sudan	1	0	Laboratory infection by accidental injury from a contaminated needle.
1977	Zaire (DRC)	Ebola	1	1 (100%)	Noted retrospectively in village of Tandala.
1979	Sudan	Sudan	34	22 (65%)	Recurrent outbreak at the same site as the 1976 Sudan epidemic.
1989	USA	Reston	0	0	Introduced into quarantine facilities by monkeys imported from the Philippines.
1990	USA	Reston	4 (asymptomatic)	0	Introduced into quarantine facilities by monkeys imported from the Philippines. Four humans seroconverted from asymptomatic infection.
1989-1990	Philippines	Reston	3 (asymptomatic)	0	High mortality among macaques in a primate facility responsible for exporting animals in the USA. Three workers seroconverted without evidence of disease.
1992	Italy	Reston	0	0	Introduced by monkeys imported from the Philippines. No humans infected.
1994	Gabon	Ebola	52	31 (60%)	Occurred in gold-mining camps deep in the rain forest.
1994	Ivory Coast	Tai Forest	1	0	Scientist became ill after autopsy on a wild chimpanzee in the Tai Forest. Patient treated in Switzerland.
1995	DRC	Ebola	315	250 (81%)	Epidemic spread through families and hospitals.

Year(s)	Country	Ebola Subtype	Reported No. of human cases	Reported number (%) of deaths among cases	Description
1996	Gabon	Ebola	37	21 (57%)	Chimpanzee found dead in the forest eaten by people hunting for food. Nineteen of these became ill, and subsequently infected other family members.
1996-1997	Gabon	Ebola	60	45 (75%)	Index case was a hunter who lived in a forest camp. A dead chimpanzee found in the same forest at the time was also infected.
1996	South Africa	Ebola	2	1 (50%)	Index case was a medical professional who travelled from Gabon to South Africa after having treated EVD-infected patients. A nurse who took care of him became infected and died.
1996	USA	Reston	0	0	Introduced by imported monkeys from the Philippines.
1996	Philippines	Reston	0	0	Identified in monkey export facility. No human infections.
1996	Russia	Ebola	1	1 (100%)	Laboratory contamination.
2000-2001	Uganda	Sudan	425	224 (53%)	Spread associated with attending funerals of EVD patients, being in contact with patients within a family, and providing medical care to Ebola patients without using adequate PPE.
2001-2002	Gabon	Ebola	65	53 (82%)	Occurred over the border of Gabon and the Republic of the Congo.
2001-2002	Republic of Congo	Ebola	57	43 (75%)	Outbreak occurred over the border between Gabon and the Republic of the Congo. This was the first time that Ebola haemorrhagic fever was reported in the Republic of Congo.
2002-2003	Republic of Congo	Ebola	143	128 (89%)	Outbreak occurred in the districts of Mbomo and Kéllé in Cuvette Ouest Département.
2003	Republic of Congo	Ebola	35	29 (83%)	Outbreak occurred in Mbomo and Mbandza villages located in Mbomo district.
2004	Sudan	Sudan	17	7 (41%)	Concurrent with an outbreak of measles in the same area

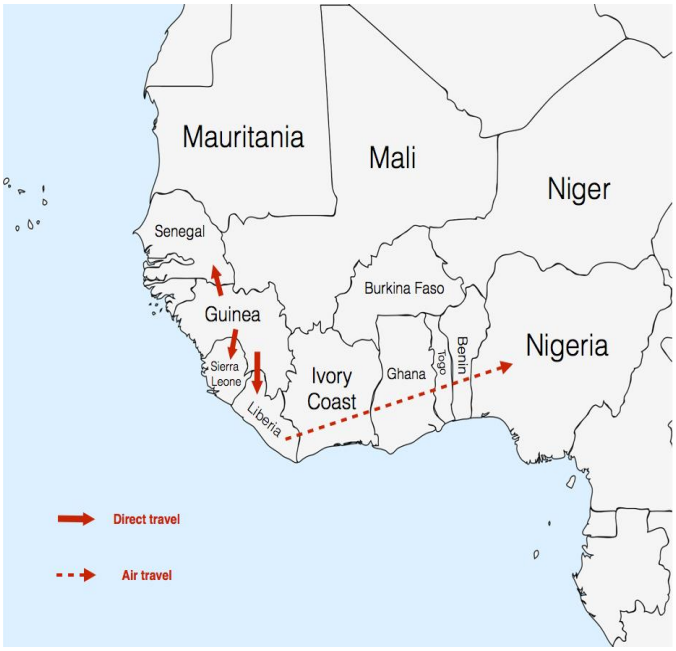
Year(s)	Country	Ebola Subtype	Reported No. of human cases	Reported number (%) of deaths among cases	Description
2004	Russia	Ebola	1	1 (100%)	Laboratory contamination
2007	DRC	Ebola	264	187 (71%)	Outbreak occurred in Kasai Occidental Province
2007-2008	Uganda	Bundibugyo	149	37 (25%)	First reported occurrence of a new strain
2008	Philippines	Reston	6 (asymptomatic)	0	First known occurrence in pigs. Six workers from the pig farm and slaughterhouse seroconverted
2008-2009	DRC	Ebola	32	15 (47%)	Outbreak occurred in the Mweka and Luebo health zones of the Kasai Occidental Province
2011	Uganda	Sudan	1	1 (100%)	The Ugandan Ministry of Health informed the public that a patient with suspected EVD died on May 6th, 2011 in the Luwero dietrict, Uganda.
2012	Uganda	Sudan	11	4 (36.4%)	Outbreak in the Kibaale district of Uganda
2012	DRC	Bundibugyo	36	13 (36.1%)	Outbreak in DRC's Province Orientale: had no epidemiological link with the near contemporaneous Ebola outbreak in Uganda.
2012	Uganda	Sudan	6	3 (50%)	Outbreak in the Luwero district. The CDC assisted the Ministry of Health in the epidemiological and diagnostic aspects of the outbreak.
2014	Guinea, Liberia, Sierra Leone, Nigeria, Senegal	Ebola	-	-	Ongoing outbreak. Suspected/confirmed case count = 3707; Suspected/confirmed deaths = 1848; Lab-confirmed cases = 2106.

Sierra Leone registered its first case on the 25th May 2014, while in Nigeria 1 patient died of probable EVD on the 27th July. This case was never confirmed as the courier refused to transport the serological sample for testing at WHO Collaborating Centre at the Institut Pasteur in Dakar, Senegal. Twenty other cases have been reported in Nigeria, with seven subsequent deaths. Sixteen cases were confirmed EBOV positive by laboratory testing.[5]

On the 25th July, Sierra Leone's top Ebola doctor, Sheikh Umar Khan, succumbed to the disease, highlighting the risk of healthcare workers acquiring EVD through contact with Ebola patients. More than 100 medical workers are estimated to be amongst the victims of this outbreak.[15] Healthcare workers are at an increased risk of contracting EVD, because of prolonged contact with infected patients and the associated risk of contact with body fluids or infected needles.[16] The proper use of PPE during contact with such patients is essential, and ensuring availability of PPE, as well as

training in its use, has been one of the priorities listed by WHO in response to the current Ebola outbreak.[17]

***Figure 1**: Spread of the 2013-2014 West African Ebola* Outbreak



On the 29th of August, reports emerged of the first case of EVD in Senegal, another West African country which borders Guinea. The case is that of a 21-year old male from Guinea who arrived in Dakar, Senegal by road on the 20th August, and stayed with relatives in the outskirts of the city. He developed fever, diarrhoea and vomiting and was later diagnosed with EVD.[17]

Characteristics of the current Ebola outbreak

Previous Ebola outbreaks tended to occur in rural areas, such as remote parts of Uganda and DRC, and thus were for the most part self-contained due to geographic isolation of cases. The EVD outbreak that is ongoing this year, however, marks the first outbreak in a densely populated urban area within Conakry's large shanty towns.[18] The scale of this outbreak has raised a concern on the potential of a pandemic, with epidemiological modelling based on the data from previous Ebola outbreaks producing a basic reproduction number (R_0) of 2.7 (95% confidence interval: 1.9-4.1)[19] meaning that every case of EVD leads to infection in another 2.7 individuals, a figure that is comparable to the R_0 of influenza.[20]

The extent of the current Ebola outbreak is also unprecedented. The previous total death toll since 1976 was estimated to be 1590,[15] while, since December 2013, EVD has already caused at least 1427 deaths.[5] Spread between non-neighbouring African countries by travellers, as occurred between Liberia and Nigeria demonstrates the ease of spread of Ebola, raising fears of its potential for uncontrolled escalation of this outbreak.[15]

Mortality Rate

In contrast to previous outbreaks, this outbreak has an estimated mean case mortality rate of 56%, a sharp drop compared to the 90% observed previously.[15] This discrepancy is most probably due to the smaller scale of previous outbreaks with the deaths occurring in the few that were infected resulting in a high case fatality rate. Data on the number of cases, deaths and lab-confirmed cases in the 4 affected countries, as of the 22nd August, 2014 are shown in table 3.[5]

