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Metal Concentrations in the Blood and Tissues after Implantation of Titanium Growth Guidance Sliding Instrumentation

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Abstract

Background. Growth guidance sliding treatment devices such as Shilla (Medtronic, USA) or LSZ-4D (Conmet, Russia) used for the treatment of scoliosis in children who have high growth potential have unlocked fixtures allowing rods to slide during growth of the spine which avoids periodical extensions. However, the probability of clinical complications associated with metallosis after the implantation of such devices is poorly understood. The content of metal ions in the blood and tissues of pediatric patients treated for scoliosis using fusionless growth guidance sliding instrumentation, have not yet been investigated.

Purpose. The aim of this study was to measure the content of metal ions in blood and tissues surrounding implanted growth guidance sliding LSZ-4D devices made of titanium alloy (Ti6Al4V) and to identify the incidence of metallosis associated clinical complications in some patients with these devices.

Study design. One center case-control retrospective study.

Patients sample. Study group included 25 patients with high growth potential (3 males, 22 females, average age at primary surgery for scoliosis treatment is 11.4±1.2 years old) who had sliding growth guidance instrumentation LSZ-4D (Conmet, Moscow, Russia) implanted on 13 (range 10-16) spine levels for 6±2

years. The LSZ-4D device was made from titanium alloy Ti6Al4V and consisted of two rectangular section rods and fixture elements. Locked fixtures were used on one spinal level, while the others were unlocked (sliding). The control group consisted of 13 patients (12 females and 1 male, 11±1.2 years old) without any implanted devices.

Outcome measures. The content of Ti, Al and V metal ions in the whole blood and tissues around the implanted device was measured. Incidence of metallosis associated complications in the study group were recorded.

Methods. Metal ion content was measured by ICP-MC on quadrupolar Nexion 300D (Perkin Elmer, USA).

Results. 5 of 25 patients in the study group developed metallosis associated complications (two sinuses and three seromas in the lumbar part of the spine). Revisions were carried out in two of these patients. 90% of patients in the study group had increased content of Ti and V ions in the blood (2.8 and 4 times respectively). Median content of Ti ions in soft tissues adjacent to implanted sliding device was more than 1,500 fold higher compared with the control group. These levels are much higher than previously reported for spinal instrumentation.

Conclusion. Increased content of Ti and V ions in the blood and especially in tissues around the titanium growth guidance sliding device LSZ-4D accompanied by clinical manifestations (seromas and sinuses) indicate the importance of improving of wear resistance of such instrumentation with the

coatings and the necessity to exchange sliding instrumentation once the child is fully grown.

Introduction

Fusionless instrumentation enabling growth of the spine is used for early onset scoliosis treatment or for the treatment of adolescent scoliosis in case of high growth potential in order to avoid early fusion in pediatric patients. Mechanically or magnetically extendable rods are widely used for this purpose [1-2]. These extendable growing rods require intermittent extension (at least twice a year). Long-term complication of proximal junction kyphosis is another drawback of these devices [3]. In growth guidance sliding instrumentation such as Shilla (Medtronic, USA) or LSZ-4D (Conmet, Russia) unlocked fixtures are used allowing the rods to slide during growth of the child's spine, thus avoiding periodical extensions [4-5].

Potentially as these rods slide in the guiding fixtures excessive metal debris (metallosis) could be generated. Metallosis associated with CoCr debris generated at the articulation of metal-on-metal total hip prosthesis is associated with pseudotumors and sensitivity to metal debris and is the main reason for the revision of these implants [6]. Excessive amounts of more biologically compatible Ti wear debris produced by spinal implants have been reported to cause inflammation and osteolysis in animal experiments [7-9]. A case report identifying wear debris induced osteolysis around a pedicle screw after posterior spine fusion in a pediatric patient has recently been reported [10].

However, the probability of clinical complications associated with metallosis after implantation of fusionless growth guidance sliding spinal instrumentation is poorly understood since these devices have been recently released. The question of changing of other fusionless instrumentation into a more traditional fusion device after child's growth has stopped has not yet been addressed also since there are no long-term follow-up studies with such spinal instrumentation.

