THE POSSIBLE ROLE OF MUMPS VIRUS IN THE DEVELOPMENT OF INSULIN DEPENDANT DIABETES MELLITUS

R. N. Taha*, Dawood S. D. **, Mustafa L. K. ***
*College of Midicine , Nahrin University. Baghdad -Iraq.
**College of Health and Medical Technology, Foundation of Technical Education, Baghdad -Iraq.
***Educational Laboratories, Baghdad. Baghdad -Iraq.

Abstract

Mumps is an acute viral illness associated with different types of complications, Pancreatitis is one of infrequent mumps complications followed by diabets mellitus type one in few cases. The present study was designed to determine whether a relationshipe exposure to mumps by natural infection or vaccination with MMRvaccine and diabetes type one.

Seventy two patients with Insulin dependent diabetes mellitus exposed to mumps by vaccinor natural infection compared with ١٨ (healthy) age and sex matched control were included in this study . Blood samples were taken for investigation of Glutamic acid decarboxylasw antibody (GADA), Islet cell antibody (ICA) and Mumps IgG Antibody by using ELISA and immunoflorescent technique.

Islet cell antibody was detected in ١٣ (١٨.١%) patients ٦ (٨.٣%) males and ٧ (٩.٧%) females. GADA was detected in ٤٥ patients (٦٤.٥%) ٢٤ males (٣٣.٣%) and ٢١ (٢٩.٢%) females. Mumps IgG Antibody was found in ٢١ (٢٩.٢%) of patients

الدور المحتمل للفايروس المسبب للنكاف في احداث مرض السكري المعتمد على الانسولين

رفل نزار طه*،داود سلمان داود **، لين خلوق مصطفى***
* كلية الطب، جامعة النهرين، بغداد- العراق.
**كلية التقنيات الصحية والطبية، هيئة التعليم التقني، بغداد- العراق.
***المختبرات التعليمية، بغداد، بغداد- العراق.

الخلاصة

نكاف هو إصابة فيروسية حادة تصاحبها أنواع مختلفة من المضاعفات ، الإصابة الحادة للبنكرياس تعتبر واحدة من المضاعفات القليلة الحدوث يصاحبها مرض السكري الغير معتمد على الأنسولين. إن الدراسة الحالية صممت لمعرفة العلاقة المحتملة من الإصابة السابقة بالنكاف RMM أو التلقيح باللقاح ومرض السكري الغير معتمد على الأنسولين.

اثنان وسبعون مريضا مصابين بداء السكري المعتمد على الأنسولين تعرضوا للأصابة بالنكاف أما عن طريق اللقاح أو عن طريق الإصابة المباشرة وقد تمت مقارنتهم مع ثمانية عشر من الأصحاء الذين كانت أعمارهم وأجناسهم متوافقة مع المصابين . وقد جمعت نماذج الدم لأجراء الفحص حول وجود الأجسام

المضادة لـ(**GAD**) ولـ(**ICA**) والمضاد نوع (**IgG**) لفيروس النكـاف وقـد اجـري الفحـص بطريـقة الـ **ELISA** و**IF**.

النتائج أظهرت عن وجود الأجسام المضادة لـ(**ICA**) في ١٣ (١٨.١%) من المصابين.

٦ (٨.٣%) من الذكور و ٧ (٩.٧%) كانوا من الإناث . من ناحية أخرى الأجسام المضـادة لـ ـ(**GAD**) كانت في ٤٥ (٦٤.٥%) من المصابين موزعين ٢٤ (٣٣.٣%) ذكور و ٢١ (٢٩.٢%) من الإناث وقـد أظهرت النتائج أن ٢١ (٢٩.٢%) من المصابين كان لديهم أجسام مضادة نوع **IgG** ضد فيروس النكاف.

Introduction

Mumps is a common childhood infection caused by the mumps virus. The hallmark of infection is swelling of the paroited gland. Aseptic meningitis and encephalitis are common complication of mumps together with orchitis and oophoritis, other complications include deafness and pancreatitis [١].