Public health measures

WHO has been following this outbreak since late 2013, and is continually providing updated infection control recommendations as well as aiding their implementations in an effort to control this epidemic. It has been suggested that the scale of this EVD outbreak, as well as the speed with which it has escalated, places other countries in West Africa at a significant risk of being affected. Kenya and Togo in particular, where healthcare infrastructure is poor and appropriate facilities for early identification, isolation and treatment of cases are lacking, have been identified as being at a high-risk.[17] WHO recommendations have largely focused on the need for the availability and correct use of personal protective equipment (PPE), in addition to the appropriate management of suspected cases through the use of guidelines on diagnosis, isolation of cases and contact tracing.[15] WHO has also explicitly expressed the need for more funds and resources, emphasising that this outbreak and its subsequent spread is a result of the poor infrastructure and quality of healthcare in the countries affected.[15] On the 31st July, WHO pledged $100 million for this purpose, while the World Bank has added a further $200 million. Médecins Sans Frontièrs and the International Committee of the Red Cross have both shown hope that with more resources and investment, the disease can realistically be contained by the end of this year.[15]

***Table 3**: Number of cases and deaths from suspected and laboratory-confirmed EVD until 15th September, 2014.[5] Continuous updates to these figures are available at http://www.afro.who.int*

	Guinea	Sierra Leone	Liberia	Nigeria	Senegal	Total
Suspected/ confirmed cases	771	1216	1698	21	1	3707
Suspected/ confirmed deaths	494	476	871	7	0	1848
Lab-confirmed cases	579	1107	403	16	1	2106

WHO has provided Interim Infection Control Recommendations, published in March 2008 and updated in August 2014, for those exposed to cases of suspected EVD with a focus on thorough washing of contaminated surfaces, detailed medical evaluation and follow-up, isolation pending exclusion of Ebola infection, and contact tracing.[21] A more recent document, updated in August 2014, has also been published by the UK Department of Health, and makes similar basic recommendations to those mentioned by WHO.[22] WHO also suggests preventive measures for avoiding spread of the virus, and recommends that if any HCW is within 1m of an affected patient, then a face-shield or medical mask with goggles, gloves, and a clean, non-sterile long-sleeved gown should be worn.[21] The affected countries have taken measures to ensure that the spread of the outbreak is controlled, placing patrols at the borders, while enforcing quarantine of suspected cases as well as proper burial of deceased patients.[5] Despite this, the increasing sense of panic has led to suspected patients escaping from medical facilities so as to avoid quarantine, while international news agencies have reported that families are leaving the bodies of deceased relatives in the street out of fear of contracting the disease or of being forced into quarantine, instead of waiting for doctors to visit their homes and dispose of the bodies appropriately.[15]

Countries outside of Africa are also making preparations and advising on precautionary measures to contain any inadvertently imported cases in order to prevent local spread of Ebola. The European Centre for Disease Prevention and Control (ECDC) has issued guidelines suggesting measures to prevent exportation of cases to other countries and spread within the European Union (EU).[23] These suggest that, in the event of the outbreak reaching a European country, local authorities should consider barring known EVD cases, as well as their contacts, from leaving the country, for a minimum of 21 days following exposure (the incubation period of the EBOV).[23] The ECDC also suggests that travellers from affected areas should be informed about the clinical presentation of EVD, the importance of revealing their travel history when seeking medical care, the need to indicate possible contact with sick individuals or wild animals, and the procedures for contacting public health authorities for support if infection is suspected.[23] Recommendations also extend to informing healthcare providers about the possibility of EVD among returning travellers from affected areas, the clinical presentation of the disease, the availability of protocols for the ascertainment of possible cases and procedures for referral to healthcare facilities, and the need for strict implementation of barrier management, use of PPE and disinfection procedures when providing care to suspected EVD cases.[23] The Department of Health in the UK has published guidelines on the assessment and management of suspected EVD in febrile travellers who visited affected countries within the prior 21 days.[22] The CDC has provided similar guidelines for hospital use in the USA, as well as advice on infection control procedures designed to prevent in-hospital spread of viral haemorrhagic fever.[5] Based on these guidelines, several governments have invested heavily in training of hospital staff to follow recommendations, as well as to ensure availability of all necessary PPE, diagnostic kits, isolation and contact-tracing facilities, and treatment requisites.[22]

Treatment

Currently there is no licensed treatment for EVD. Management of affected patients is supportive and includes the administration of intravenous resuscitative

fluids, maintenance of electrolyte balance, and intensive care measures.[1] The allegedly successful treatment of two US nationals with ZMAPP, an experimental treatment consisting of a mixture of three humanised monoclonal antibodies against Ebola that is being developed by Mapp Biopharmaceuticals, San Diego, California and which has not yet been studied in humans,[24] has fuelled speculation on the effectiveness and the need for availability of such treatment. The rarity of EVD and VHF in general meant that little investment was made to develop preventive or therapeutic medicinals. This has led to calls for experimental drugs to be opportunistically distributed during the current outbreak in the form of a clinical trial, in the interest of developing better therapeutic agents.[15] However, there are several issues that need to be carefully considered with such a clinical trial, apart from the huge associated expense. Traditionally, West African populations are suspicious of Western European doctors,[15] an attitude that will complicate attempts in contact tracing, correct burial of deceased cases, and isolation of suspected cases and which will hinder the use of experimental drugs against Ebola. Questions have also been raised over the ethics of testing populations within poverty-stricken demographic areas.[15]

The FDA however, has previously brought forward a 2-animal rule on drug testing, suggesting that, in an emergency, a drug that has shown efficacy in two different animal models, and that has been proven not to have serious side effects in healthy humans can be made available on compassionate grounds.[25]

Published reports on experimental approaches to treat Ebola are limited. Jahrling et al, in separate publications in 1996 and 1999, suggested that the use of hyperimmune horse anti-Ebola serum is protective in animal models.[26,27] Maruyama et al, also in 1999, reported success with human monoclonal antibodies acting against the EBOV surface protein (derived from mRNA extracted from bone marrow of survivors of EVD).[28] A novel approach for extracting immunoglobulins from survivors of EVD has reportedly been highly successful in animal trials, with results expected to be published in the upcoming months.[15] Tekmira Pharmaceuticals in Canada are developing an experimental drug called TKM-Ebola which consists of small interfering RNAs that target the EBOV and halts viral replication by blocking DNA synthesising proteins.[29] TKM-Ebola had entered Phase I human safety clinical trials in January 2014.[24] However, the FDA halted the trials on the 3rd July, and is requesting more information on the proposed mechanism of action of TKM-Ebola which is administered according to a complicated dosage regimen.[15,24] BioCryst Pharmaceuticals in North Carolina have adopted a similar approach to develop an experimental drug called BCX4430, which has allegedly been proven to be effective in preventing death from Marburg virus, the other member of the Filoviridae family of viruses causing VHF, in animal trials.[24]

Furthermore, the potential of favipiravir, an antiviral agent against Ebola is being investigated with Ostereich et al reporting promising results with its use in a murine model.[30] This drug selectively inhibits the RNA-dependent RNA polymerase of the virus, and was initially developed and promoted for its role in treating influenza.[31]

Vaccine Prevention

The development of a vaccine against Ebola has been hindered by the lack of interest and investment by pharmaceutical companies in researching an infection with a previously very low disease burden confined to poor developing countries. Dr Anthony Fauci, director of America's National Institute of Allergy and Infectious Diseases (NIAID) recently announced that phase I clinical trials of a promising Ebola vaccine are to be initiated in September, hoping for favourable results by January and very optimistically to have this vaccine manufactured and available for distribution by late 2015. The precise components of this proposed vaccine have not been published, though a study in 2005 by Geisbert et al showed promising results with a vaccine made from the Vesicular Stomatitis Virus.[32] In this study recombinant Vesicular Stomatitis Virus vectors expressing homologous filoviral glycoproteins were found to partially protect 4 of 5 macaques challenged with the Zaire Ebolavirus.[32]

Conclusion

The magnitude of this year's EVD outbreak is already much larger than any previous Ebola outbreaks, partly due to the very poor infrastructure of healthcare systems in affected countries, failure to follow adequate barrier precautions, and unavailability of PPE. Cultural attitudes such as fear of quarantine, as well as mistrust in advice provided by developed countries have hindered containment of the current outbreak. Fear and panic have resulted in an increased scattering of contacts, making contact tracing difficult.

Still, WHO is optimistic that with proper funding and investment, the current outbreak can be controlled effectively through the use of simple infection control measures, aided by emerging drug therapies and possibly vaccination.

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Review Article

Neurogenic Disturbances of Cardiac Rhythm

Daniel Loh, Patrick Pullicino

Abstract

Arrhythmias are disturbances of electrical activation of the heart and are commonly encountered clinical conditions. Although typically associated with cardiac pathology, they have also been described in stroke and epilepsy. Two closely related structures, the insula and the temporal lobe, particularly the mesial region, have been implicated. Derangement of central autonomic control appears to be a key driver in neurogenic arrhythmogenesis and both these structures appear to play some role in influencing autonomic activity. Our understanding of this phenomenon is only in its infancy, and more research will be necessary to further it.