Extensive analysis of wear damage of total hip and knee replacements (THP and TKR) revealed that excessive debris release is normally accompanied by the increasing metal ion levels in the patients' whole blood and serum [11-12]. Increases of titanium ion levels in the blood of patients with implanted titanium spinal instrumentation was reported by Cundy et al [13], Kasai et al [14] and Richardson et al [15], even in arthrodesis procedures. Elevated titanium ion concentration of up to 50 times normal levels was observed by Wang et al. in tissues surrounding spinal implants [16].

However, the content of metal ions in the blood and tissues of pediatric patients treated using fusionless, especially growth guidance sliding instrumentation, have not yet been investigated. The aim of our study was to measure the content of metal ions in blood and tissues surrounding implanted growth guidance sliding LSZ-4D devices made of titanium alloy (Ti6Al4V) and to identify the incidence of metallosis associated clinical complications in some patients with these devices. It was hypothesized that the level of metal ions in

the blood and tissues of patients after implantation of sliding growth guidance instrumentation would be higher compared to data previously reported for traditional fusion spinal devices.

Methods

Study design and participants

This is one center case-control retrospective study.

25 patients (3 males and 22 females having high growth potential, average age at primary surgery is 11.4±1.2 years old) who had sliding growth guidance instrumentation LSZ-4D (Conmet, Moscow, Russia) implanted for 6±2 years were recruited into the study group for the measurements of metal ion content in their whole blood and tissues. Recruitment was carried out in the Center for Scoliosis Correction, Medical Department of the Peoples' Friendship University of Russia (Moscow, Russian Federation) from May to October 2013. These patients were undergoing the routine surgery of exchanging of sliding LSZ-4D devices with traditional fusion instrumentation when they became skeletally mature (second surgery).

LSZ-4D sliding instrumentation was made from titanium alloy Ti6Al4V (Ti-6wt. %Al-4wt. %V) and consisted of two rectangular section rods (6x4mm) and 40±8 fixture elements (20±4 hooks and 20±4 clips). Locked fixtures were used on one spinal level. Other fixtures were unlocked (sliding) thus enabling sliding and continued spinal growth (Figure 1). The device was implanted on 13

(range 10-16) spine levels for 6±2 years (Table 1). According to Lenke classification [17] patients in the study group had the following scoliosis types: 1 – IA+; 1 – IBN; 7 – IIBN; 7 – IIIBN; 7 – IIICN; 1 – IVCN; 1 –VCN. Approximately 80-90% of correction was achieved for patients having initial Cobb's angle less than 60° (n=8), while 70-78% of correction was observed for those with initial Cobb angle more than 60° (n=17).

For the measurements of Ti, Al and V metal ions content the blood was collected on the day before such routine surgery and tissues around the rod and screw junction during the surgery. Any incidence of metallosis related complications in the study group of patients were recorded.

Metal ion levels and tissue analysis were also carried out in a control group consisting of 13 patients (12 females and 1 male, 11±1.2 years old) with no implanted devices. These patients were recruited in the same center during the same period before they had their primary surgery for scoliosis .

Measurement of metal ions in the whole blood and tissues

Content of Ti, Al and V metal ions was measured in the whole blood and tissues of the study and control groups of patients.

To limit possible contamination venipuncture was performed with cannula. Venous blood specimens were collected into the green-cap Vacuette (sodium heparin containing) collecting tubes (Greiner Bio-One International AG, 4550 Kremsmünster, Austria) and diluted 1:30 with an acidified diluents ((v/v) of 1% 1-Butanol, 0.1% Triton X-100 and 0.07 % HNO_3 in distilled

deionized water (DDIW)). The amounts of titanium, aluminum and vanadium were measured using inductively-coupled mass spectrometry method (ICP-MS) using Nexion 300D ICP-MS spectrometer (PerkinElmer Inc., Shelton, CT 06484, USA).

Soft tissues were taken at the time of surgery from the capsule surrounding the fixture-rod junction and 3 cm away from the capsule. Tissue specimens were digested with HNO_3 in the Berghof SW-4 DAP-40 microwave system (Berghof Products + Instruments GmbH, 72800 Eningen, Germany), diluted 1:150 with DDIW and run into the ICP-MS system within 2-3 hours to prevent possible precipitation of titanium salts.

