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Prevalence of Sensitization to *Anisakis simplex* Among Professionally Exposed Populations in Sicily

Walter Mazzucco MD^a, Guido Lacca MD^c, Rosanna Cusimano MD^a, Ambra Provenzano MD^c, Antonella Costa^d, Anna Maria Di Noto^d, Maria Fatima Massenti MD^{a b}, Maria Stefania Leto-Barone MD^e, Gabriele Di Lorenzo MD^e & Francesco Vitale MD^{a b}

^a Dipartimento Scienze Promozione della Salute-Sezione Igiene, University of Palermo, Palermo, Italy

^b Laboratorio Centralizzato Chimico, Clinico AOUP "P. Giaccone," Palermo, Italy

^c Dipartimento Scienze Promozione della Salute-Sezione Medicina del Lavoro, University of Palermo, Palermo, Italy

^d Istituto Zooprofilattico Sperimentale della Sicilia "A. Mirri," Area Microbiologia degli Alimenti, Centro di Referenza Nazionale Anisakiasi, Palermo, Italy

^e Dipartimento di medicina Clinica e delle Patologie Emergenti, University of Palermo, Palermo, Italy

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Prevalence of Sensitization to *Anisakis simplex* Among Professionally Exposed Populations in Sicily

Walter Mazzucco, MD; Guido Lacca, MD; Rosanna Cusimano, MD;
Ambra Provenzani, MD; Antonella Costa; Anna Maria Di Noto; Maria Fatima
Massenti, MD; Maria Stefania Leto-Barone, MD; Gabriele Di Lorenzo, MD;
Francesco Vitale, MD

ABSTRACT. *Anisakis simplex* (AS) is a cause of allergic sensitization and potential occupational risk is suggested in fishermen and workers assigned to fish processing and sale. A cross-sectional study was conducted in order to assess possible health effects of occupational exposure to AS in workers recruited from western Sicily fisheries sector. Social, demographic, and occupation-related data were collected. Serum total immunoglobulin E (IgE) and specific IgE levels to AS (threshold >0.35 kU/L) were determined by an fluoroimmunoassay technique. Ninety-four subjects with potential occupational exposure (fishmongers, fishermen, fish industry employees) were recruited. Specific AS IgEs were detected in 20.2% of the study population. AS IgE seroprevalence was elevated 6.7-fold ($p = .03$) among fishermen/sailors compared with fish industry workers. The study suggested the importance to adopt specific prevention strategies against exposure to AS in the occupational setting.

KEYWORDS: *Anisakis simplex*, occupational risk, public health

A *nisakis simplex* (AS) is a nematode that parasitizes fish and cephalopods. Humans become accidental hosts by eating raw or undercooked or in-brine fish or seafood, containing live parasite larvae, leading to a gastrointestinal disease known as anisakiasis.¹

AS has been recognized as a cause of allergic conditions²⁻⁴ and some cases classified as “fish allergy” could find its origin in this parasite.⁵ Particularly, it is responsible for immunoglobulin E (IgE)-mediated allergic reactions, such as anaphylaxis, in some sensitized patients and acute and recurrent urticaria.⁶

The increasing warning about *Anisakis* infestation effects in human health has gradually ramped up in the last 2 decades, either for the introduction of sensitive diagnostic techniques and efficient surveillance and reporting systems, or, more recently, in reason of the diffused global consumption of raw, in-brine, or undercooked fish, determining a growing interest for public health.⁷⁻⁹

The first reported by literature case in Italy dates back to 1997 in a patient with epigastric pain associated with vomiting and diarrhea.¹⁰ Since then, the reporting systems have documented a steady increase of reports on *Anisakis*