Mumps viruses are nowadays known to be pancreatropic viruses (viruses that cause inflamation of pancreas). However, the development of insulitis after viral infection is related to the genetic factor [٢].

Type ١ diabetes (T١D) results from the destruction of pancreatic beta cells. Viruses are one environmental factor that is implicated in the pathogenesis of T١D in at least two distinct ways: by including beta cell-specific autoimmunity, with or without infection of beta cells [٣].

The measles, mumps, rubella vaccine (MMR) was licensed for use in ١٩٧١ [٤, ٥]. There is a hypothesis suggest that mumps vaccine may be an environmental factor for childhood diabetes [٦].

Materials and Methodes

A prospective study was done from July to September ٢٠٠٩, Seventy two patients with Insulin dependent diabetes mellitus exposed to mumps by vaccine or natural infection compared with ١٨ (healthy) age and sex matched control were included in this study. One – two ml of venous blood were collected from them by a disposable syringe, blood sample was allowed to clot then centrifuged, the sera obtained were subdivided in three partitions and stored at (-٢٠˚C), each partition was used after thawing in one of the following tests, the first patition was analyzed for Glutamic acid decarboxylase antibody (GADA) by ELISA kit [Anti-GAD ELISA (IgG), Company EUROI-MMUN Gremany]. The second partition was analyzed for islet cell antibody (ICA) by Immunofluorescence technique [Company EUROIMMIUN Germany]. The third partition was analyzed for mumps IgG antibody (Ab) by ELISA kit [company NovaTec Germany].

Result and Discussion

١) Distribution of Diabetic patients and control according to the age and gender

Seventy tow patients with insulin dependant diabetes mellitus (IDDM) and eighteen control individuals were participated in this study. Table (١) shows that control group is matched with patients in Gender. It is also demonstrate age group distribution, minimum age was ٤ years in patients group, ٣ years in the control, while maximum age was ٣١ for each of them. There was no significant difference between patient and control age groups P=٠.٨٥٧.

Table ١: distribution of patients and control according to the Age and Gender

group		Frequency	Percent	Cumulative Percent
Disease	> ٥ yrs	٤	٥.٦	٥.٦
	٥ _ ٩ yrs	٩	١٢.٥	١٨.١
	١٠ _ ١٤ yrs	٣٤	٤٧.٢	٦٥.٣
	١٥ _ ١٩ yrs	١٦	٢٢.٢	٨٧.٥
	٢٠ _ ٢٤ yrs	٤	٥.٦	٩٣.١
	٢٥ _ ٢٩ yrs	٤	٥.٦	٩٨.٦
	< ٣٠ yrs	١	١.٤	١٠٠
	Total	٧٢	١٠٠	
Control	> ٥ yrs	٢	١١.١	١١.١
	٥ _ ٩ yrs	٥	٢٧.٨	٣٨.٩
	١٠ _ ١٤ yrs	٣	١٦.٧	٥٥.٦
	١٥ _ ١٩ yrs	٢	١١.١	٦٦.٧
	٢٠ _ ٢٤ yrs	٤	٢٢.٢	٨٨.٩
	٢٥ _ ٢٩ yrs	١	٥.٦	٩٤.٤
	< ٣٠ yrs	١	٥.٦	١٠٠
	Total	١٨	١٠٠	

group	N	Minimum	Maximum	Mean	Std. Deviation	C.S. P-value
Patient age	٧٢	٤ year	٣١ year	١٣.٧١	٦.٠٧	P=٠.٨٥٧ NS
Control age	١٨	٣ year	٣١ year	١٤.٠٨	٨.١٨	

group		Frequency	Percent	Cumulative Percent
Patient	Male	٣٨	٥٢.٨	٥٢.٨
	Female	٣٤	٤٧.٢	١٠٠
	Total	٧٢	١٠٠	
Control	Male	١٢	٦٦.٧	٧٧.٨
	Female	٦	٣٣.٣	١٠٠
	Total	١٨	١٠٠	

To spot light on Patients Gender and age table (١) shows that the patients were ٣٨ males and ٣٤ females. The incidence of type one diabetes in males was (٥٢.٨%) while it was less in females ٤٧.٢%, the difference remaining non significant p= ٠.٧٢٤ this is similar to other study in Finland [٧] which showed that the incidence of IDDM was higher in males and to another study in Finland [٨] that showed male to female ratio was ١.١ while it differ from that in Russian Karelia [٧] which was ٠.٦٢.