Histological examination of tissues was carried out using light microscopy (Carl Zeiss AXIOSCOP 2 plus microscope). For light microscopy formalin-fixed and paraffin wax embedded sections of 4μm thickness were taken and stained with Hematoxylin and Eosin. Titanium particles appear black in stained histological sections and their composition was confirmed using energy dispersive x-ray analysis.

Statistical methods

The number of patients in the study and control groups (25 and 13 respectively) was calculated using G*Power 3.1.7 software based on the data from internal pilot study and necessity to check the hypothesis of statistically significant difference of Ti, Al and V content in blood and tissues at significance level α=0.05 and power 0.95.

After metal ion content was measured for all patients the Mann-Whitney U test was used to determine if there was statistically significant difference in Ti, Al and V content in the blood of patients with implanted LSZ-4D device and those from control group. A *p* value of less than 0.05 was defined as statistically significant. This test was chosen after Kolmogorov-Smirnov test revealed that metal content in blood and tissues significantly deviated from a normal distribution. This statistical analysis was performed with SPSS 22.0 software (IBM Corp., USA). The same test was carried out for two subgroups of the study group of patients (those who developed metallosis related complications and those who did not). Because of the small number of patients in the subgroup with metallosis complications, power of this test was calculated.

Results

Metallosis associated complications

Five of 25 patients in the study group who returned to the clinic for the surgery of exchanging sliding growth guidance titanium LSZ-4D devices with traditional fusion instrumentation developed metallosis associated complications in the lumbar part of the spine (Table 1).

Two of such patients required revision surgery because of these complications. One of these patients developed seroma accompanied with elevated body temperature and increased erythrocyte sedimentation rate in her blood which were regarded as signs of inflammation 10 years after the surgery.

The second patient developed a sinus with local inflammation 5 years after the surgery. Clinical symptoms were resolved once the device had been exchanged or shortened. In both of the revised cases exhaustive microbiological analysis of samples taken during s revision surgery using both aerobic and anaerobic bacterial cultures failed to identify any organisms.

Another three patients developed seromas or sinus without inflammation 0.5 – 2 years after the implantation of LSZ-4D devices (Table 1). However, these seromas and sinus were successfully treated by compression dressing and antibiotic therapy and patients were recommended to avoid intensive physical exercises. Antibiotic therapy was used as a precaution to prevent revision surgery.

Content of metal ions in whole blood

The median values of titanium, aluminum and vanadium in the whole blood of patients from the control group without implants was 30 ppb (range 30-40) for titanium, 30 ppb (range 20-40) for aluminum and 0.08 ppb (range 0.06-0.1) for vanadium. Patients with implanted LSZ-4D sliding devices had much higher ion levels with 85 ppb (range 28-180) of titanium, 30 ppb (18-150) of aluminum and 0.3 ppb (range 0.2-0.5) of vanadium. Statistical analysis using Mann-Whitney non-parametric test revealed statistically significant ($p=0.0001$) raised levels of titanium and vanadium (2.8 and 4 times respectively) in the whole blood of patients with implanted LSZ-4D devices (Figure 2). However, content of aluminum in the control and study groups was not statistically

significant (p=0.16, power 0.95) due to the variability associated with aluminium ion content in the study group (Figure 2).

The content of titanium, aluminum and vanadium for patients with implanted LSZ-4D devices who had seromas and sinuses (n=5) was also compared with that observed in patients who did not have these complications (n=20). Statistical analysis revealed no statistically significant difference of aluminum and vanadium ion content in these groups (p=0.07 and p=0.05 for aluminum and vanadium respectively). Even slightly lower content of titanium was revealed in the blood of patients who developed these metallosis associated complications (p=0.035). However, because of the small number of patients in the subgroup of patients with complications (n=5) the power of the test was less than 0.80 (0.60 for Ti and V ions; 0.10 for Al), which might require further studies.

Content of metal ions in tissues surrounding implants

Black discoloration of soft tissues adjacent to growth guidance sliding LSZ-4D devices was observed in all patients, indicating significant amounts of wear debris (Figure 3). Median concentration of titanium, aluminum and vanadium in the soft tissues taken at the time of surgery in patients of control group operated for scoliosis for the first time and having no metal implants was 0.7 μg/g (range 0.15-0.95) for titanium, 0.7 μg/g (range 0.1-0.9) for aluminum and 0.06 μg/g (range 0.01-0.1) for vanadium.

