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Olfaction and Colour Vision: What Can They Tell Us about Parkinson's Disease?

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Abstract: Parkinson's disease is a neurodegenerative disorder with the pathological accumulation of alpha synuclein in the brain and peripheral nerve tissue. Early stages of synucleinopathies, often present clinically with rapid eye movement (REM) sleep disorder (RBD). Clinical markers that indicate early progression from RBD to manifest synucleinopathies include abnormal dopamine transporter (DAT) imaging, motor and non-motor symptoms. Despite the high diagnostic strength of DAT imaging and motor abnormalities, they are not the earliest biomarkers. Non-motor signs of neurodegeneration such as colour vision and olfaction abnormalities are detectable by clinical examination as early as 20 years before disease onset. Detailed analysis of olfactory and colour vision dysfunction can provide valuable information regarding brain pathologies, further specifying clinical phenotypes, and giving clues to underlying pathophysiological mechanisms in Parkinson's disease and related disorders.

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Introduction

Parkinson's disease (PD) belongs to the synucleinopathies, distinct neurodegenerative syndromes that are associated with progressive aggregation of alpha-synuclein in the nervous system. This group of disorders includes, additionally to PD, dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) (Spillantini and Goedert, 2000). PD was first described by James Parkinson in 1817, however the histopathological abnormalities of PD were found almost 100 years later. In 1912, Friedrich Lewy discovered large eosinophilic neuronal kidney-shaped inclusions and thread-like structures now known as Lewy bodies and Lewy neurites respectively (Goedert et al., 2013).

Neurodegeneration in PD, DLB and MSA is linked to the process of accumulation of pathological alpha-synuclein aggregates, described by Friedrich Lewy in the brain, forming cytoplasmic inclusions in the central and peripheral nervous systems (Marques and Outeiro, 2012). Current research suggests that the spread of alpha-synuclein pathology in the nervous system may occur in a prion-like process (Bernis et al., 2015). This theory is supported by several animal and cell culture studies, as well as, neuropathological findings in transplanted fetal grafts (Halliday et al., 2011). The theory supports the notion that the synuclein pathological molecular template spreads inter-synaptically along neurons. On the other hand, different hypotheses about alpha-synuclein propagation have been postulated including neuroimmune activation, injury response, and aberrant proteostasis (Uchihara and Giasson, 2016).

Alpha-synuclein pathology is present years or decades before affected subjects fulfil clinical criteria for a particular synucleinopathy syndrome. This pathology is mirrored by mild clinical abnormalities such as isolated rapid eye movement (REM) sleep behaviour disorder (RBD), hyposmia, autonomic dysfunction including constipation and orthostasis, minor motor impairment manifested as speech changes and impaired dexterity and abnormalities on dopamine transporter (DAT) imaging (Postuma and Berg, 2016). Based on these symptoms, the prodromal stage of synucleinopathies was defined (Mahlknecht et al., 2015). From these abnormalities, RBD is a biomarker with by far the strongest association with synucleinopathies. It was discovered in 1986 by Schenck et al. and was thereafter classified as a parasomnia. A strong link between RBD and synucleinopathies was not unveiled until several decades later. In 1996, it was demonstrated that patients with RBD progressively convert to parkinsonism and this discovery opened a new period in synucleinopathy research (Schenck et al., 2013).

The initial clinical symptoms in prodromal PD and later in clinically established PD are in concordance with the pathological staging put forward by Braak et al. (2003). According to this theory, alpha-synuclein pathology initially affects the most vulnerable long unmyelinated nerve fibres of the autonomic nervous system and the anterior olfactory nucleus, later proceeding to the brain stem and olfactory bulb, and finally reaching the mesocortex, association and primary sensory-motor

cortical areas (Braak et al., 2003). Olfaction dysfunction, constipation, RBD as well as a combination of other motor and non-motor symptoms form the diagnostic criteria for prodromal PD. Colour vision abnormalities are like olfactory dysfunction present several years before the onset of PD (Postuma et al., 2011). These markers can alert us to an early disease process, years before PD diagnosis, providing a unique opportunity to better understand the pathogenesis of synucleinopathies.

Synucleinopathies: Clinical presentation and diagnostic criteria

The main clinical symptom of synucleinopathies is parkinsonism, its responsiveness to levodopa and the presence of other symptoms helps in distinguishing the main three clinical syndromes.

The essential diagnostic criterion for PD is the presence of parkinsonism, which is defined as bradykinesia plus rigidity and/or tremor. In addition to these cardinal motor symptoms, diagnosis of clinically established PD requires absence of absolute exclusion criteria such as cerebellar dysfunction or vertical gaze palsy, absence of red flags such as rapid progression of gait impairment, no progression for five years, or early bulbar dysfunction, and presence of at least two supportive criteria. The latter are positive features that increase confidence of the PD diagnosis; olfactory loss is one of them (Postuma et al., 2015a).