The demographic distribution of the age group in agreement with previous study in Europe [٩] who found that the largest incidence of type one diabetes was in the age group ١٠-١٤ years and with other study in Iraq showed that the peak incidence was at puberty [١٠].

٢) Incidence of mumps in diabetic patients associated with Vaccine, ICA, GADA, mumps IgG Antibody.

Sixty six patients out of ٧٢ (٩١.٧%) received MMR vaccine (two doses), only ٦ (٨.٣%) did not receive the complete vaccine doses. Eight (١١.١%) patients had a previous history of mumps (Table ٢). One of these ٨ cases (١٥ year old) had recent mumps infection immediately fallowed by diabetes the serology was positive for mumps IgG Antibody, GADA and typical islet cell antibody. Second case had diabetes less than one year after mumps infection, the remained cases had long duration of diabetes after mumps that makes it difficult to determine the exact serological marker immediately after mumps infection.

The end result were ٢ patients out of ٨ showed positive ICA, ٥ out of ٨ showed positive GADA, and very interesting results that despite history of mumps infection and complete vaccine doses, ٢ patients out of ٨ showed seronegative for mumps IgG Antibody that result may increase the suggestion that the mumps IgG Antibody decline in diabetic patients similar to other studies [١١, ١٢].

These results are in agreement with other studies that mumps virus may be an etiological factor of type ١ diabetes [٢, ١٣, ١٤].

Table ٢: cross tabulation causes correlation ship among Vaccinated Status in the two groups related that Mumps Parameretes responding.

			Vaccine		Total	CS P-value
			Incomplete vaccine	Complete vaccine		
mumps	Neg.	Count	٦	٥٨	٦٤	F.E.P.T. P=٠.٤٨٠ NS
		% of Total	٨.٣%	٨٠.٦%	٨٨.٩%	
	pos.	Count	٠	٨	٨	
		% of Total	٠%	١١.١%	١١.١%	CC=٠.١٠٦ P=٠.٣٦٦ NS
	Total	Count	٦	٦٦	٧٢	
		% of Total	٨.٣%	٩١.٧%	١٠٠.٠%	

٣) Seroprevalence of mumps IgG antibody in diabetic patients from previous infection and/or vaccine &vaccinated control.

More than ٩٧% of recipients of a MMR vaccine develop antibody, clinical efficacy has been estimated to be ٩٥% (range ٩٠-٧٠%) the duration of vaccine induced immunity is believed to be greater than ٢٥ years, and is probably life long in most vaccine recipients [١٥].

Previous studies that depended on mumps IgG Antibodies detection by ELISA in Iran ٢٠٠٩ showed (٨٠.٢%) seropositivity rate for mumps [١٦], in Greece showed (٧٢%) was protected against mumps [١٧].

Table (٣) shows the protection of MMR vaccine that given to control and patient groups, Control group showed only ٨persons (٤٤.٤%) protection against mumps infection while ١٠ persons (٥٥.٦%) were seronegative incomparable with other studies this may be attributed to primary or secondary MMR vaccine failure. Insufficient childhood vaccination coverage may result in an epidemiological shift in the incidence of mumps to older age groups. If a large proportion of the population remains seronegative for mumps, vaccination of adults should be considered [١٧,١٨].

It is very important to say that significant low measles-mumps-rubella IgG Ab protection level was detected in poor country like in Bagladeshi children suggesting an intergral vaccination strategy [١٩].