Median concentration of these elements in tissues of patients with implanted growth guidance sliding devices LSZ-4D taken from the capsule around fixture-rod junction increased dramatically up to 1,300 μg/g (range 103 - 5,750) for titanium, 18 μg/g (range 2 – 106) for aluminum and 11 μg/g (range 2 – 109) for vanadium, indicating statistically significant increase of all elements (Figure 4).

The concentration of metal ions was measured in soft tissues collected 3 cm away from the capsule indicating that elevated ions were not just associated with capsular tissue adjacent to the implant but were found at a deeper level. Median values were 6.5 μg/g (range 1.3 – 34) for titanium, 0.9 μg/g (range 0.4 – 6) for aluminum and 0.1 μg/g (0.02 – 0.8) for vanadium, which are significantly higher compared with control group, but significantly lower compared with tissues collected from the capsule.

Content of metal ions in the soft tissues adjacent to fixture-rod junction was also compared for the subgroup of patients with implanted LSZ-4D device who developed metallosis associated complications (n=5) and those who did not (n=20). No statistically significant difference was found for any compared elements (p=1.0; 0.77 and 0.86 for titanium, aluminum and vanadium ions respectively). Due to the high scattering of the metal ion content the power of the test for all ions was much lower than 80% (0.10 for Ti, 0.3 for V and 0.2 for Al).

Histology analysis of tissues and metal debris particles

Histology analysis of the tissues isolated from patients with implanted sliding LSZ-4D devices all showed a similar appearance. There were regions which contained macrophages with large numbers of titanium particles. Individual particles could not be seen with light microscopy as they were of a small size. These macrophages often occurred in well vascularised tissue and there was an infiltration of plasma cells within the tissue. In other regions there was necrosis where the cell number was reduced and a-cellular regions of collagenous tissue were observed (Figure 5).

Discussion

We are reporting the incidence of metallosis associated complications that involved the formation of seromas and sinuses after implantation of titanium sliding growth guidance devices LSZ-4D in 5 of 25 patients. All cases of seromas and sinuses were observed in the lumbar part of the spine, which may be explained by the higher mobility of the lumbar spine region compared with the thoracic region.

The observed frequency of metallosis associated complications (20%) is relatively high, regardless of the fact that only two of these five patients required revision surgery. However, the complication rates for other spinal instrumentation for scoliosis treatment in immature patients such as the growing rods or Shilla devices are also high [18-19] since the fusionless approach combined with periodic lengthening (growing rods) or sliding mechanisms

(Shilla or LSZ-4D) necessary for the retaining of spinal growth of pediatric patients makes the treatment more complex compared to that used for adult patients.

Recent extensive analysis of metallosis associated complications for metal-on-metal total hip replacements made of CoCr alloys revealed positive correlation between the content of cobalt ions in patients' blood and pseudotumors formation and implant loosening [11].

Back in 1990s it was also revealed that patients with failed titanium-on-polyethylene total knee and hip implants had several times higher titanium concentrations in their blood compared with subjects with normally functioning prostheses [12, 20]. Since increased levels of metal ions in patients' blood were reported in literature even after fusion spine surgeries, we hypothesized that the implantation of fusionless, and especially sliding instrumentation would result in higher level of metal ions in the blood.

Results of our study revealed that 90% of subjects in the study group with implanted LSZ-4D sliding devices had increased Ti and V ions levels in the blood. The amount of Ti and V ions in whole blood of these patients was increased 2.8 and 4 folds respectively compared with the control group of patients. No statistically significant difference was observed for aluminum content due the scattering of its content. The content of vanadium ions in the blood is higher than that of titanium and does not reflect the ratio of these elements in titanium alloy composition which contains 6wt. % of Al and 4wt. %

of V, which is possibly due to the excretion of titanium from the body and the retention of vanadium.

However, the increase of titanium content in the blood of patients after implantation of fusionless sliding LSZ-4D devices in our study is similar to values demonstrated by others who investigated patients with fusion devices.