Recently, diagnostic criteria for prodromal PD, understood as the disease stage before overt motor syndrome manifestation, has become available. These diagnostic criteria include non-motor features such as RBD, constipation and other symptoms of autonomic dysfunction, daytime sleepiness, depression, and abnormal DAT imaging (Berg et al., 2015).

The diagnosis of probable DLB requires progressive cognitive decline affecting predominantly attention, executive function, and visuoperceptual abilities along with at least two from the core features: profoundly fluctuating cognition, parkinsonism, RBD, and recurrent visual hallucinations. Supportive clinical features include sensitivity to antipsychotics, postural instability, repeated falls, syncope, autonomic dysfunction, hypersomnia, delusions, apathy, depression, anxiety, and hyposmia (McKeith et al., 2017).

MSA is a sporadic, progressive disorder with onset of symptoms after 30 years of age. The diagnosis of probable MSA requires the following abnormalities: autonomic dysfunction and a levodopa poorly responsive parkinsonism or a cerebellar syndrome (Gilman et al., 2008). Apart from the listed core criteria, there are also supportive criteria including severe dysarthria, dysphonia and dysphagia, postural abnormalities such as camptocormia or antecollis, inspiratory sighs and snoring. Contrary to PD and DLB, there are distinctive MRI signs, which can be used to support the diagnosis of MSA; these include atrophy of the putamen, middle cerebellar peduncle, and the pons along with T2 signal abnormalities including posterior putaminal hypointensity, middle cerebellar peduncle hyperintensity,

and the hot cross bun sign in the pons (Brooks et al., 2009). Of note, hyposmia is uncommon in MSA; RBD frequently occurs in MSA but is not mentioned in the diagnostic criteria.

REM sleep behaviour disorder: Clinical presentation, diagnosis

RBD is a parasomnia disorder manifesting with a loss of physiological atonia in REM sleep and dream enactment. To diagnose RBD, following the International Classification of Sleep Disorders (3rd edition), there must be vocalizations and/or complex motor behaviours during REM sleep on videopolysomnography or as part of the patient history. In order to identify REM sleep with loss of physiological atonia, polysomnography must be performed (American Academy of Sleep Medicine, 2014).

RBD manifests frequently in PD, LBD, MSA, and in narcolepsy. Rarely, RBD can be caused by focal brain lesions and neuroimmune diseases (Manni et al., 2011). In such cases, where a disease mentioned above is present, RBD is referred to as secondary. In the absence of a demonstrable disorder causing RBD, this disorder is considered as idiopathic (iRBD) (Ferini-Strambi et al., 2014a).

Idiopathic REM sleep disorder: Phenoconversion to clinically manifest synucleinopathy syndromes

In 1996, the first iRBD prospective study investigated 29 patients in Minnesota. Initially, the phenoconversion to clinically manifest synucleinopathy syndromes was found to be 38% following a mean interval from RBD symptoms to neurodegeneration of 3.7 years (Schenck et al., 1986). Several years later in 2013, further follow up showed an even higher 81% conversion rate after up to 29 years, with a mean conversion time of 14 years after iRBD onset (Schenck et al., 2013).

Another prospective cohort of iRBD encompassing 174 patients was followed between 1991 and 2013 in Spain. The median age at diagnosis of iRBD was 69 years, with a median conversion time of 11 years to a manifest neurodegenerative disorder (Iranzo et al., 2014). Interestingly, like in previous studies, there was a large variation in the conversion interval from iRBD to a defined synucleinopathy syndrome; in some cases, it took as little as 2 years, while in others it took up to 24 years from symptoms onset. This variation encouraged a closer analysis of the differing phenotypes of individual iRBD patients in attempt to assess the probability of early phenoconversion. To compare the integrity of the nigrostriatal pathway in iRBD patients and controls using DAT imaging techniques, the uptake of Ioflupane was measured in a 3-year time frame. Patients with iRBD had lower Ioflupane uptake compared to controls, moreover only patients in the iRBD group converted to PD (Iranzo et al., 2011).

In Canada, a further 10-year prospective study of 89 patients with iRBD was published in 2015. In this cohort, the total conversion to a neurodegenerative synucleinopathy was 66% after 7.5 years. In this study, several symptoms including

olfactory dysfunction, cognition, depression, anxiety and sleep problems were analysed as markers of phenoconversion. From this analysis, it emerged that hyposmia, a higher age, colour vision dysfunction and motor abnormalities increase the risk of early phenoconversion to synucleinopathy in patients with iRBD (Postuma et al., 2015b). Patients taking anti-depressants with iRBD displayed a lower rate of synucleinopathy conversion, nevertheless they still displayed neurodegenerative symptoms, indicating that antidepressants may unveil iRBD at an earlier stage of the same neurodegenerative process (Postuma and Montplaisir, 2014).