Keywords

Stroke, epilepsy, arrhythmias

Cardiac arrhythmias, stroke and epilepsy

Cardiac arrhythmias are disorders of electrical myocardial activation that manifest as abnormalities in the rate and rhythm of contraction. They fall loosely into two categories: tachyarrhythmias and bradyarrhythmias, and are conventionally thought to be phenomena related to cardiac lesions. Rhythm disturbances have, however, also been reported with certain cerebral insults: stroke and epilepsy.

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A *stroke* is an acute episode of neurological deficit of presumed vascular origin persisting ≥ 24 hours.[1] It may be ischaemic or haemorrhagic in nature and both aetiologies have been observed to be arrhythmogenic.

Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures, and diagnosis requires the occurrence of at least one epileptic seizure.[2]

Growing evidence suggests an independent association between these conditions and arrhythmias and this article will review existing research and opinion linking them.

Vascular Insults

Neurogenic involvement in arrhythmogenesis was first proposed in 1930,[3] but until the 1970s little mention was made of this relationship with only isolated case reports implicating subarachnoid haemorrhage.[4] Cardiac causes have been identified as the single largest precipitant of death after stroke. There is collective evidence that the presence of cardiac arrhythmias adversely affects stroke survival and together with the lack of post-mortem findings of cardiac ischaemia or thrombosis,[3] strongly argues for a neurological component to arrhythmias.

Type & Incidence of Arrhythmias

The incidence of arrhythmias of any kind is higher in patients with stroke than without. Exact values vary between studies and type of stroke: Lavy et al.[5] reported a 39% incidence of transient arrhythmias in stroke patients without previous cardiac disease. The sample included both haemorrhagic and ischaemic stroke, and when looking at haemorrhagic stroke alone, the incidence went up to 71%. Norris et al.[6] studied 35 patients each in a stroke vs non-stroke group matched for age and sex that revealed a nearly 3x increased incidence of cardiac arrhythmias. Goldstein[7] found a significantly greater frequency of new QT prolongation (32% vs 2%) and arrhythmias of any type (25% vs 3%) in strokes collectively compared to controls. Atrial fibrillation (AF) was the most common arrhythmia (9% vs 0%), followed closely by ventricular arrhythmias (8% vs 2%). QT prolongation was significantly more frequent in subarachnoid haemorrhage (71%) compared to other stroke types (39%) while new AF was more common in cerebral embolus (50%) than non-embolic

stroke (0%).

The range of conduction disturbances observed runs the gamut from sinus bradycardia or nodal escape to ventricular tachycardia. Studies focus mainly on ventricular arrhythmias as they pose a greater risk. Mikolich et al.[8] observed significantly more cases of ventricular ectopy (50%) in the stroke group compared to controls (15%). More worryingly, catastrophic arrhythmias occurred in 20% of the stroke group, resulting directly in death in at least one patient, while none occurred in the controls. 93% of the strokes were ischaemic. Using 24-hour Holter monitoring, Pasquale et al.[9] found arrhythmias in 90% of their cohort of subarachnoid haemorrhage (SAH) patients. Ventricular arrhythmias were observed in 82%, and 4 patients developed torsades de pointes. More recent studies reveal a lower overall incidence: Bruder et al.[10] reports a 35% incidence after SAH, with 5-8% potentially fatal while Kallmunzer et al.[11] detected arrhythmias in 25.1% of a cohort of 501, of which 92% were ischaemic strokes. Ventricular arrhythmias accounted for 27% and incidence of any arrhythmia was highest in the first 24 hours after admission.

Localisation & Lateralisation of cortex

Attempts were made early on to delineate a relationship between the stroke location and frequency of arrhythmias. Lavy et al.[5] estimated that arrhythmias occurred in 100% of brain stem strokes and only 80.5% of hemispheric strokes. Norris et al.[6] found the reverse to be true, with arrhythmias occurring in 52% of hemispheric strokes compared to 38% of brain stem ones. Among hemispheric strokes, arrhythmias were more prevalent in ischaemic strokes (53% vs 42%) while the reverse was true for brain stem strokes (35% vs 67%). Mikolich et al.[8] observed a predominance of arrhythmias in patients with anterior circulation strokes although the small number of posterior circulation strokes included in the study detracts from its value. In SAH, no correlation was noted between site and extent of haemorrhage and either the frequency or severity of arrhythmias.[9]

More recently, the insular cortex (which lies beneath the operculum formed from frontal, parietal and temporal lobes) has been implicated in arrhythmogenesis. Stimulation of the insula in humans produced autonomic cardiovascular effects with apparent lateralisation: parasympathetic effects were more frequently produced on left sided stimulation while right insular stimulation showed the reverse.[12] It would be remiss, however, to assume complete lateralisation of autonomic control exists, and the conflict within the literature attests to this: one study involving seven patients with lesions confined mainly to the left insular cortex found a shift toward increased basal sympathetic tone and a corresponding increase in heart rate.[13]

Conversely, Lane et al.[14] reported an association between right hemispheric stroke and the incidence of supraventricular tachycardia. Daniele et al.[15] did not observe any hemispheric association with type of arrhythmia, although the data showed arrhythmias occurred more frequently in right compared to left hemisphere strokes. Colivicchi et al.[16] found that ventricular and supraventricular tachycardia was 3.0x and 2.6x respectively more common in right insular stroke compared to left insular stroke. This discrepancy can be explained in part by the existence of inter-hemispheric connections between some insular tracts and by the fact that insular lesions are usually part of a larger infarct, confounding the results.[17] More research is necessary before definite conclusions are drawn.

Pathophysiology of arrhythmogenesis in Stroke

Based on established knowledge of the cardiovascular effect of sympathetic and parasympathetic limbs, initial speculation was that a stroke leads to an autonomic imbalance that favours sympathetic activation, resulting in catecholamine excess which alters the electrical properties of cardiomyocytes, giving rise to arrhythmias.[7-8] Recent evidence continues in the same vein: Strittmatter et al.[18] found that plasma noradrenaline and adrenaline levels were significantly elevated in right hemisphere strokes compared to controls at point of admission and throughout the 5 days of monitoring. Regression analysis by Colivicchi et al.[16] revealed that the standard deviation of all normal-to-normal R-R intervals was a significant predictor of the presence of arrhythmias, with lower values (reflecting diminished vagal tone) strongly associated with its presence. Greater age and more neurological deficit from the stroke, leading to more autonomic instability and increased sympathetic tone, were also independently associated with arrhythmias.[11] This theory is now widely accepted, and the term catecholamine storm used to describe it.[19]

Hyperactivation of β-adrenergic receptors is another effect of catecholamine excess, which in turn leads to tonically open calcium channels such that sequestration of intracellular calcium ions necessary for muscle relaxation fails to occur.[17] This ultimately leads to cell death and a characteristic lesion termed coagulative myocytolysis which has the histological features of myofibrillar degeneration and contraction band necrosis. This lesion is predominantly subendocardial and could therefore involve the cardiac conduction system, serving as a substrate for arrhythmogenesis.[20]

Epilepsy

Ictal arrhythmias were first noticed in 1906, with an episode of cardiac asystole at onset of seizure.[21] They have particular relevance with respect to their role in

sudden unexpected death in epilepsy (SUDEP), which has an incidence of 0.09-9 per 1000 patient-years[22] and accounts for 8-17% of deaths in people with epilepsy.[23] Understanding and controlling these arrhythmias are therefore vitally important.

Type & Incidence of Arrhythmias

Variations in heart rate are the most common ictal change reported and tachycardia is the most commonly seen. Zijlmans et al.[24] recorded an increase of more than 10 beats/minute in 93% of patients and more than 20 beats/minute in 80% of patients. Children and adolescents respond similarly; Mayer et al.[25] saw it in 100% of their cohort who were younger than 18 years while 80.6% of seizures observed fulfilled age-adjusted criteria for absolute tachycardia. Onset of tachycardia is usually in the early ictal phase, and can even precede EEG onset.[23] Bradycardias are significantly less common, Leutmezer et al.[26] documented them in 1.4% of seizures while Rugg-Gunn et al.[27] found them in 0.24% of reported seizures and 2.1% of seizures recorded on an implantable loop recorder. Men are more commonly affected[21] and episodes typically occur in the late ictal phase.[27] The potential for evolution into asystole exists, and this was observed by Schuele et al.[28] in 0.27% of 6825 patients. These periods typically last for 5-10 seconds.[29] Although rare, these events can be serious enough to warrant permanent pacemaker insertion; 21% in the study by Rugg-Gunn et al.[27]

As with stroke, a wide range of arrhythmias have been observed. Nei et al.[30] observed arrhythmias in 39% of patients, the most common of which were atrial premature depolarisations (47%) and sinus arrhythmia (35%). Of the patients with arrhythmias, 20% had potentially serious ones. The authors also noted that longer seizure duration and generalised tonic-clonic seizures rather than complex partial seziures were independent predictors of arrhythmia occurrence. Children are also not spared; Standridge et al.[31] found ictal arrhythmias in 40% of patients, which were potentially serious in 12%. Significant associations with gender were also noticed: arrhythmias were more common in boys, and of the potentially serious ones, all those with an abnormal QRS complex and 73% with irregular variable rhythm occurred in boys. Peri-ictal and post-ictal rate changes were more common in girls.