Cundy et al. revealed 2.4 folds elevated level of titanium in pediatric patients after fusion surgery (9 spine levels) [13]. Kasai et al. and Richardson at al. reported 4 fold and 3.6 fold increase in the adult patient's blood with instrumentation implanted on 2 or 3 levels of lumbar spine [14-15]. Data, presented by Ipach et al also demonstrate 2-3 fold increases of titanium content in some adult patients with 5 fused segments [21]. Statistically significant correlation between the number of fused segments, length of rods, quantity of screws and content of titanium in the blood was not found by Richardson et al and Ipach et al. in their studies. However, the power of such comparisons in their studies might not be high due to the small number of patients in the tested subgroups [15, 21].

Nevertheless, the number of operated spine segments might possibly be related to the number of patients who have increased Ti content. 90-95% of patients in our study (10-16 spine levels) and in that carried out by Cundy et al (9-10 spine levels) demonstrated increased Ti content [13]. In contrast, only 35% and 65 % of subjects with up to 3 spine segments fused had increased

metal levels [14-15]. However, further studies with the same instrumentation would be necessary to support this hypothesis.

Similar increase of Ti in patients' blood demonstrated in previous studies and the absence of statistically significant difference in these metal content in the subgroup of patients who developed seromas and sinuses and those who did not (power 0.60 for Ti and V ions) might imply that the content of metal ions in the blood of patients with spinal instrumentation might not be used for the predicting of clinical complications such as seroma or sinus formation and the amount of wear debris generated by the spinal devices.

Content of metal ions in the soft tissues adjacent to spinal implants is not extensively covered in literature. Wang et al. reported 30.36 μg/g of titanium in tissues of patients who developed pseudarthrosis after previous lumbar decompression and fusion with titanium pedicle screw instrumentation surrounding titanium spinal instrumentation, while those with solid fusion had 0.6 μg/g [16]. In our study content of metal ions, especially titanium, in the tissues surrounding fixture-rod junction of sliding LSZ-4D device is dramatically higher being 1,300 μg/g compared with 0.7 μg/g observed in tissues collected from control group of subjects. Similar massive deposition of titanium debris (up to 3,700 μg/g, average amount was 1047 μg/g) was reported by Agins et al within tissues which surrounded failed total knee implants [22].

Our previous work has revealed that more than 50% of wear particles retrieved from tissues which surrounded LSZ-4D devices are less than 0.400 μm in size [23]. This is similar in size to that described for cobalt chromium and titanium wear particles retrieved from total hip replacements [24]. Histology observations of the tissues in this study revealed high content of metal debris, macrophages and even necrosis areas, which are often observed as an adverse inflammatory reaction of tissues to excessive metal debris after total hip replacements [25]. Based on these findings it might be assumed that high concentrations of titanium and vanadium ions in tissues surrounding sliding spinal implants LSZ-4D might possibly be the reason for such clinical manifestations as seromas and sinuses, some of which require surgical revision.

Based on the results of this study, which revealed increased content of Ti and V ions in the blood of 90% of patients in the study group, high levels of metal content in the tissues around sliding device and cases of clinical complications like seromas and sinuses, it might be concluded that the additional efforts for improving the wear performance of growth guidance sliding instrumentation are necessary in order to fully exploit the benefits of such instrumentation. Since the biocompatibility of Ti is much higher compared to Co and Cr, which are present in CoCr and stainless steels, it might be hypothesized that the optimization of titanium instrumentation design and improvements in its wear resistance by the application of biocompatible wear resistant coatings would certainly be beneficial.

Limitations of the study.

The limitation of this study is that our results are from a specific sliding device which has been used clinically. Although this device utilizes similar materials to those used in other spinal instrumentation the volume of wear debris released will be dependent upon the design and the way the rods are fixed. Nevertheless, our findings indicate the importance of using wear resistance materials for sliding and extending instrumentation which is used for the treatment of scoliosis in immature patients. It also indicates that replacement of the sliding and possibly extending devices in the spine after the completion of growth would be important as continual small cyclic movements may generate significant wear particle that have the potential to be problematic.

Conclusions. 5 of 25 patients with implanted growth guidance sliding LSZ-4D devices made of titanium alloy Ti6Al4V developed metallosis associated complications. Two patients had sinuses and three had seromas in the lumbar part of the spine. Content of titanium and vanadium ions in the whole blood of 90% of patients with implanted LSZ-4D devices was increased compared with control group (2.8 and 4 times respectively) but did not exceed values reported previously in literature for fusion spinal instrumentation. Median content of titanium ions in soft tissues adjacent to implanted sliding device was measured to be more than 1,500 folds higher compared with control group,

which are much higher levels than previously reported for spinal instrumentation. No statistically significant difference in metal ion content in blood (power 0.60 for Ti and V ions) was revealed in patients with and without metallosis associated complications. Our findings imply that either the use of wear-resistant coatings on titanium alloy sliding devices or the use of a different material for such instrumentation would be beneficial.