In China, a prospective study of 43 patients with iRBD showed a phenoconversion of 42% to a synucleinopathy after a median interval of 10.5 years from symptom onset. Patients with higher scores on the Nonmotor symptoms questionnaire (NMSQ), higher scores on Scale for Outcomes in Parkinson Disease-Autonomic (SCOPA-AUT) and a lower uptake of the DAT binding substrate in the left striatum had a significantly shorter neurodegeneration free survival time. Among specific non-motor symptoms, constipation and olfactory dysfunction increased the risk of phenoconversion, but the results were not statistically significant, possibly because of the small sample size (Li et al., 2017).

So far, there has been a lack of studies evaluating the phenoconversion of iRBD to synucleinopathies in the central and eastern European Slavic population. According to our own data, median age of iRBD symptoms onset was 62 years in a retrospective cohort of 34 Czech subjects with iRBD. In this cohort, the median conversion time to parkinsonism or dementia was 5 years (ranging from 1 to 27 years) from the diagnosis (Peřinová et al., 2018). Further studies are required to evaluate the Czech iRBD population with greater accuracy.

Taking into account the above discussed studies, iRBD has been proven to represent a considerable risk for developing a neurodegenerative disorder. Once iRBD is diagnosed, there are no validated scales to monitor iRBD progression. Thus, the intensity of iRBD symptoms is not easily quantifiable, moreover, the severity apparently fluctuates over years. However, drawing from recent iRBD studies, there are several biomarkers, which indicate increased likelihood of conversion to neurodegeneration. These signs include: abnormal DAT imaging, autonomic symptoms, mild motor symptoms including speech abnormalities, hyposmia and colour vision dysfunction (Iranzo et al., 2011; Postuma et al., 2011; Ferini-Strambi et al., 2014b; Rusz et al., 2016). The following part of this article, covers current knowledge and unresolved questions on olfaction and colour vision as markers of neurodegeneration in synucleinopathies.

Olfaction: Clinical correlates, methods of investigation, progression of hyposmia in synucleiopathies

Olfaction is the ability to process chemosensory information. The olfactory pathway consists of the olfactory epithelium, nerve and bulb. This pathway

contributes information to the thalamus, hippocampus, orbitofrontal cortex, amygdala and, hypothalamus; structures indispensable for numerous functions such as homeostasis and sleep regulation (Purves, 2004).

Hyposmia is defined as a reduced olfactory function, anosmia represents total loss of olfactory function. The cause of olfactory dysfunction can be divided into obstructive affecting nasal and paranasal sinuses, sensory olfactory loss involving impairment of nerve endings or receptors, and neural olfactory loss attributed to dysfunction of structures from the bulb to primary olfactory cortex. Therefore, an abundant number of causes may result in olfactory dysfunction including allergic disorders of nasal and paranasal sinuses, head traumatic injury, medications, radiotherapy, surgical procedures, psychiatric diseases, intracranial tumours, metabolic disorders, endocrine disorders, infections, intracranial vascular disorders, and neurodegenerative disorders (Doty, 2005).

Along with increasing age, there are corresponding olfactory changes resulting in reduced capacity of odour identification and discrimination. It is therefore essential in clinical studies to compare patients to age equivalent healthy controls.

The most widely used commercially available tests to objectively examine olfaction include, the University of Pennsylvania smell identification test (UPSIT) and the Sniffin' test. The UPSIT entails 40 multiple choice questions, where the patient is asked to identify the encapsulated smell released by scratching the surface with a pen (Doty et al., 1984). The Sniffin test has two versions one with 16 and another with 12 multiple-choice questions. Although it has a lower reliability, it is less time consuming in a clinical setting. There are various other tests available to evaluate olfaction and conversion tables have been produced to compare attained olfactory data (Lawton et al., 2016).