Walter Mazzucco, Rosanna Cusimano, Maria Fatima Massenti, and Francesco Vitale are with the Dipartimento Scienze Promozione della Salute–Sezione Igiene, University of Palermo, Palermo, Italy. Maria Fatima Massenti and Francesco Vitale are also with the Laboratorio Centralizzato Chimico, Clinico AOUP “P. Giaccone,” Palermo, Italy. Guido Lacca and Ambra Provenzani are with the Dipartimento Scienze Promozione della Salute–Sezione Medicina del Lavoro, University of Palermo, Palermo, Italy. Antonella Costa and Anna Maria Di Noto are with the Istituto Zooprofilattivo Sperimentale della Sicilia “A. Mirri,” Area Microbiologia degli Alimenti, Centro di Referenza Nazionale Anisakiasi, Palermo, Italy. Maria Stefania Leto-Barone and Gabriele Di Lorenzo are with the Dipartimento di medicina Clinica e delle Patologie Emergenti, University of Palermo, Palermo, Italy.

larvae presence in fish products (European System RASFF, 2006).¹¹

The interest on the effects of exposure to this parasite increased in occupational health context^{12–15}: evidence of the correlation between exposure to the parasite and professional activity was recently hypothesized, demonstrating that surface antigens, which would be expressed also by the killed or inactivated larvae by normal heat cooking or conservative treatment, can cause an IgE-related sensitization in exposed subjects, either through contact, inhalation, and/or ingestion of allergens in infested fish.^{16–19} As consequence, a potential occupational risk was suggested in fishermen and workers assigned to fish processing and sale.²⁰

Sicily, the largest Mediterranean island, is characterized by a strong vocation to fishing and fish industrial conservation and distribution. Therefore, the aim of the present study was to evaluate the prevalence of AS sensitization in occupational setting and the possible association between parasite contact in occupational setting and human health effects in order to elucidate potential exposure pathways and suggest possible prevention strategies.

METHODS

From January to December 2009, a cross-sectional study was carried out on subjects working in western Sicily fisheries sector (fishmongers/fish cleansing employees, fishermen, fish industry employees). A total of 94 individuals, 78 males (83.0%) and 16 females (17.0%), mean age 42.1 years, SD ± 12 years, and median age 41.9 years, gave their consent to the study and were recruited. Of them, 36 subjects (38.3%) operated in Sciacca's navy, 19 subjects (20.2%) worked in companies involved in fish conservation, packaging, and distribution located in Mazara del Vallo, 18 (19.1%) were employed in a tuna storage factory located in Palermo area, and 21 (22.4%) were fishmongers, working in Palermo City's small fish markets.

All the recruited subjects were submitted to a structured questionnaire, aimed to collect social and demographic data, occupation-related habits, including use of individual protection devices (IPDs), type and frequency (times/last year) of contact with raw or marinade fish (diet intake, skin contact), and allergy history as anamnestic, referred as previous allergic reaction in terms of type and period of documented allergy and frequency of symptoms (asthma, rhinitis, conjunctivitis, urticaria/angioedema, abdominal pain, diarrhea, vomiting).

Furthermore, a blood sample was collected from each participant in order to evaluate both levels of total serum IgE and specific IgE for *Anisakis simplex*.

Briefly, serum total IgE and specific IgE levels to *Anisakis simplex* were determined by using the Unicap 100 with the fluoroimmunoassay technique (Phadia, Uppsala, Sweden), according to the manufacturer's instructions. Results for both serum total IgE and specific IgE measurements were expressed in kilounits per liter (KU/L) employing the World

Health Organization standard in which 1 kU for total IgE and 1 k_AU for specific IgE was equal to 2.4 ng/mL, respectively. Serum total IgE levels were determined with a detection limit of 2 kU/L and an upper limit of 5000 kU/L. Serum specific IgE levels were determined with a detection limit of 0.10 k_AU/L and an upper limit of 100 k_AU/L.²¹ For total IgE, the diagnostic cutoff was set at >100 kU/L, whereas for specific IgE, at >0.35 kU/L, as recommended by manufacturer.

Statistical methods

Mean, median, and range were computed as descriptive statistics for continuous variables.

Distributions of continuous variables in different groups were analyzed by nonparametric methods (Kruskal-Wallis test). For categorical variables, frequency distributions were compared by using chi-square test and Fisher's exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as appropriate.