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Figure captions

Figure 1. Illustration of LSZ-4D sliding growth guidance device. Locked fixture is used at one spinal level. Unlocked fixtures are used at distal and proximal end of the device enabling sliding and continued spinal growth

Figure 2. Content of titanium, aluminum and vanadium measured using ICP-MS in the whole blood of patients for control group of patients (without implants) and study group (with implanted sliding LSZ-4D device for 6±2 years). Box lengths represent the interquartile range (first to third quartiles). The line in the center of the boxes shows the median value. Data indicated by "o" are outliers (being more than 1.5 to 3.0 times the interquartile range over the third quartile), and data flagged by "*" are extreme values (more than 3 times the interquartile range over the third quartile).

Figure 3. The intraoperative photograph shows the black discoloration of tissues in the lumbar part of the spine after disassembling of the sliding LSZ-4D instrumentation at routine surgery to exchange this device with traditional fusion instrumentation when the child became skeletally mature (patient did not have any complications)

Figure 4. Content of titanium, aluminum and vanadium measured using ICP-MS method, in the soft tissues directly adjacent to fixture-rod junction in the

lumbar part of the spine for study group of patients (with implanted sliding LSZ-4D device for 6±2 years) and control group (without implants)

Figure 5. Histology analysis of tissues surrounding LSZ-4D sliding device from patient without complications (A) and from patient developed seroma accompanied with elevated body temperature and increased erythrocyte sedimentation rate in the blood (B) showing densely stained tissue and macrophages (yellow arrows) and areas of necrosis (green arrows)

Table 1. Clinical information and metallosis related complications observed in the study group of patients with implanted LSZ-4D sliding devices

Patient N	Gender	Age at impla n-n	Number of operated levels	Lenke scoliosis type	Implantation time, years and months	Metallosis related complications
1	Female	13	14 (T2-L4)	IIBN	5y 10m	
2	Female	12	10 (T4-L2)	IIBN	3y 6m	
3	Male	10	10 (T2-T12)	IA+	3y 6m	
4	Female	11	13 (T2-L3)	IIBN	5y	Fistula with inflammation (5 years after surgery)
5	Female	12	14 (T2-L4)	IIIBN	10y 1m	Seroma, paleness, elevated body temperature, weight loss (10 years after surgery)
6	Female	11	14 (T2-L4)	IIICN	5y	Seroma (1 year after surgery)
7	Female	13	14 (T3-L5)	IIICN	5y 5m	Seroma, fistula without inflammation (2 years after surgery)
8	Female	12	14 (T2-L4)	IIBN	6y	Seroma (6 months after surgery)
9	Female	12	15 (T2-L5)	IIIBN	10y	
10	Female	13	14 (T2-L4)	IIICN	6y	
11	Female	10	14 (T2-L4)	IIIBN	3y 6m	
12	Male	13	15 (T2-L5)	IIICN	8y 3m	
13	Female	11	16 (T1-L5)	IVCN	6y 3m	
14	Male	13	15 (T2-L5)	IIIBN	5y 4m	
15	Female	10	14 (T2-L4)	IIIBN	7y 4m	
16	Female	13	14 (T3-L5)	IIICN	8y 2m	
17	Female	10	14 (T2-L4)	IIICN	4y 2m	
18	Female	12	14 (T2-L4)	IIIBN	5y 6m	
19	Female	11	10 (T4-L2)	IIBN	4y 2m	
20	Female	10	14 (T2-L4)	IIIBN	5y 6m	
21	Female	11	14 (T3-L5)	VCN	5y 6m	
22	Female	10	14 (T2-L4)	IIBN	4y 6m	
23	Female	12	14 (T2-L4)	IIBN	5y 1m	
24	Female	11	15 (T2-L5)	IIICN	4y 1m	
25	Female	10	10 (T2-T12)	IBN	5y 3m	

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