Hyposmia in PD has a high prevalence, affecting 90% of patients (Doty, 2012). Through the olfactory bulb, the first cranial nerve provides a direct pathway from the periphery to cholinergic and adrenergic systems implicated in the pathophysiology of neurodegenerative disorders. Despite the high sensitivity of hyposmia for alpha-synucleinopathies, it can occur in non-neurologic conditions limiting its specificity for diagnosis of prodromal neurodegeneration. As a result, olfaction abnormalities necessitate combination with other more specific biomarkers such as RBD. In a 64 iRBD patient cohort, the 5-year Kaplan-Meier disease free survival in patients with normal olfaction was 86% but only 35% in those with hyposmia (Postuma et al., 2011). This is significant, because it aids in the early identification of patients that are at a higher risk of conversion to manifest synucleinopathies. In a further prospective study of patients with newly diagnosed PD, 46% of those with hyposmia developed dementia, compared to patients without initial hyposmia in whom dementia was only diagnosed in 21% (Domellof et al., 2017). This indicates that hyposmia may be a symptom of a more severe or distinct PD phenotype. Patients with severe olfactory dysfunction, compared to those with a less severe olfactory dysfunction, were in the group of patients

that showed the greatest cognitive decline in a further study. Neuroimaging data supported these findings; in the group of patients with the most severe hyposmia there was marked metabolic reduction in the posterior cingulate, precuneus, medial occipital and parieto-occipital-temporal cortex (Baba et al., 2012). In contrast, normosmic patients with PD have a varying phenotype, with less severe motor deficits and a younger age of onset than patients with olfactory dysfunctions (Lee et al., 2015).

Limited data on olfactory function is available in patients with LBD. Studies evaluating this cohort of patients have found significant olfactory dysfunction. Lewy bodies, in LBD, are widespread throughout the brain including the limbic and cortical areas. This is accompanied with an olfactory deficit similar to that in PD suggesting that the olfactory pathway is severely affected as part of the pathophysiological disease process. In MSA, a marginally lower olfactory function compared to controls has been described. Despite this, in MSA the extent of the olfactory dysfunction does not appear to exceed moderate impairment. This could indicate that the pathological progression in MSA does not differ in propagation, but affects some brain regions to a greater extent, prevailing for example in the brainstem and the cerebellum (Doty, 2012).

According to a recent study, longitudinal follow-up of olfaction in patients with progressive neurodegeneration did not show worsening of olfactory function (Iranzo et al., 2013). This counterintuitive result suggests that despite identifying patients at a higher risk of conversion, olfactory function is not a useful marker for monitoring disease progression. Supplementary studies with longer follow-up are required to assess olfactory dysfunction progression in iRBD and in synucleinopathies to confirm whether olfactory loss reaches a plateau long before neurodegeneration affects other neural structures.

Colour vision: Clinical correlates, method of investigation, progression of colour vision in synucleiopathies

Colour vision is the ability to identify the four basic colours known as pure hues: red, yellow, green, and blue as well as the colour variations obtainable from them. Colour vision is made possible by the trichromatic system of cone cells. In this system, differing photopigments in each subtype of cone cells detect colours of different wavelengths, namely blue, green and red light sensitive cones (Purves, 2004). Dysfunctions in colour detection and processing can occur at any stage from the ocular apparatus to the visual cortex, rendering a vast number of possible pathologies, divided into acquired and congenital disorders.

Congenital colour vision abnormalities affecting cone cells are classified according to the type of deficient cells. Most congenital deficiencies are inherited in an X-linked recessive fashion and, therefore, are more common in men, affecting 8% of males and 0.5% females in studied populations. There is usually little lifetime variation and both eyes are affected equally. On the other hand, acquired colour

vision abnormalities may progress or regress and often do not only affect cone cells. Acquired colour vision abnormalities occur in glaucoma, diabetic neuropathy, optic neuritis and PD among some causes (Simunovic, 2016).

Colour vision tests can be split into: pseudoisochromatic plate tests and matching tests, both useful in the diagnosis of congenital colour blindness, arrangement tests for grading colour deficiencies and naming tests which are mostly used in an occupational setting. To assess acquired colour vision deficiencies, an arrangement test, the Farnsworth-Munsell 100-hue test (FM100) is widely used, as it is able to detect subtle differences in colour vision abilities. In this test, there are 4 sets of caps and in each set the patient attempts to order the caps according to hue (Dain, 2004).

In PD loss of dopaminergic cells in the substantia nigra represents the neuropathological hallmark of the disease, but, notably, other parts of the central nervous system (CNS) including the retina and visual cortex undergo neurodegenerative changes (Armstrong, 2015; Normando et al., 2016). Colour discrimination has been shown to be impaired in PD patients (Muller et al., 1998). Despite this, it remains unclear how retinal function is related to substantia nigra dopamine deficiency and whether and to what extent are retinal dopaminergic pathways affected in PD (Willis and Freelance, 2017). In a study employing optical coherence tomography, it has been shown that retinal thickness is not altered in PD patients with or without visual hallucinations compared to healthy controls (Kopal et al., 2015). In RBD, colour vision abnormalities appear at least 5 years before the onset of parkinsonism and/or dementia. When comparing patients with colour vision abnormalities and without colour vision abnormalities in an iRBD cohort, the Kaplan-Meier 5-year disease free survival was 70% in those with normal and 26% in those with abnormal colour vision (Postuma et al., 2011). Chromatic discrimination using the FM100 worsened over time in a PD patient cohort, showing a progressive worsening in line with ongoing neurodegeneration (Diederich et al., 2002). Interestingly, an early PD patient cohort did not show consistent changes in colour discrimination compared to controls, thereby indicating that colour vision abnormalities may represent a specific PD phenotype (Vesela et al., 2001).