Table ٣: Seroprevalence Mumps IgG Antibody in diabetic patients and control

			Mumps IgG		Total	C.S. P-value
			Neg.	pos.		
group	Disease	Count	٥١	٢١	٧٢	F.E.P.T. P=٠.٢٩٩ NS
		% within group	٧٠.٨%	٢٩.٢%	١٠٠.٠%	
		% of Total	٥٦.٧%	٢٣.٣%	٨٠.٠%	
	Control	Count	١٠	٨	١٨	
		% within group	٥٥.٦%	٤٤.٤%	١٠٠.٠%	
		% of Total	١٢.٢%	٧.٨%	٢٠.٠%	
Total		Count	٦١	٢٩	٩٠	CC=٠.٠٨٤ P=٠.٤٢٥ NS
		% of Total	٦٨.٩%	٣١.١%	١٠٠.٠%	

Regarding patients ٢١(٢٩.٢%) had mumps IgG Ab positivity. [depending on questioner ٢ of them don't have a complete vaccine doses] and this percentage was less than control group which was in agreement with other studies that showed decline of mumps IgG Ab in diabetic patients [١١, ١٢]. This percentage may slightly increase to ٣١.٨% if we exclude the incompletely vaccinated patients (٦ patients) but still less than control group.

In Table (٤) total number of patients with positive ICA was ١٣ (١٨.١%), while ٢١(٢٩.٢%) patients were positive mumps IgG Ab, ٦ (٨.٣%) patients had positive results for both of them (٢ of ٦ had history of mumps). ٤٤ patients had negative result for ICA and mumps IgG Ab p= ٠.١٢٦ there is a confidence level equal to ٨٧.٤% which might indicate a relation between them.

Table ٤: Mumps IgG antibody associated with ICA

Parameter	Responding	Count & Percent	ICA		Total
			Neg.	pos.	
Mumps IgG Antibody	Neg.	Count	٤٤	٧	٥١
		% of Total	٦١.١%	٩.٧%	٧٠.٨%
	pos.	Count	١٥	٦	٢١
		% of Total	٢٠.٨%	٨.٣%	٢٩.٢%
Total		Count	٥٩	١٣	٧٢
		% of Total	٨١.٩%	١٨.١%	١٠٠.٠%
C.S. P-value			F.E.P.T P=٠.١٢٦		C.C.=٠.١٧٣ P=٠.١٣٧

Relationship between mumps IgG Antibody GADA was demonstrated in Table (٥) the number of patients with positive GADA was ٤٥(٦٢.٥%).

Fourteen (١٩.٤%) out of ٧٢ patients showed positive result for both GADA and mumps IgG Ab, on the other hand ٢٠(٢٧.٨%) out of ٧٢ patients were negative for both of them the result remained non significant p= ٠.٤٢٤.

Table ٥: Mumps IgG Antibody associated with GADA.

Parameter	Responding	Count & Percent	GADA		Total
			Neg.	pos.	
Mumps IgG Ab	Neg.	Count	٢٠	٣١	٥١
		% of Total	٢٧.٨%	٤٣.١%	٧٠.٨%
	pos.	Count	٧	١٤	٢١
		% of Total	٩.٧%	١٩.٤%	٢٩.٢%
Total		Count	٢٧	٤٥	٧٢
		% of Total	٣٧.٥%	٦٢.٥%	١٠٠.٠%
C.S. P-value			F.E.P.T P=٠.٤٢٤		C.C.=٠.٠٥٥ P=٠.٦٣٩

A study dependent on clustering of cases of type one diabetes mellitus occurring ٢-٤ years after vaccination with clustering after infection and progression to type one diabetes in autoantibody positive individuals, demonstrate that a distinct rise in these cases after MMR vaccine [٢٠].

Another studies showed that very fewpatients may developed some autoimmune diseases following viral vaccine and for the overwhelming majority of people, vaccines are safe and no evidence linking viral vaccines with type one diabetes [٢١, ٢٢], and the prevalence of ICA positivity was unaffected by MMR vaccine [٢٣].