Location & Lateralisation of Cortex

It was noticed early on that the degree of ictal tachycardia depended largely on the volume of cerebral structures involved in the seizure, with heart rate (HR) increase directly proportional to the regions recruited.[32] This is corroborated by work from Opherk et al.[33] who found that sinus tachycardia was more common in generalised than non-generalised seizures (100% vs 73%). Absolute values both ictally (mean 186 vs 162) and postictally (mean 159 vs 117) were also greater. In the non-generalised seizures, neither hemisphere nor region of onset influenced the ictal HR. The authors did note that left hemispheric seizures more commonly caused benign arrhythmias and noticed a non-significant trend suggesting that mesial temporal sclerosis was linked to serious arrhythmias. Rugg-Gunn et al[27] also found no evidence for seizure lateralisation in tachycardia, although by contrast, three of the four patients with episodes of prolonged asystole had left hemispheric seizures.

The temporal lobes are well known to be invoved in arrhythmogenesis, with the mesial temporal lobe particularly implicated. Leutmezer et al.[26] reported that the absolute increase in ictal HR was significantly greater in patients with mesial temporal lobe seizures (TLS) compared to nonlesional and extratemporal TLS. Lateralisation of onset was also apparent; absolute and relative increases in HR were significantly greater in right compared to left hemisphere onset. Standridge et al.[31] noted that the right hemispheric localisation was significant only in TLSs with ictal sinus tachycardia while Mayer et al.[25] found that early and high HR increases were principally associated with right mesial TLSs. HR changes were more frequently found in mesial TLSs compared to lateral/neocortical TLSs (56 vs 13). Within the mesial TLSs, HR changes were more prominent in right than left (36 vs 20). Furthermore, HR changes at the extremes of the spectrum were nearly exclusively associated with right mesial TLSs.

Ictal bradycardias are also associated with TLSs but do not appear to demonstrate any lateralisation. Britton et al.[34] found that 52% of ictal bradycardias were bitemporal in onset, accounting for nine of the 13 patients studied. The presence of contralateral insular activation via transcallosal connections was not ruled out however, and this may be an avenue worth exploring.

Pathophysiology of arrhythmogenesis in epilepsy

There is evidence to suggest that the mechanisms involved in the stroke pathway also play a part in epilepsy. Myocytolysis has been demonstrated in SUDEP patients, indicating direct catecholamine activity on the heart.[33] Basal autonomic control also appears to be deranged, and this dysfunction increases the more severe the epilepsy is.[35] Decreased heart rate variability, reflecting a loss of vagal tone, has also been reported in epileptics and is associated with an increased risk of lethal arrhythmias.[23]

A separate mechanism by which arrhythmias may be generated is called the lock-step phenomenon in which cortical epileptiform discharges directly influence postganglionic activity at the heart such that synchrony between seizure and cardiac autonomic activity exists, inducing lethal bradyarrhythmias or asystole.[23]

Sudden Unexpected Death in Epilepsy

Besides fatal arrhythmias, SUDEP is also commonly attributed to two other pulmonary conditions: central apnoea and neurogenic pulmonary oedema. Although mechanistically dissimilar, there appear to be several risk factors that operate irrespective of aetiology. Nearly all witnessed cases of SUDEP occur in the context of a generalised tonic-clonic seizure.[36] Seizure frequency was found to be the strongest risk factor, while early onset of epilepsy and a longer duration of the condition are also independent risk factors.[37] The risk of SUDEP appears correlated to severity of epilepsy; it is higher in those with refractory epilepsy (reflected by anti-epileptic drug polytherapy) as well as patients with epilepsy who are not receiving treatment and highest in patients deemed suitable for epilepsy surgery or those who continue to suffer even after surgery.[23, 36] Genetic channelopathies have become the focus of late, and mutations in KCNQ1, SCN1A and RYR2 among others have been identified in several studies.[23]

Concluding Remarks

It is certain that stroke and epilepsy can give rise to arrhythmias. Intuitively, it might appear that these conditions are two sides of the same coin: one causes hypofunction, the other hyperfunction, both of which lead to autonomic imbalance. Unfortunately, the truth is rarely so simple and this is not completely borne out by experimental evidence; the complex interconnections between different regions and hemispheres of the brain almost certainly part of the reason. Further work examining these regions, particularly in the limbic system, with which the insula and mesial temporal lobe are closely associated, will be required for a better understanding. From a more immediate clinical perspective, broadening awareness of clinicians to the arrhythmogenic potential of stroke and epilepsy is the earliest, and arguably a key, step in improving patient outcomes: appropriate cardiac monitoring in the context of telemetry monitoring or in HASUs could be potentially life saving while also providing incontrovertible data for future research.

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Review Article

A biomarker guided approach in heart failure

Mark Abela

Abstract

Heart failure is one of the commonest diagnoses presenting to physicians in the community or hospital care. Symptoms are often subjective, with clinicians having to rely on clinical assessment and radiological imaging to manage these patients. Treatment is often symptomatic with no clear therapeutic goals as yet identified. To date, there are no objective measures to diagnose, predict, prognosticate or guide therapy in compensated and decompensated heart failure, which is why a novel biomarker guided management approach is gaining so much momentum in the clinical community. This review encompasses recent data on this new approach and details on the potential clinical benefits of the most widely studied cardiac biomarkers currently available.

Key Words

Acute Decompensated Heart Failure, Biomarker, Remodelling, Prediction, Prognosis, Risk Stratification

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What is a biomarker?

The term biomarker was first introduced in 1989 and was defined as a ‘*’measurable and quantifiable biological parameter which is used to asses health and physiology in a patient in terms of disease risk and diagnosis*’’. This definition was later amended in 2001 by a National Institute of Health (NIH) working group as an ‘*’objectively measured parameter that is an indicator of normal biological processes, pathogenic processes or as a response to pharmacological therapy’’*.[1] Ever since the concept’s birth, its potential prospects are slowly gaining momentum in the medical community.

Biomarkers: The new paradigm in heart failure

Heart failure (HF) symptoms are often very misleading and subjective, particularly if not associated with signs of fluid overload. In spite of better resources, there are limited tools at the physician’s disposal to objectively diagnose and follow up this ever growing pathological entity. The genomic changes associated with the physiological factors involved, contribute to multiple molecular, cellular and interstitial changes. These changes occur as a result of chronically activated response systems. Signs of cardiac de-compensation happen when remodelling is excessive.

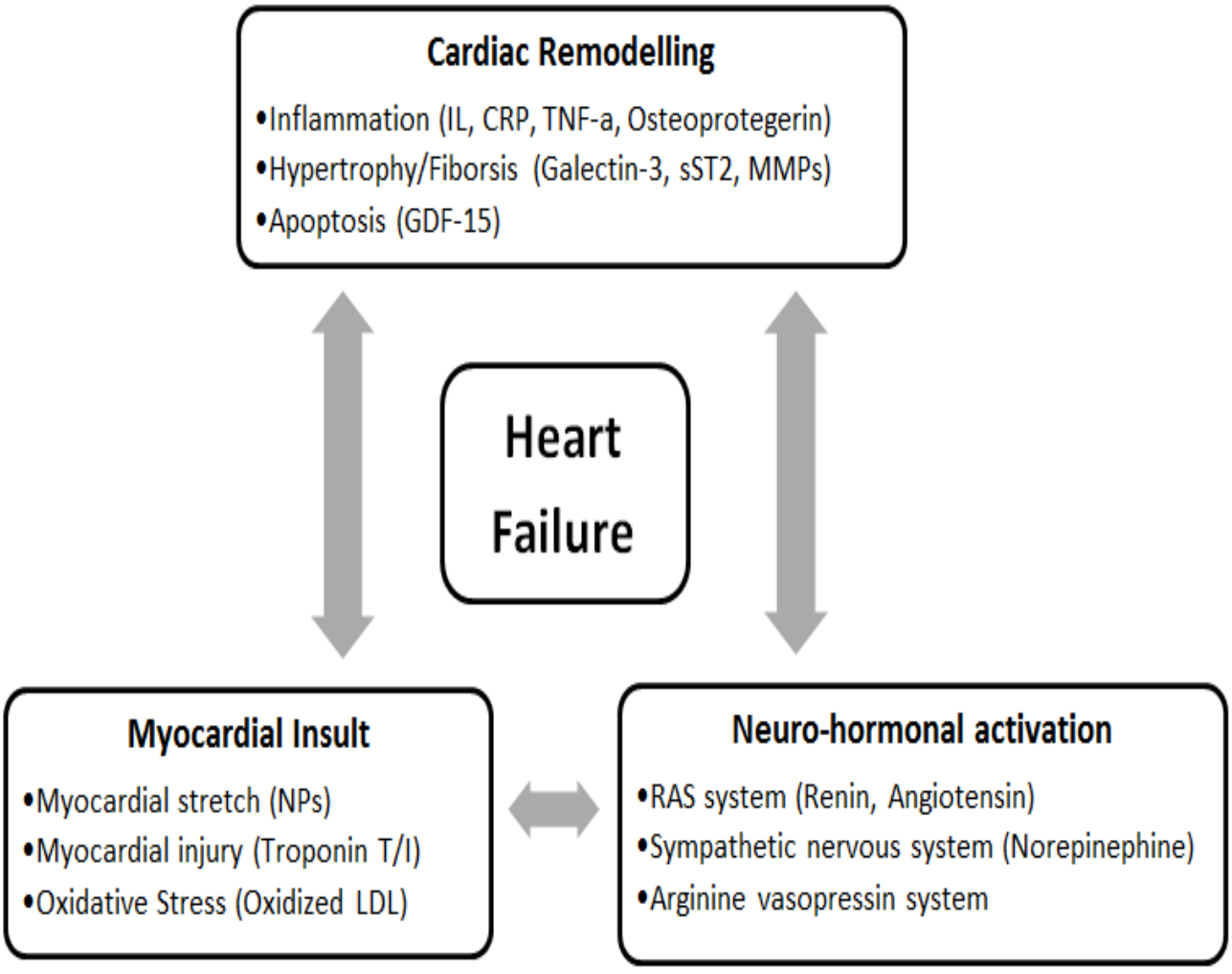
HF is a complex multi-system disorder (Figure 1) characterised by abnormalities in cardiac myocytes, altered renal function and neurohormonal changes. All these act as compensatory mechanisms to maintain adequate cardiac output in the presence of cardiac insults. Neurohormonal systems (renin-angiotensin (RAS), sympathetic (SNS) and arginine-vasopressin (AVS) systems) are activated to increase myocardial contractility, heart rate, peripheral vasoconstriction and promote salt and water retention. When these systems fail to compensate, various structural change take place in the myocardium. Fluid overload because of worsening cardiac output results in myocardial stretch and release of natriuretic peptides (NPs). Oxidative stress and myocardial injury take place when vascular supply is disproportionately low compared to demand. Recurrent cell damage up-regulates certain inflammatory and remodelling mediators at the point of decompensation. Modelling mediators like galectin-3, soluble ST2 (sST2), matrix metalloproteinases (MMP), tumour necrosis factor alpha (TNF-α) and endothelin stimulate a number of signal transduction cascades. The consequent myocyte hypertrophy, fibroblastic activity and apoptosis,