A study of PD patients investigated the relationship between cognitive impairment, colour discrimination dysfunction, and anatomical magnetic resonance imaging. A strong link was found between cognitive impairment and alterations of posterior white matter that belongs to the visual processing pathway. Specifically, the white matter pathologies were located in the superior longitudinal fasciculus, right fronto-occipital fasciculus, the splenium, the inferior longitudinal fasciculus and the posterior body of the corpus callosum (Bertrand et al., 2012). These findings provide further insight into the mechanism of colour vision dysfunction, which does not appear to be limited to the visual apparatus. Colour discrimination dysfunction thus signals a widespread disease process, affecting posterior white

matter. Visual hallucinations in LBD could be explained by the widespread presence of Lewy bodies, including in these posterior white matter locations.

By summarizing these findings, some studies show that, not only do colour vision changes appear a considerable time before the onset of clinically apparent motor or cognitive changes, but also indicate a worse disease prognosis. The examination of the progressive relationship between colour vision, visual hallucinations and cognitive decline, as well as disease progression, in PD and other synucleinopathies, should be a focus of further studies.

Conclusion

A wide array of biomarkers, have been proven to precede the clinical manifestation of PD and other synucleinopathies. iRBD is the strongest predictor of future clinically manifest neurodegenerative disorder and using other biomarkers, we can further stratify iRBD patients with respect to the risk of early phenoconversion. Clinical markers that increase the likelihood of progression from iRBD to synucleinopathies include decline of tracer uptake on DAT imaging methods as well as motor and non-motor symptoms. Despite the high diagnostic strength of DAT imaging and subtle motor abnormalities, they are not the earliest biomarkers. Non-motor signs of synucleinopathy such as colour vision and olfaction impairment are detectable by clinical examination several years before disease onset.

The timely selection of patients that are at the highest risk of future neurodegeneration allows us to identify and monitor patients that would benefit the most from neuroprotective drugs once they become available. In conclusion, olfaction and colour vision testing can help us select patients with iRBD that are at greatest risk of phenoconversion to PD and other synucleinopathies. An advantage of monitoring these non-motor symptoms is their much earlier time onset compared to other markers of neurodegeneration. Detailed analysis of olfactory and colour vision dysfunction can provide valuable information regarding brain pathologies, further specifying clinical phenotypes, and giving clues to underlying pathophysiological mechanisms in PD and related disorders.

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Anorectal Malignant Melanoma: Retrospective Analysis of Six Patients and Review of the Literature

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Abstract: Malignant melanomas are rare aggressive tumours originating from the pigment-producing melanocytes. In our study, a review of the literature and a retrospective analysis of patients undergoing surgery at our clinic due to anorectal malignant melanoma were performed. The information of 6 patients undergoing surgery in our clinic due to anorectal malignant melanoma between January 2010 and January 2018 was retrieved retrospectively. The patients were assessed regarding demographic data, physical examination and imaging findings, the surgical method performed, postoperative complication, histopathological findings, oncological treatment and follow-up results. Four of the patients were female and 2 were male and the mean age was 61.6 (46–83) years. Two patients (33%) had liver metastases at the time of initial presentation. Abdominoperineal resection (APR) was performed in all patients 3 with laparoscopic method. The mean length of hospital stay was recorded to be 6.5 ± 1 days (5–12 days). Adjuvant chemotherapy and radiotherapy were administered in all patients. Also, interferon treatment was administered in one patient additionally. During the follow-up, 4 patients died due to extensive metastatic disease determined approximately in the 13th month. Two patients with regular follow-up are well and free of disease and their mean postoperative lifetime has been determined to be 12.5 months (6–26 months). Anorectal malignant melanomas (ARMM) are rare but aggressive tumours. The treatment should be focused on minimizing morbidity and maximizing the quality of life and function while removing the gross tumour.