In our study depending on the patient's history ٦٦ patients had a history of complete mumps vaccine doses, from those ١٩ patients had positive mumps IgG Ab mean while ١٦ of them had GADA and/or ICA (Figure ١) interestingly the onset of diabetes occurred ٢-٤ years after first or second dose of vaccine in ٦ of them.

Another important thing was from the group of the vaccinated patients and control the highest level of immunoglobulin G antibody to mumps was found in a female ٣.٥ year old which has a typical ICA and elevated GADA without history of mumps infection. These results may be in agreement with the hypothesis that viral vaccine may have a role in type one diabetes and in the big jump in the number of cases of juvenile diabetes [٢٠, ٢٤].

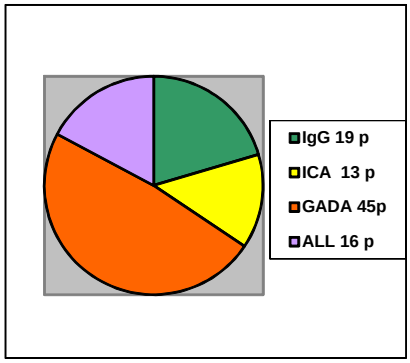

Figure ١: shows number of the patients that positive mumps IgG Antibody, ICA, GADA, and the number of patients that had a positive result for mumps IgG Antibody, GADA and/or ICA (١٦ patients)

References

١. Hviid, A.; Rubin, S. and Mühlemann, K. M. **٢٠٠٨.** Mumps. *Lancet*, ٣٧١(٩٦١٦):٩٣٢-٤٤.

٢. Katona-Dureković, A. ٢٠٠٧. The role of virus infections in the pathogenesis of type ١ diabetes--a case report. *Med Pregl*, ٦٠(٧-٨):٣٩٧-٤٠٠.

٣. Jun, H. S. and Yoon, J. W. ٢٠٠٣. A new look at viruses in type ١ diabetes. Diabetes. *Metab Res Rey*, ١٩(١), pp. ٨-٣١.

٤. Tanne, J. H. ٢٠٠٥. Increase in autism due to change in definition, not MMR vaccine. *British Medical journal*, ٣٣٠(٧٤٨٣):١١٢.

٥. Dales, L.; Hammer, S. J. and Smith, N. J. **٢٠٠١.** Time trends in Autism and in MMR immunization coverage in California. *JAMA* **٢٨٥:**١١٨٣-١١٨٥.

٦. Milne, L. M. **٢٠٠٠.** Difficulties in assessing the relationship, if any, between mumps vaccination and diabetes mellitus in childhood. *Vaccine*, ١٩(٩-١٠):١٠١٨-٢٥.

٧. Kondrashova, A. ٢٠٠٩. Epidemiology and risk markers of autoimmune diseases in Russian karelia and Finland. Academic dissertation, Medical school of the University of Tampere, Teiskontie ٣٥, Tampere.

٨. Harjutsalo, V., Sjöberg, L. & Tuomilehto, J. (٢٠٠٨) Time trends in the incidence of type ١ diabetes in Finnish children: a cohort study. Lancet, ٣٧١(٩٦٢٦):١٧٧٧-٨٢.

٩. Patterson, C. C.; Dahlquist, G. G.; Gyürüs, E. *e. al.* **٢٠٠٩.** Incidence trends for childhood type ١ diabetes in Europe during ١٩٨٩-٢٠٠٣ and predicted new cases ٢٠٠٥-٢٠: a multicentre prospective registration study. Lancet, ٣٧٣(٩٦٨٠):٢٠٢٧-٣٣.

١٠. Dawood, D. S. **١٩٩٨.** Screening for autoantibodies and viral antibodies in diabetes mellitus. M.Sc. University of Baghdad (College of medicine).