give rise to a vicious cycle of cardiac structural remodelling. The capillary versus myocyte mismatch in response to these structural changes worsens myocardial dysfunction, decreasing cardiac chamber compliance and diastolic dysfunction.

Such insights into the pathophysiology of HF have brought about promising advances in the discovery and clinical utility of specific cardiac biomarkers. If used wisely, cardiac biomarkers can be used as i) prognostic predictors (predict onset or worsening of HF), ii) objectively diagnose compensated or decompensated HF, iii) risk stratify patients, iv) develop new specific target therapy (at the biochemical level) or v) as a biological tool to guide therapy.[2]

Understanding the physiological pathways and functions of biomarkers (Figure 1) will help clinicians better understand the potential of these biomarkers in the clinical field. Whilst most of the available biomarkers are still in their infancy in terms of their roles and clinical utility in heart failure, NPs, galectin-3, sST2, growth differentiation factor-15 (GDF-15) and troponin T are showing potential in this field. NPs definitely stand out, with the markers most studied and utilised in biomarker guided HF management. In the following sections, a closer look is taken in the various biomarkers available, all of which will be discussed separately in the next sections.

***Figure 1**: Pathophysiological pathways of cardiac biomarkers in Heart Failure*



**Abbreviations: IL (Interleukins), CRP (C-reactive peptide), TNF-a (Tumour Necrosis Factor alpha), MMPs (Matrix Metallo-proteinases), GDF-15 (Growth Differentiation Factor), NPs (Natriuretic Peptides), LDL (Low density lipoprotein), RAS (Renin-Angiotensin System)*

Natriuretic Peptides (NPs)

NPs including brain natriuretic peptide (BNP), N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) and adrenomedullin (ADM) are peptides released in response to myocardial strain (particularly atrial stretch) during fluid overload. This is the case in acute decompensated HF (ADHF). These peptides work by promoting vasodilation, natriuresis and diuresis. Both BNP and NT-proBNP are released in their precursor form.[3] The short half-life and disease dependent fluctuant levels make NPs very useful in the management of dyspnoeic patients. ADM on the other hand, has a very short half-life hence making it a poor predictive biomarker. Its precursor MR-proADM has a longer half-life, overcoming ADM's problem in this regard. According to the multicentre BACH trial,[4] MR-proADM was deemed non-inferior to BNP.

NPs have been extensively studied as objective diagnostic markers of HF. A high value in an acutely dyspnoeic patient can be used to quantify acute decompensated heart failure (ADHF) severity whilst a low value (<100pg/mL of BNP) effectively excludes ADHF as a differential for acute dyspnoea due to its excellent sensitivity (96.98% as per *BACH* Trial).[4] Whilst high values might possibly reflect ADHF, one should adjust levels for renal dysfunction (higher baseline) and obesity (lower baseline). Of note, natriuretic peptide levels may be relatively low in patients presenting with flash pulmonary oedema, often because a short time interval precedes the up-regulated de-novo peptide synthesis after natriuretic peptide stores are acutely depleted.[5]

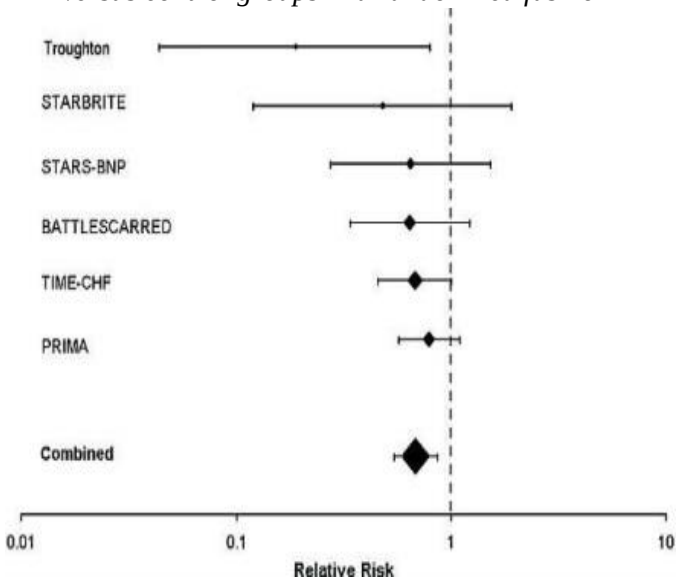
All the NPs are independent predictors of future cardiac events and hospitalisations as stated in the *Val-HeFT* trial.[3] Such markers can be used to help identify those at risk patients who would benefit from an earlier follow up and tighter risk factor control.

There is significant potential with the use of natriuretic peptides as prognostic markers. The *IMPROVE-CHF* study confirmed the usefulness of these peptides (NT-proBNP in particular) in the management of the acutely dyspnoeic patient.[6] Other studies have particularly shown their usefulness as mortality predictors with a high BNP associated with a 3-4 fold mortality in the *ADHERE* trial results. This benefit is best seen with NT-proBNP, regarded as the best predictor out of all the natriuretic peptides, itself improving the prognostic value of MR-proANP when used in combination).[3] Besides reducing in-patient mortality with relative falls in natriuretic peptide levels, the clinical usefulness of these proteins extends to outpatient mortality. The absolute NP level at discharge seems to have an excellent evaluation of ventricular function. A high level of natriuretic peptide indicates the absence of a complete optivolaemic status and is associated with a higher risk of hospitalisation after ADHF, particularly in the region of 600-700-pg/ml for BNP and >7000 pg/ml for NT-proBNP.[7]

These markers are said to be the pioneers in a biomarker guided therapeutic approach, widely used to assess fluid overload in HF patients. Studies show that angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), diuretics, spironolactone and perhaps long term beta-blockers (levels increase with short term beta-blockade) actually decrease natriuretic peptide levels. Several small studies and a recent meta-analysis (Figure 2) including the *Troughton, STARBRITE, STARS-BNP, BATTLESCARRED, TIME-CHF* and *PRIMA* Trials by Felker et al in 2009 suggest overall improved clinical outcomes with a biomarker guided approach using NPs. That said, one should interpret results with caution as some of these trials had wide confidence intervals for the hazard ratios, most crossing the line of no effect.[8] The on-going *GUIDE-IT* randomised control trial might yet reveal the usefulness of such an approach though at this point, actual data on the benefit is still lacking.[9]

Knowledge of a patient's baseline peptide levels may further improve diagnostic accuracy, reason being that high levels may actually be the patient's optivolaemic (dry) level due to persistent myocardial strain, even after resolution of the acute exacerbation. In any case, serial levels can be very useful in both in-patient and out-patient settings. To gain full advantage of their clinical applicability, the caring physician should aim at decreasing NP levels present during the acute volume overload (wet) phase down to optivolaemic (dry) levels.[5]

***Figure 2**: Forest plot of all-cause mortality among patients with heart failure in biomarker guided therapy versus control groups in a randomized fashion[8]*



Soluble ST2 (sST2)

ST2 is part of the Interluekin-1 (IL-1) receptor family, the gene coding for a trans-membrane receptor (ST2L) and soluble form (sST2). The ligand of ST2 (IL-33) is involved in reducing fibrosis and hypertrophy in mechanical strain. Studies have shown that excess sST2 is involved in cardiac hypertrophy, fibrosis, ventricular dilatation and reduced ventricular contractility. Iatrogenic sST2 administration blocks the anti-hypertrophic influences of IL-33 in a dose dependent fashion, highlighting its possible involvement in the pathogenesis of HF.[10]

sST2 levels are higher in ADHF when compared to control, increasing with worsening severity and reduced left ventricular ejection fraction (LVEF), making it a useful diagnostic tool.[3] Besides being associated with decompensation, high levels in a healthy asymptomatic population are also able to predict a worse cardiovascular morbidity. Correlation analysis in the Framingham heart study showed that age, sex, diabetes and hypertension where highly correlated with sST2 meaning that baseline levels should be interpreted accordingly.[10] The potential of sST2 as a predictor biomarker is quite significant and was found to be non-inferior to NT-proBNP in mortality prediction. The majority of cardiovascular events occur when both biomarkers are elevated, meaning that a combination of ST2 and NT-proBNP might synergistically increase their prediction abilities.