Moreover, a correlation analysis (Pearson's method) between questionnaire's data and presence of specific IgEs was carried out and a linear regression model was fitted to estimate the increase in AS-specific IgE.

All statistical analyses were performed by using the R free open source software, version 2.9.0.²² Statistical significance was set at $p < .05$.

RESULTS

In Table 1 are summarized sociodemographic characteristics, working habits, and self-reported allergic symptoms of the 94 subjects (working length between 1 and 60 years, mean 15.1, SD ± 12.76 , median 10.5) with potential occupational exposure, grouped by job type (part A) and the seroprevalence anti-AS measured in the whole study population by testing specific IgE levels (part B). Overall, 21 (22.4%) fishmongers/fish were cleansing employees, 38 subjects (40.4%) fishermen/sailors, and 35 (37.2%) fish industry employees.

The 3 job groups did not significantly differ neither for years of employment in the current position ($p = .7$) or for educational levels ($p = .8$), but significantly differed by gender ($p = .0001$)—being female represented only in fish industries group, IPD use during the job procedures ($p = .0001$), and contact with raw, in-brine, or undercooked fish ($p = .004$). More in detail, IPD use was more frequently reported among fish industry employees (regular: 54.3%; irregular: 45.7%), inconsistently practiced among fishermen/sailors (irregular: 42.1%; never: 42.1%), and almost absent in fishmongers/fish cleansing employees (never: 95.2%).

Moreover, 88 subjects (93.6%) declared to have had contact with raw, in-brine, and undercooked fish during the past year, either by skin contact or by diet intake. However, frequency of skin contact was significantly higher ($p = .01$) among fishmongers/fish cleansing employees (85.7%) compared with fishermen/sailors (71.1%) and with fish industry employees (51.4%), whereas dietary intake of raw or undercooked fish did not differ among job groups ($p = .24$).

Table 1.—(A) Sociodemographic Characteristics, Working Habits, and Self-Reported Allergic Symptoms of 94 Subjects With Potential Occupational Exposure to AS by Type of Employment and (B) Seroprevalence by Detection of Specific Anti-AS IgEs

Characteristics, working habits and self-reported allergic symptoms	(A) Type of employment								(B) Seroprevalence				
	Fishmongers <i>n</i> = 21 (22.4%)		Fish industry employees <i>n</i> = 35 (37.2)		Fishermen/ Sailors <i>n</i> = 38 (40.4)		Total <i>n</i> = 94 (100.0)						
									AS IgE				
									>0.35 kU/L				
									No	Yes	No	Yes	
Gender													
Male	21	100	19	54.3	38	100	78	83.0	.0001	68	87.2	10	12.8
Female	21	100.0	19	54.3	38	100.0	78	83.0	.0001	68	87.2	10	12.8
	0	0.0	16	45.7	0	0.0	16	17.0		15	93.8	1	6.2
Years of employment under current position													
<5	3	14.3	2	5.7	11	28.95	16	17.0	.7	13	81.2	3	18.8
5–9	6	28.55	9	25.7	3	7.9	18	19.1		18	100.0	0	0.0
10–19	3	14.3	17	48.6	11	28.95	31	33.0		28	90.3	3	9.7
20–29	3	14.3	5	14.3	6	15.8	14	14.9		12	85.7	2	14.3
≥30	6	28.55	2	5.7	7	18.4	15	16.0		12	80.0	3	20.0
Educational level													
High school	1	4.8	5	14.3	3	7.9	9	9.6	.8	8	88.9	1	11.1
Middle school	14	66.7	22	62.9	26	68.4	62	66.0		55	88.7	7	11.3
Elementary school	5	23.8	8	22.9	8	21.1	21	22.3		19	23.8	2	22.9
None	1	4.8	0	0.0	1	2.6	2	2.1		1	90.5	1	9.5
IPD use on working time													
Regular	0	0.0	19	54.3	6	15.8	25	26.6	.0001	24	96.0	1	4.0
Irregular	1	4.8	16	45.7	16	42.1	33	35.1		28	84.8	5	15.2
Never	20	95.2	0	0.0	16	42.1	36	38.3		31	86.1	5	13.9
(Continued on next page)													