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Introduction

Malignant melanomas are rarely seen aggressive tumours that arise from the pigment-producing melanocytes. The most common sites of malignant melanoma is the skin, followed by eyes and the anorectal region (Bolivar et al., 1982; Ceccopieri et al., 2000). Anorectal malignant melanomas (ARMM) have been described for the first time by Moore in 1987 and they account for 0.2–3% of all malignant melanomas and 0.1–4.6% of all rectal malignant tumours (Ojima et al., 1999; Damodaran et al., 2008). It is usually seen in the 5th and 6th decades in the adults and the females are affected much more than the males (Che et al., 2011). Usually, they nearly always cause similar symptoms of rectum cancer such as rectal bleeding, change in bowel habits, anal mass. Since ARMM is not sensitive to radiotherapy and chemotherapy, these treatment methods have a limited use. Surgical resection is the main therapeutic method for ARMM. Due to the delay in diagnosis and aggressive course of ARMM, approximately 26% of the patients have metastatic disease at the time of diagnosis. Therefore, the prognosis of ARMM is poor (Thibault et al., 1997). Since the incidence of the disease is low, studies related to ARMM are insufficient. Relevant information in the literature is usually as case presentation and case series. In this study, a review of the literature and a retrospective analysis of patients undergoing surgery at our clinic between 2010 and 2018 due to anorectal malignant melanoma were performed.

Material and Methods

The patients with anorectal malignant melanoma undergoing surgery at our Department of General Surgery between 2010 and 2018 were included in the study. The data of the patients were retrieved retrospectively and their demographic data, physical examination and imaging findings, the surgical method performed, the number of lymph nodes resected, histopathological findings, the length of hospital stay, morbidity and mortality, the presence of local recurrence or metastasis, follow-up results were assessed.

During the preoperative period, detailed histories of all patients were obtained, and their physical examinations were performed. Blood tests, posterior-anterior chest graph, serum carcino-embryonic antigen was routinely performed. Invasion to the surrounding tissues and distant metastasis of the tumour were assessed by using contrast-enhanced thoracoabdominal computed tomography (CT) and pelvic magnetic resonance imaging (MRI). Each patient diagnosed before surgery was referred to the relevant departments for an appropriate preoperative ophthalmologic and dermatological evaluation.

Results

Six patients have been operated due to anorectal malignant melanoma between January 2010 and January 2018. Four of patients (66.6%) were females and 2 of

Table 1 – Demographic and clinical characteristics of patients

No.	Age	Gender	Complaint	Distant metastasis/metastatic lymph node at the time of diagnosis	Surgery	Resection margin	Harvested/ positive lymph node	Complication	Adjuvant treatment	Follow-up/ outcome
1	46	F	rectal bleeding	–	APR	negative	2/11	–	dakarbazin	21 months/ exitus
2	52	F	rectal bleeding + pain	liver	APR	negative	25/26	–	dakarbazin	8 months/ exitus
3	83	M	rectal bleeding	lymph node	lap. APR	negative	7/13	–	temozolamid + ipilimumab + RT	11 months/ exitus
4	59	M	rectal bleeding	lymph node	lap. APR	negative	5/11	–	temozolamid + ipilimumab + interferon	26 months/ alive
5	70	F	rectal bleeding	liver	APR	negative	4/10	SSI	temozolamid + RT	11 months/ exitus
6	60	F	rectal bleeding + pain	–	lap. APR	negative	2/8	–	temozolamid + RT	6 months/ alive

lap. – laparoscopic; APR – abdominoperineal resection; RT – radiotherapy; SSI – surgical site infection; F – female; M –male

them (33.3%) were males and the mean age was 61.6 (46–83) years. All the patients had a complaint of rectal bleeding, 2 patients had a severe anal pain in addition to these findings (Table 1). The average length of the complaint was 10.75 ± 3.9 months (6–18 months). While no additional finding was determined at routine physical examination performed, an immobile, polypoid ulcerovegetative mass with ill-defined margins beginning from anoderm and extending to the lumen and partially narrowing of the lumen was determined in all of the patients in the rectal digital examination.

There was liver metastasis in 2 (33%) of 6 patients during the initial presentation. Abdominoperineal resection (APR) was performed for palliation in 2 patients determined distant metastasis in the preoperative period due to the presence of both bleeding and obstruction findings and APR was performed in other patients for curative treatment in accordance with oncological principles. Three APR procedures were performed through a laparoscopic approach. No complication was determined except a postoperative surgical site infection occurred in one patient. The mean length of hospital stay was recorded to be 6.5 ± 1 days (5–12 days). Surgical margin was reported to be intact in all specimens at histopathological examination. The mean diameter of the masses was measured to be 5.5 cm (3–7 cm) (Table 2).