The potential for sST2 as a prognostic biomarker has been suggested after the results of the *PROTECT* study. Higher baseline sST2 values during ADHF and chronic HF were associated with future cardiovascular events (HF hospitalisation and cardiovascular death).[10-11] The *PREDICT* Trial also showed that sST2 is the strongest predictor of death at four years in patients with acute dyspnoea, bypassing even the NPs. High baseline levels of sST2 were also associated with death or new congestive HF in acute myocardial infarction patients in the *TIMI-14* and *ENTIRE-TIMI-23* trials, meaning that sST2 may one day also be used to predict heart failure after myocardial infarction.[3]

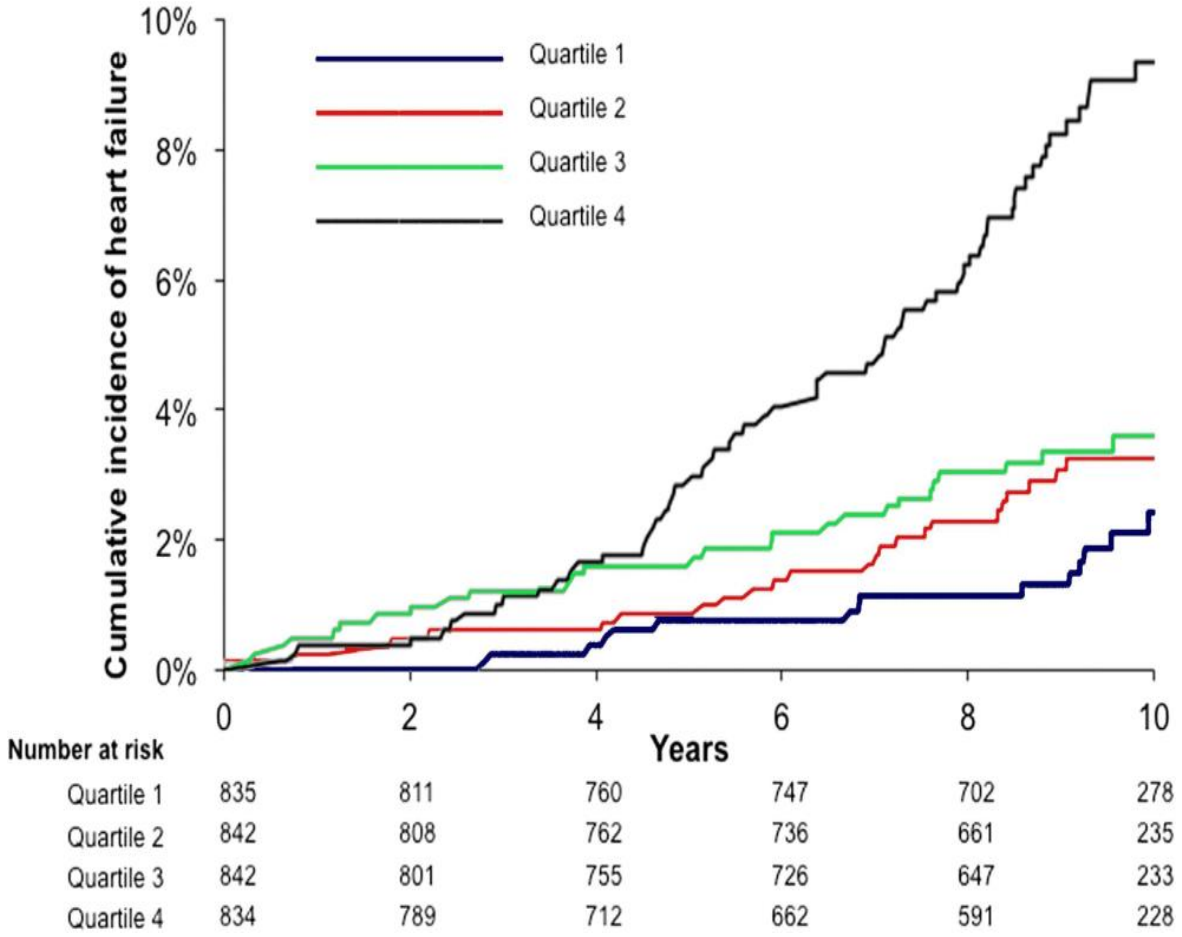
The low intra-individual biological variation of sST2 compared to other cardiac biomarkers offers a significant advantage in its utility for serial testing, as acute changes in blood levels are more diagnostic.[10] In a recently published post hoc analysis of the *PROTECT* study, Januzzi et al hypothesized the potential of sST2 in guiding beta blocker therapy, similar to guiding anti-HF treatment according to NP levels. sST2 decreases when maximizing beta blockade, indicating that the latter in some way interferes with cardiac remodelling by inhibiting sST2, thus improving prognosis. This tends to be most effective in patients with high levels of sST2 at baseline, possibly being of some use in a select cohort of heart failure patients, especially as it mimics decompensated states.[11]

Galectin-3

Galectin-3 is another promising biomarker, associated with the cumulative development of fibrosis and apoptosis in cardiac remodelling. Studies in rats have showed that galectin-3 is already high in those with compensated hypertrophy of failure prone hearts. The gene for galectin-3 was the strongest up-regulated gene in ADHF. In this same study, a pericardial infusion of galectin-3 in previously normal rats also induced ADHF, revealing it actually plays a role in the pathophysiology of heart failure, possibly by direct cardio-toxicity or by indirect acute kidney injury.[12-14]

While its expression is maximal at peak fibrosis and virtually absent after recovery,[14] there seems to be no promise as a diagnostic marker of HF, since its expression occurs way before ADHF is clinically evident.[3] Analysis of the Framingham heart study did however provide conclusive evidence that galectin-3 levels in well and asymptomatic patients in the community, accurately predicted an increased risk for future heart failure and mortality (Figure 3). Levels where positively associated with left ventricular mass, with no difference in baseline values present when comparing future ADHF of normal versus reduced LVEF.[15] Results by De Boer et al (2011) who looked at galectin-3 levels in two equal and comparable groups of low or preserved LVEF HF revealed that galectin-3 appeared to be a better prognostic marker in the latter group, with one hypothesizing that it plays a more prominent role in the pathophysiology of preserved LVEF.[16]

***Figure 3**: The cumulative incidence of heart failure (HF) increasing with higher galectin-3 quartiles*[15]



Galectin-3 also has the potential as an important prognostic biomarker during admission with ADHF, predicting death or re-hospitalisation with ADHF after discharge. Plasma levels in patients presenting with acute dyspnoea have a higher 60 day mortality or recurrent admissions with HF, marginally better than NT-proBNP.[17] Both biomarkers complement each other and improve mortality prediction. Higher galectin-3 levels showed a higher four-year mortality rate in patients presenting with ADHF.[14] According to the PROVE-IT-TIMI 22 study, high Galectin-3 levels in patients admitted with acute coronary syndrome predicted the onset heart failure after the index admission.[6] As per the *DEAL-HF* study, its prognostic ability also applies to compensated HF irrespective of New York Heart Association (NYHA) functional class.[18]

Different to other biomarkers, in-vivo studies in animals have shown galectin-3 to be directly involved in the pathophysiology of HF, precipitating ADHF when compensatory measures fail. It is also associated with inflammatory cytokines (CRP), Interleukin-6 (IL-6) and Vascular Endothelial Growth Factor (VEGF) in the overall remodelling pathway, further revealing its role in structural changes in the heart. Treating the cause rather than the effect of ADHF might someday hold promise in galectin-3 targeted therapies and galectin-3 can someday be used to risk stratifying remodelling (high-risk) versus non-remodelling (low-risk) ADHF. Similarly to the effect of sST2 with beta blockade, future research might develop specific galectin-3 targeted therapies which could hypothetically directly reverse remodelling and treat the cause rather than the effect.[3]

Growth Differentiation Factor 15 (GDF-15)

GDF-15 is a member of the transforming growth factor beta (TGF-β) superfamily, expressed in stressful situations including inflammation and remodelling, in an attempt to inhibit myocyte hypertrophy, apoptosis and adverse remodelling [2]. Levels are high in ADFH when compared to a control group, correlated with severity and reduced LVEF, just like sST2. It is particularly diagnostic, as seen in the study by Wang et al also suggesting it can help differentiate reduced from preserved LVEF ADHF.[8] GDF-15 is however non-specific, with high levels also present in severe liver disease, pregnancy and certain cancers.[3]

GDF-15 can be used to help predict mortality and heart failure. Levels also correlate with NT-proBNP in

post-myocardial infarction, possibly implying that it might be useful to risk stratify those patients at risk of adverse cardiac events in the early or late stages after discharge.[19] There are however no studies to date about GDF-15 serial testing and GDF-15 targeted drug therapies.