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Table 1.—(A) Sociodemographic Characteristics, Working Habits, and Self-Reported Allergic Symptoms of 94 Subjects With Potential Occupational Exposure to AS by Type of Employment and (B) Seroprevalence by Detection of Specific Anti-AS IgEs (Continued)

Characteristics, working habits and self-reported allergic symptoms	(A) Type of employment										(B) Seroprevalence					
	Fishmongers <i>n</i> = 21 (22.4%)			Fish industry employees <i>n</i> = 35 (37.2)			Fishermen/ Sailors <i>n</i> = 38 (40.4)			Total <i>n</i> = 94 (100.0)						
	<i>n</i>	%		<i>n</i>	%		<i>n</i>	%		<i>n</i>	%		No		Yes	
	<i>n</i>	%		<i>n</i>	%		<i>n</i>	%		<i>n</i>	%		<i>n</i>	%	<i>n</i>	%
	<i>n</i>	%		<i>n</i>	%		<i>n</i>	%		<i>n</i>	%		<i>n</i>	%	<i>n</i>	%
Contact with raw, in-brine, undercooked fish/past year	Yes	21	100.0	29	82.8	38	100.0	88	93.6	.004	78	88.6	10	11.4		
Type of contact	Not	0	0.0	6	7.2	0	0.0	6	6.4		5	83.3	1	16.7		
	None	0	0.0	10	28.6	2	5.3	12	12.8	.01	11	91.7	1	8.3		.7
	<10	1	4.8	4	11.4	2	5.3	7	7.4		7	100.0	0	0.0		
	10–100	2	9.5	3	8.6	7	18.4	12	12.8		10	83.3	2	16.7		
Skin times/past year	≥100	18	85.7	18	51.4	27	71.1	63	67.0		55	87.7	8	12.7		
	None	4	19.0	9	25.7	5	13.2	18	19.1	.24	12	66.7	6	33.3		.001
	<10	10	47.6	15	42.9	15	39.5	40	42.6		35	87.5	5	12.5		
	10–100	7	33.3	11	31.4	18	47.4	36	38.3		36	100.0	0	0.0		
Allergic symptoms (self-reported)	Yes	4	19.0	17	48.6	13	34.2	34	36.1	.08	28	82.3	6	17.7		.15
	Not	17	81.0	18	51.4	25	65.8	60	63.9		55	91.7	5	8.3		

Table 2.—Distribution of Total IgEs and AS-Specific IgEs by Type of Work Categories

		Type of employment								<i>p</i>
		Fishmongers <i>n</i> = 21 (22.4%)		Fish industry employees <i>n</i> = 35 (37.2)		Fishermen/Sailors <i>n</i> = 38 (40.4)		Total <i>n</i> = 94 (100.0)		
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Serology										
Total IgEs > 100	Yes	2	14.3	4	11.4	11	28.9	18	19.1	.13
	No	3	14.3	4	11.4	11	28.9	18	19.1	.13
AS-specific IgEs >0.35 kU/L*	Yes	18	85.7	31	88.6	27	71.1	76	80.9	
	No	3	14.3	1	2.9	7	18.4	11	11.7	.09
		18	85.7	34	97.1	31	81.6	83	88.3	

*Odds ratio (1 Ref. = fish industry employees) and 95% CI:

Fishmongers/fish cleansing = 5.07 (0.54–153.06).

Fishermen/sailors = **6.74 (1.1–178.9)**.

In part B of Table 1 are also represented seroprevalence data. Overall, an inverse association between dietary fish intake and the prevalence of AS-specific IgE was observed ($p = .001$). Furthermore, a total of 36.1% of the subjects self-reported symptoms potentially suggestive of allergic history ($p = .08$) and 17.7% of them had elevated levels

of AS-specific IgE, although not statistically significant ($p = .15$), as compared with 8.3% of those who did not referred allergic symptoms. None of the other variables were significantly associated with AS-specific IgE levels.