A malignant tumour composed of normal colonic mucosa and afterwards tumour islands including usually fusiform cells was observed at histopathological examination (Figure 1). The tumour was composed of pleomorphic cells with large hyperchromatic nuclei, and large cytoplasm. A higher mitotic index was observed. Atypical mitoses were a striking feature. Neoplastic cells were observed to be positive for S-100 and HMB-45 and Melan A in the immunohistochemical examination (Figure 2). Adjuvant chemotherapy and radiotherapy were administered in all of the patients. Also, interferon treatment was administered in one patient additionally. During follow-up, 4 patients died due to extensive metastatic disease determined approximately in the 13th month. Two patients with

Table 2 – Histopathological features

No.	Tumour diameter (cm)	Invasion depth (mm)	Grade	Melan A	S-100 protein	Pan-keratin	HMB-45	BRAF mutation
1	3	2	2	NA	+	–	NA	NA
2	7	full thickness	4	NA	+	NA	+	NA
3	5	15	3	–	+	–	+	–
4	6	3	2	+	+	NA	+	–
5	7	3	4	+	+	–	+	NA
6	5	17	3	+	+	NA	+	–

NA – not recorded

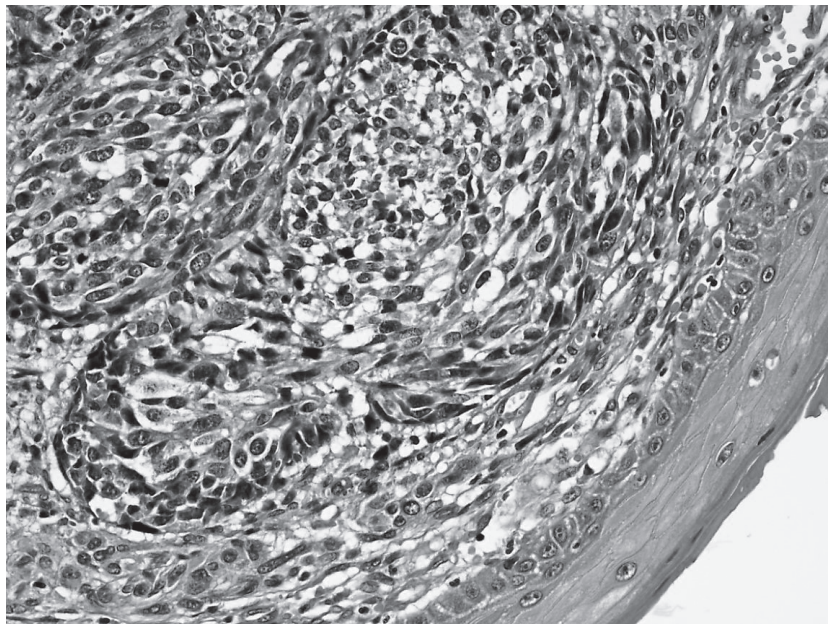

Figure 1 – Tumour observed in the subepitelial area is composed of epiteloid and fusiform-looking cells (hematoxylin-eosin, 40×).

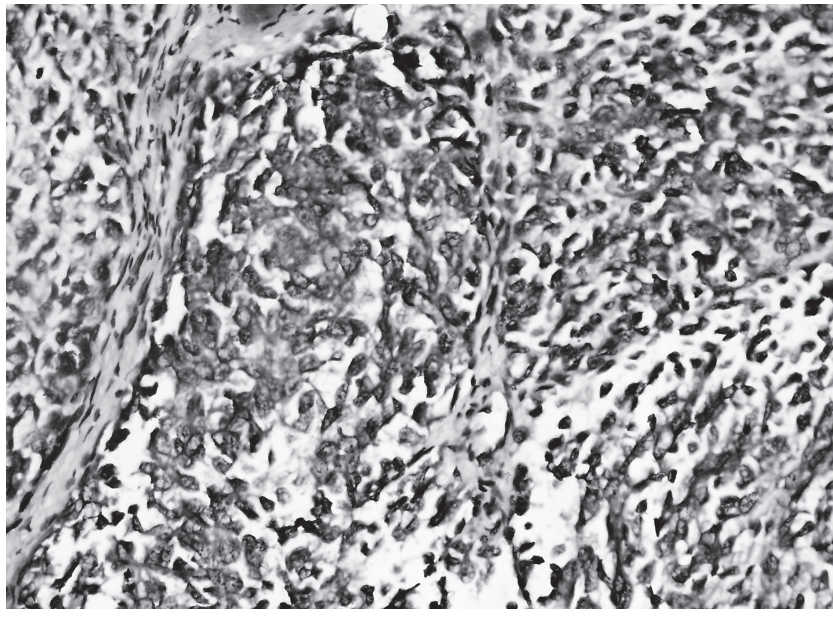

Figure 2 – HMB-45 positivity in neoplastic cells (hematoxylin-eosin, 40×).

regular follow-up are well and free of disease and their mean postoperative lifetime has been determined to be 12.5 months (6–26 months).