١١. Hyöty, H.; Hiltunen, M.; Reunanen, A. *et al.* **١٩٩٣.** Decline of mumps antibodies in type ١ (insulin-dependent) diabetic children and a plateau in the rising incidence of type ١ diabetes after introduction of the mumps-measles-rubella vaccine in Finland. Childhood Diabetes in Finland Study Group. *Diabetologia*, ٣٦(١٢):١٣٠٣-٨.

١٢. Hiltunen, M.; Hyöty, H.; Leinikki, P. *et al.* **١٩٩٤.** Low mumps antibody levels induced by mumps-measles-rubella vaccinations in type ١ diabetic children. *Diabet Med*, ١١(١٠): ٩٤٢-٦.

١٣. Kuchmerovskaia, T. M.; Karpov, A. V. and Donchenko, G. V. **٢٠٠٥.** Viruses as the etiological factor of type ١ diabetes. Animal models. *Ukr Biokhim Zh*, ٧٧(١):٣٢-٤٠.

١٤. Bach, J-F. ٢٠٠٢. The effect of infections on susceptibility to autoimmune and allergic diseases. *N. Engl. J. Med.*, **٣٤٧:**٩١١-٩٢٠.

١٥. Pickering, L. **٢٠٠٣.** Red Book. ٢٦th ed. Elk Grove Village, IL: American Academy of Pediatrics. pp.٤٣٩–٤٣.

١٦. Avijgan, M.; Habibian, R. and kheiri, S. ٢٠٠٩. Seroprevalence of mumps before inclusion of mumps vaccination in the Iranian Expanded Programme onImmunization. *Eastern Mediterranean Health* Journal, **١٥**(٢).

١٧. Fylaktoul, A.; Haidopoulou, K.; Goutaki, M. *et al.* **٢٠٠٨.** Measles and mumps immunity in northern Greece, ٢٠٠٤-٢٠٠٧. EURO-SURVEILLANCE, ١٣٠ Issues ٤–٦. www.eurosurveillance.org

١٨. Pogorzelska, M.; Ołdak, E. and Sulik, A. **٢٠٠٥.** Mumps-still actual epidemiological problem in Poland. Przegl Epidemiol, **٥٩**(٤):٨٤١-٩.

١٩. Sultana, R.; Rahman, M. M.; Hassan, Z. *et al.* **٢٠٠٦.** Prevalence of IgG Antibody Against Measles, Mumps and Rubella in Bangladeshi Children: A Pilot Study to Evaluate the Need for Integrated Vaccination Strategy. Scandinavian Journal of Immunology, ٦٤(٦):٦٨٤-٦٨٩.

٢٠. Classen, J. B. and Classen, D. C. **٢٠٠٣.** Clustering of cases of type ١ diabetes mellitus occurring ٢-٤ years after vaccination is consistent with clustering

after infections and progression to type ١ diabetes mellitus in autoantibody positive individuals. *J. Pediatr. Endocrinol. Metab*, ١٦(٤):٤٩٥-٥٠٨.

٢١. Schattner, A. ٢٠٠٥. Consequence or coincidence. The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines. *Vaccine*, ٢٣(٣٠):٣٨٧٦-٨٦.

٢٢. DeStefano, F.; Mullooly, J. P.; Okoro, C.A. *et al*. ٢٠٠١. Vaccine Safety Datalink Team: Childhood vaccinations, vaccination timing, and risk of type ١ diabetes mellitus. Pediatrics, ١٠٨(٦):E١١٢.

٢٣. Lindberg, B.; Ahlfors, K.; Carlsson, A. *et al*. ١٩٩٩. Previous exposure to measles, mumps, and rubella-but not vaccination during adolescence- correlates to the prevalence of pancreatic and thyroid autoantibodies. *PEDIATRICS*, ١٠٤ (١).

٢٤. National vaccine Information Center. Juvenile Diabetes and Vaccination: New Evidence for a Connection. Online available at http://www. Nvic .org / vaccines - and - diseases /Diabetes /juvenilediabetes.aspx