As shown in Table 2, diagnostic tests showed an overall prevalence of 19.8% (18/94) individuals with serum detection

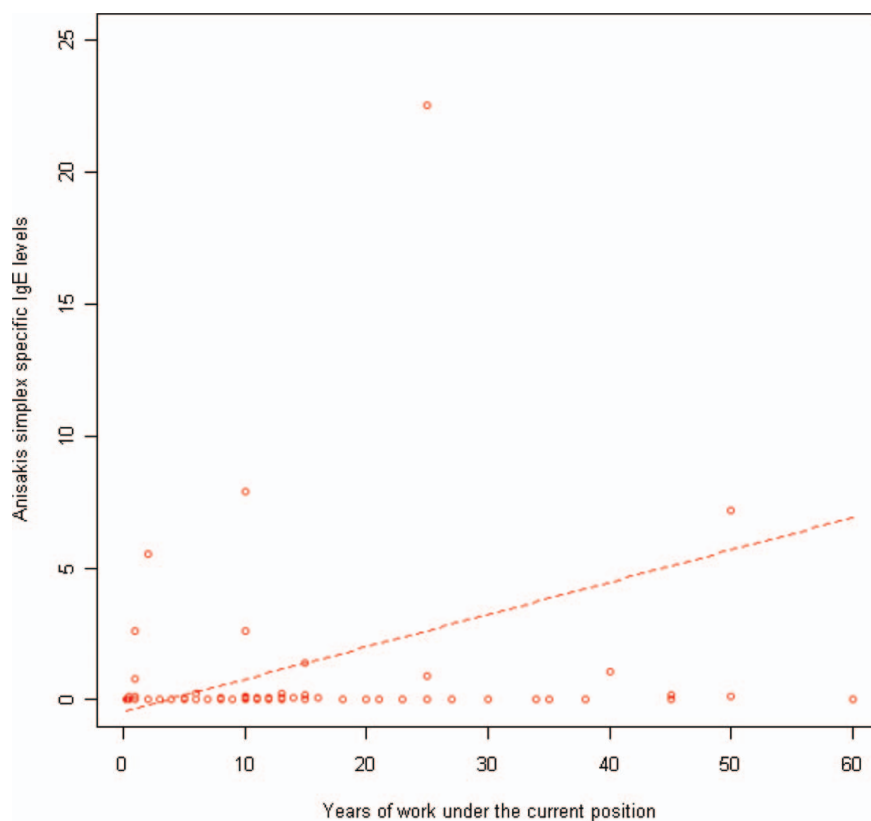


Fig. 1. Linear correlation matrix of working length (years of work under the current position) and AS-specific IgE levels (color figure provided online).

of total IgE above normal range, and of 11.7% (11/94) for specific AS IgE. Furthermore, no statistical differences were revealed among job groups neither for total IgE ($p = .13$) or AS-specific IgE ($p = .09$).

By using “fish industry employees” as the reference category, fishermen/sailors showed a 6-fold significant increase in risk of AS seroconversion (OR = 6.74; 95% CI = 1.1–178.9; $p = .03$), whereas fishmongers/fish cleansing employees experienced a nonsignificant 5-fold increase in the odds of seroconversion.

Figure 1 represents the correlation between years of employment under the current position and AS-specific IgE levels. A slightly linear positive correlation (r Pearson = .19; $p = .06$) resulted, suggesting an increasing risk of sensitization to AS with length of employment under the current position. The linear regression model confirmed the same trend ($p = .06$), estimating an average increase of 0.12 kU/L of AS-specific IgE for each additional year of employment.