Troponin T

Troponin T is a regulatory protein attached to tropomyosin in cardiac myocytes, released in response to myocardial infarction secondary to coronary (atherosclerosis) or non-coronary causes (cytotoxicity, apoptosis and inflammation).[3]

It is a sensitive marker of myocardial injury with levels correlated to the degree of myocardial necrosis, with high sensitivities now available detecting even lower levels. It is however not a specific diagnostic marker for ADHF with high levels also possible in acute kidney injury, sepsis, subarachnoid haemorrhage, amongst others.[3]

Since elevations in Troponin levels are often associated with unclear therapeutic ramifications in the non-acute setting, they are at present not useful for risk stratification or prediction. However, Miller et al demonstrated a higher mortality risk and increased rates of cardiac transplantation in patients with persistently high levels in asymptomatic stable NYHA Class III and IV HF patients.[20]

Troponin T is an independent prognostic predictor of mortality, mimicking NT-proBNP and sST2, with addition of both biomarkers improving prognostic capabilities significantly.[3] There are no studies regarding Troponin T targeted therapies or the management implications of serial testing.

Conclusion

More studies are needed to fully validate established biomarkers for clinical practice. Better biomarkers are currently needed for diagnosis, screening and monitoring. With the integration of genomic, proteomic, phenotypic and transcriptional profiling, a new era in cardiology of "personalized medicine' might at some point become a reality.[9]

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Tinea capitis due to Trichophyton tonsurans in a Maltese patient

Godfrey Baldacchino, Stephen Decelis, Dino Vella Briffa, Michael J. Boffa

Abstract

We report a case of tinea capitis caused by *Trichophyton tonsurans* in a 16-year-old male. This appears to be the first documented case of tinea capitis caused by this dermatophyte in a native Maltese patient.

Key words

Trichophyton tonsurans, tinea capitis, Malta.

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Introduction

T. tonsurans is the commonest cause of tinea capitis in the Americas, Europe, Asia, and Australia and is responsible for more than 60% of cases.[1-4] It has replaced *Microsporum canis* and *Microsporum audouinii* as the main pathogen causing tinea capitis. In contrast, in Malta the commonest causes of tinea capitis are *M. canis* and *T. Mentagrophytes*; *T. tonsurans* has only rarely been reported.[5] The causative organisms of tinea capitis in Malta are not following the global trend despite extensive travel and population movements. The latest study in Malta dates back to 2003, and only two cases of *T. tonsurans* were reported at that time, both in non-Maltese patients.[6] To our knowledge, this case is the first report of such infection in a native Maltese patient.

Case report

A healthy 16-year-old male was referred to the Dermatology Department at Sir Paul Boffa Hospital in February 2014 because of a 6 x 5 cm elliptical area of incomplete hair loss over his right temporo-occipital scalp. The duration of alopecia was unclear as the patient had only noticed the bald area after a recent very short haircut. He had been treated by his general practitioner with a steroid lotion for two weeks for a tentative diagnosis of alopecia areata, with no improvement. He lived with his parents and sister who had no evidence of similar lesions. He had no contact with animals and had not travelled abroad in the preceding two years.

Examination revealed an area of incomplete scalp hair loss with a fine grey scale. The remaining hairs were broken with loss of lustre. The patient also had a few erythematous annular scaly lesions on the chest and the medial aspects of both upper arms. All the lesions described were asymptomatic, with no significant pruritus. Tinea capitis was suspected and scalp scrapings and plucked hairs were collected and sent for mycological investigation. Wood's light examination showed no fluorescence. Terbinafine 250 mg daily was prescribed for four weeks.

Direct KOH microscopy showed fungal elements especially within hair shafts and cultures yielded *T.*

tonsurans.

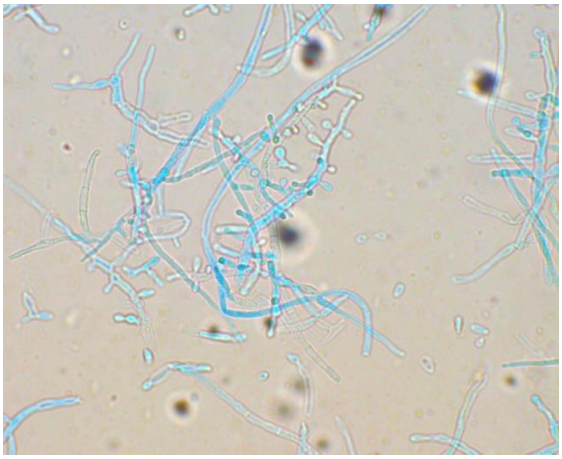
On re-examining the patient after 6 weeks, normal hair growth was evident on the entire scalp and all other lesions on the arms and chest had disappeared. Repeat mycological examination of plucked hairs from the previously affected areas was negative.

Mycology

Direct microscopy of a 20% KOH and calcafluor white preparation of plucked hairs taken at presentation showed endothrix hair invasion with multiple arthroconidia visible within the hair shaft replacing the cortex. This pattern results from growth of dermatophyte hyphae down the hair follicle and invasion of the hair cortex. Cultures on Sabouraud Dextrose Agar with chloramphenicol and cycloheximide yielded a pale buff to yellow with suede-like to powdery surface and yellow to red-brown reverse appearance. The colonies were raised with some folds and sulci [Fig. 1]. Microscopic examination of samples from cultures showed broad irregular septate hyphae with a lot of branching. Microconidia of various sizes and shapes were seen branching at right angles to the hyphae. The microconidia varied from long clavate forms to broad pyriform shapes and stained poorly with lactophenol cotton blue. This is diagnostic of *T. Tonsurans* [Fig 2].

Figure 1*: Colonial morphology of a subculture of T. tonsurans.*
a) Yellowish –white suede-like colonies with some surface folds.
b) red-brown reverse appearance

Figure 2: *Microscopy of T. Tonsurans (Lactophenol blue). Mass of branching septate hyphae with variable shape microconidia growing laterally.*



Discussion

T. tonsurans is an anthropophilic dermatophyte causing several clinical variants of tinea capitis. These include patchy alopecia, mild scaling of the scalp, grey-type tinea (fine grey scaling), black dot tinea (broken hairs within the hair follicles), pustulosis, crusting, and kerion (raised, often discharging, boggy lesions of the scalp). Our case had grey-type tinea. All these patterns have the potential to cause permanent alopecia if neglected.[7] Many of these clinical variants, other than kerion, produce very mild symptoms, possibly due to development of host tolerance to *T. Tonsurans.*[8] This can lead to underdiagnosis with subsequently delayed or inappropriate treatment (as happened with our patient when prescribed a steroid lotion). This highlights the importance of awareness of this dermatophyte as a cause of alopecia.

T. tonsurans is transmitted from one infected human to the other by direct contact or fomites. Outbreaks in Germany, Turkey and Japan have linked transmission of *T. tonsurans* to physical contact in wrestlers and judokas, thus termed tinea capitis gladiatorum. [9-11] Other modes of transmission are the sharing of hair implements such as combs and hair brushes, and household contact.[11] Other factors promoting *T. tonsurans* tinea capitis include tight braiding of hair and application of oily hair products which enhance contact of spores with the scalp. This explains a higher incidence in Afro-Caribbean populations.[3]

T. tonsurans is commoner in crowded environments. Asymptomatic carriage of *T. tonsurans* is a potential threat, and studies in which unaffected household contacts were screened with the hairbrush technique yielded between 12 - 40% positive cultures.[2,3,14]

We questioned our patient extensively to determine the origin of his infection. The only possible source we

identified was his regular attendance at a gym where he did bench presses. We postulate that contact of his unprotected scalp with the bench surface infected by a previous user may have been the mode of acquisition, with lesions on the arms and chest caused by autoinoculation. The absence of lesions on his back may be explained by protection provided by wearing a t-shirt. However we have not seen any other cases of infection with *T. Tonsurans* from this gym.