COMMENT

This study showed the seroprevalence of AS-specific IgEs and evaluated the potential risk of sensitization to AS by investigating the correlation between the contact with raw, in-brine, or undercooked fish in occupationally exposed population. Overall, 3 working settings were compared in relation to different habits in ingestion/manipulation of sea products from direct fishing to fish manufacturing (processing, packaging) for commercial distribution. Our experience highlighted a seroprevalence excess as well as an higher seroconversion risk in fishermen/sailors compared with the fish industry employees (reference group).

Among the demographic and behavioral characteristics, the only significant association observed was an inverse relation between increasing levels of dietary fish intake and prevalence of AS-specific IgE response. Because this was a cross-sectional study, interpretation of this apparent interference between dietary intake and IgE response is unclear; however, we cannot exclude that the development of allergy in the past may have reduced fish consumption among the workers, leading to the present pattern.

Furthermore, it is possible that the lack of correlation between self-reported allergy symptoms and seroprevalence of sensitization or allergy indicates misclassification of allergy history, possible due to the workers' concerns about disclosing a condition that may be incompatible with continued employment, as documented by literature in other occupational settings.²³

Correlation and regression analyses suggested that AS-specific IgE levels tend to increase as a function of the duration of occupational exposure to the parasite ($p = .06$); although this observation could be useful to contribute to the understanding of the AS allergy natural history, it should be confirmed by larger studies.

Although in our series a criticism could be addressed to the lack of information about possible initial exposure at a young age, because of the design of the study again, we were not able to exclude the possibility that the most sensitive workers (the ones who developed urticaria or anaphylaxis) could have quit their jobs and weren't included in the study population.

However, several case reports and small-size studies documented *Anisakis*-related allergic reactions in fish industry employees,^{12,15,17,18,24} only a smaller number of studies have considered fishermen or fishmongers job type,^{20,25,26} and none to our knowledge has raised a concern of a possible correlation between risk of sensitization and years of occupationally exposition.

In our country, Purello-D'Ambrosio et al²⁰ indicated that fishermen/fishmongers could be a population at risk for *Anisakis simplex* sensitization, suggesting enlarging these investigations also in subjects who handle fish for other reasons. In a more recent study carried out in Spain,⁹ it was pointed out that subjects who ate fresh fish were more likely to be seropositive than subjects who mainly ate frozen fish. This result could support our finding about the higher risk of sensitization found among fishermen/sailors, mostly ascribed to the frequently ingestion of seafood or manipulation for quick-freezing immediately after death, when parasite larvae migrate from gastrointestinal system to muscles, whereas fishmongers' fish cleansing as well as fish industry employees handle seafood generally after hours/days of freezing process, with less probability of AS larvae survival. In some studies carried out with AS in USA,⁷ the parasites have been found to survive -20°C for short periods and therefore prolonged freezing for at least 1 week or at -18°C for at least 96 hours is recommended by the European Food Safety Authority (EFSA).²⁷

These preventive measures have been adopted by the fish industry as Hazard Analysis and Critical Control Points (HACCP) systems.^{28–30}

In recent years, the development of better diagnostic tools and greater awareness about AS sensitization risk has resulted in an increase in the frequency of reports worldwide.^{6,29,31–33} Furthermore, the increased sensitization to AS-specific IgEs in fishermen and sailors, as compared with industrial workers, could be partially explained by inadequate information and training for such workers, as demonstrated by the irregular/never use of individual protective devices.

Undoubtedly, human migratory movements and globalization and the consequent increase in consumers' interests for exotic dishes, together with an increasing trend not to overcook food and the acknowledged benefits of the Mediterranean diet (characterized in part by high fish consumption) to prevent heart diseases,^{34,35} will be taken in consideration to better define new emergent public health risks in food consumption.

Future studies should be considered, either increasing the number of occupationally exposed subjects and/or extending to the general population, in order to document potential

health effects related to the global consumption of raw, in-brine, or undercooked fish.

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For comments and further information, address correspondence to Walter Mazzucco, Dipartimento Scienze Promozione della Salute—Sezione Igiene, University of Palermo, Via del Vespro n.133, 90127 Palermo, Italy.

E-mail: waltermazzucco@unipa.it

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