The treatment of choice for *T. tonsurans* tinea capitis is terbinafine 3-6mg/kg/day for 2-4 weeks.[13] Our patient had a complete response to this regime with clinical and mycological cure. It has also been suggested that contacts should be treated with an antifungal shampoo to eradicate asymptomatic carriage.[14]

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Sir Charles Ballance: A pioneer surgeon in Malta

Alex Manché

Abstract

Charles Ballance was arguably the most eminent surgeon stationed in Malta during the Great War. On the 16th February 1918 he removed a bullet from the heart of trooper Robert Martin who was shot in the chest in Salonika three months previously. Sadly the patient died of sepsis one month later, a fact that obscured the importance of this landmark operation, the third of its kind worldwide. This paper sets the background to this achievement and celebrates the impact that this surgical pioneer left on our shores.

Key words

Ballance, heart surgery, 1918

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The scene in Malta, WWI

In its role as Nurse of the Mediterranean during the Great War, Malta received 57,991 sick and wounded from the Mediterranean Expeditionary Force and 78,130 from the Salonika Expeditionary Force.[1] One hundred and sixty five medical officers, 82 women doctors, and over 400 nurses treated these patients in 27 hospitals converted for the purpose.[2] Among the eminent senior consultants stationed here in 1915 were Colonel Charles Ballance, surgeon to St Thomas' Hospital, who performed the second successful splenectomy in 1895,[3] Colonel Charters Symonds, surgeon to Guy's Hospital, amongst the first in England to remove the appendix for acute inflammation in 1883,[4-5] Colonel Archibald Edward Garrod, physician to St Bartholomew's Hospital, author of Inborn Errors of Metabolism,[6] and Colonel Purves Stewart, physician to Westminster Hospital and a distinguished nerve specialist.[7] The motto of the presiding British Army Medical Administrator Sir Alfred Keogh, K.C.B. was "We wish to bring to the humblest soldier the best available surgery, and that which is not the best is not good enough". All serious cases were brought to the attention of these learned men, who worked as a team, performed regular ward rounds and decided on all major surgical interventions.[8]

Charles Ballance

Charles Ballance was born in 1856. He studied medicine at St Thomas's Hospital where he served as house surgeon and anatomy demonstrator. He won gold medals in the final examination in 1881 and in the Master of Surgery degree the following year. In 1888 he was appointed aural surgeon and became a pioneer in mastoid surgery, developing the specialty along scientific lines, introducing the Hunterian experimental method. Among his research areas of interest were arterial wall changes after ligation,[9-10] the repair of peripheral nerves,[11-12] and the parasitic theory of cancer.[13-14] He progressed at St Thomas' to assistant surgeon in 1891, surgeon in 1900 and consulting surgeon in 1919. Charles Ballance was amongst the first to perform splenectomy for trauma, publishing his early experience.[15] Fixed dullness elicited in the left flank is known as Ballance's sign.[16] In 1908 he was also elected consulting surgeon to the National Hospital for the Paralysed and Epileptic in Queen Square. In 1915, on the outbreak of war, he was posted to Malta, where, together with his surgical colleague Charters Symonds, he organised and supervised numerous emergency hospitals, for which he was honored MD from the University of Malta and knighted, Order of St John of Jerusalem.[17]

The operation

On 16th February 1918 Charles Ballance cut into the right ventricle and retrieved a bullet with an artery forceps from the inferior interventricular septum adjacent to the apex of the heart. Significant haemorrhage was stemmed with internal sutures and a blood transfusion was also administered at the time, and stopped when the donor became hypotensive.[18] Dr Sarah Marguerite White assisted Ballance and Lt Col Shirley administered the anaesthetic. The 21-year old patient, Robert Hugh Martin, a Derbyshire Yeomanry trooper, was shot in the chest in Salonika on 14th November 1917. He underwent exploratory surgery two days later at the 40th Casualty Clearing Station Hospital and was then transferred to Malta, where he arrived on 13th January 1918 at St Elmo Hospital, under the care of Ballance. X-rays confirmed the presence of a bullet lodged in the heart and the necessary preparations were made for its surgical removal almost 5 weeks later. Although the operation was a technical success Martin died of sepsis on the 14th March. Ballance observed "it is a common experience that bullets frequently lodge in the tissue and induce neither local nor general infection until attempts at removal are made". Sepsis was encountered at surgery, which was performed 3 months after the injury.[19]

The importance of this landmark operation is not widely appreciated. Indeed Ballance's great grandson Peter, a recently retired consultant anaesthetist, when interviewed, remarked that "he was known more as a neurosurgeon and ear, nose and throat specialist, rather than for his cardiac surgery, but he was renowned as quite experimental and innovative".[20]

A surgical landmark

In 1883 Theodore Billroth issued a warning when he declared "any surgeon who operates on the heart should lose the respect of his colleagues".[21] In 1896, Stephen Paget expressed similar pessimism in his textbook, The Surgery of the Chest, when he commented "surgery of the heart has probably reached the limits set by nature".[22] That same year Cappelen sutured a cardiac wound but the patient died from a damaged left anterior descending artery.[23] A second failed attempt by Farina[24] was followed success in the hands of Ludwig Rehn on the 9th September 1896.[25] By 1907 Rehn reported 124 cases of cardiac suture with a 40% survival,[26] and in 1909 Peck[27] and Vaughan[28] published further series with comparable results.

The progression from simple suture of penetrating injuries to the removal of foreign bodies embedded within the heart took surgery to a new dimension. George Grey Turner was the first to attempt removal of a bullet from the left ventricle in 1917. When the surgeon lifted the heart, it went into asystole and was resuscitated. The bullet was left in-situ and the patient went on to live a normal life.[29] That same year Henri Hartmann successfully extracted a bullet from the right ventricle of a French soldier, almost three years after the injury.[30] The following year Sir Berkeley, later Lord Moynihan of Leeds, who incidentally was born in Malta on 2nd October 1865, had similar success when he removed a foreign body embedded in the wall of the left ventricle adjacent to the atrioventricular groove, fourteen months after the injury.[31] Ballance's case also took place in 1918 but is not given historical prominence because the patient succumbed one month post-operatively. Perhaps the shorter interval between injury and operation may have contributed to the fatal sepsis.

Recognition

The following year Ballance delivered the Bradshaw lecture entitled "The surgery of the heart" in which he discussed other authors' series including those of Borchardt,[32] Rehn, Vaughan, Peck and Pool,[33] and estimated that over 400 operations on the heart had been performed since Farina's case. On two occasions Ballance referred to his own case and he celebrated the survival of 44 patients of 58 War cases of which he possessed the case records. He discussed the technical aspects of removing a foreign body from a heart chamber and also described his experience when he successfully dealt with a ruptured innominate aneurysm. In Ballance's words "the surgeon having this job in hand will take it all in a day's work".[34] Clearly here was a man

of stature, a surgeon at the cutting edge of an exciting new field. In being nominated as a Bradshaw lecturer Ballance was included in a long line of illustrious doctors including such names as Sir James Paget, Sir Thomas Spencer Wells, Sir William Watson Cheyne, Sir Berkeley Moynihan and Sir Henry Souttar. Sir Russel Brock who delivered the lecture in 1957 entitled "The Present Position of Cardiac Surgery" praised Ballance's message of 1919 for "the change from fear of the heart to the realization that it could be operated on in the same way as other organs". Brock went on to say "in reading Ballance's lecture one is impressed that it contains little different from what would have been written in 1947", a strong commendation if ever there was one.[35]

Ballance was anatomy examiner for the Royal College of Surgeons 1887-1891, and a member of the Court of Examiners 1900-1919. He was President of the Medical Society of London in 1906 and the first President of the Society of British Neurological Surgeons in 1927. He gave other prestigious lectures including the Erasmus Wilson lecture in 1888 "The pathology of haemorrhage after ligation in continuity", the Vicary lecture in 1921 "A glimpse of the surgery of the brain",[36] the Macewen memorial lecture in 1930 "The dawn and epic of Neurology and Surgery",[37] and finally the Lister memorial lecture in 1933 "On nerve surgery".[38]

Conclusion

The Great War brought about momentous advances in surgery, during which time Malta hosted many eminent doctors, foremost among whom was Sir Charles Ballance. His landmark operation of the removal of a bullet from the heart was probably the third such attempt worldwide and has, thus far, failed to attract its well-deserved credit. Ballance's many other achievements in the areas of aural surgery, neurosurgery and scientific research put his cardiac surgical feat into perspective. This was not a singular adventure but yet another mark of a great man that Malta was fortunate to receive.

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Corinthia Group Prize in Paediatrics, 2014

The Corinthia Group Prize in Paediatrics for 2014 was awarded to Dr Lauren Abela, who obtained the highest aggregate mark over the combined examinations in Paediatrics in the fourth and final year of the undergraduate course. Whilst offering our congratulations to Dr Abela, we would also like to congratulate all those who performed admirably during the undergraduate course in Paediatrics, some of whom were only marginally 'pipped to the post' by Dr Abela. In the accompanying photograph, Dr Abela is seen receiving a cheque for €233 from Professor Simon Attard Montalto, Head of Paediatrics, in the Medical School Museum. Finally, the Academic Department of Paediatrics and Medical School remain indebted and are extremely grateful to the Corinthia Group for their ongoing support.

Professor Simon Attard Montalto