Discussion

While ARMMs are quite rarely seen tumours, they are most frequently located in this region of the gastrointestinal tract. They can arise from melanocytes in the non-keratinized stratified squamous epithelium below the dentate line. Although anorectal malignant melanomas are seen at any age, they have been reported to be observed usually in 50–60 years of age and most commonly in females (54% to 76%). In keeping with the literature, females are higher also in our series and the majority of our patients is in this age group. Since ARMMs have a polypoid appearance macroscopically, they can be frequently mistaken for some benign conditions such as thrombosed hemorrhoids or rectal polyps (Ceccopieri et al., 2000). While the majority of patients with ARMM have pigmented melanomas, 16–53% of the cases have amelanotic melanomas (Sielezneff et al., 1993). There is no disease specific complaint and the most common symptom at presentation is rectal bleeding (54–78%). Rectal mass (12–16%), pain (14–27%), obstipation (6%) and diarrhoea (4%) are among other symptoms (Wanebo et al., 1981; Goldman et al., 1990; Brady et al., 1995). The rectal digital examination provides information about ulceration, size, and fixation of the tumour for diagnostic evaluation. If melanin pigmentation is present clearly, rectosigmoidoscopy may support anorectal melanoma. Endorectal ultrasonography, CT, and MRI may provide valuable information in the evaluation of tumour size and presence of regional lymph node metastases. Histopathologically, ARMMs show considerable variability regarding the size and type of cells. They can mimic malignant lymphoma, small round cell sarcoma, spindle cell sarcoma, gastrointestinal stromal tumour and epidermoid carcinoma. Immunohistochemical (IHC) staining may be beneficial particularly in the patients with amelanotic melanoma where the making diagnosis is difficult. The most commonly used IHC stain in the diagnosis of ARMM is Anti-S-100 protein and it is highly sensitive for melanocytic differentiation (Chute et al., 2006). Also, HMB-45 and Melan A antibody are the stains specific for melanocytes used for diagnosis of malignant melanoma.

There are two methods used for staging of anorectal malignant melanoma. First one is the melanoma staging system of the American Joint Committee on Cancer (AJCC) and this system is based on the depth of primary tumour and tumour invasion to lymph nodes (Chang et al., 1998). In another staging system, staging is performed based on the depth of tumour invasion (stage 1, 2), regional or lymphatic metastasis (stage 3) and distant metastasis (stage 4) (Falch et al., 2013). According to the AJCC melanoma staging, 2 of our patients were stage 2, 2 of them were stage 3 and 2 of them were stage 4.

Treatment for ARMM is still controversial. Primer treatment modality is surgery. APR and wide local excision (WLE) are methods that can be chosen in the

surgical treatment. It is suggested that APR can decrease the possibility of local recurrence by means of controlling spread to the mesenteric lymph nodes and obtaining a wider negative resection margin (Damodaran et al., 2008; Choi et al., 2011). However, since APR is associated with a higher morbidity and mortality and causes a poorer quality of life due to permanent colostomy, wide local excision is preferred by some surgeons (Pessaux et al., 2004). In their study including 85 patients, Brady et al. (1995) demonstrated that APR had a better 5-year survival rate compared to WLE (27% vs. 5%) and they offered APR as a surgical method for ARMM treatment particularly in smaller tumours with no evidence of nodal metastases. Although in the study performed by Thibault et al. (1997) and including 37 patients, no significant difference was determined between WLE and APR regarding survival. Again, in the retrospective study performed by Yeh et al. (2006) comparing WLE and APR, no significant difference was determined between two groups regarding relapse and survival. Similar results were reported also by Yap and Neary (2004) in consequence of the investigation of 17 case series including 485 patients. In another recent study comparing WLE and APR, no significant difference was determined between the two groups regarding recurrence-free survival and disease-specific survival (Perez et al., 2013). Local recurrence after APR and WLE is reported to be 21–25% and 26–58%; respectively (Pessaux et al., 2004; Yeh et al., 2006; Row and Weiser, 2009). Considering local recurrence, APR seems to be a more favourable method. Also, laparoscopic abdominoperineal resection developed for the first time by Ramalingam et al. in 2009 can be used for the treatment of ARMM and it has been reported that morbidity could be reduced with this method. An APR was performed in all of our patients except 3 patients undergoing laparoscopic APR and no major complication was determined except a postoperative surgical site infection.

Sentinel lymph node biopsy (SLNB) is a method caused a radical change in the treatment and prognosis of cutaneous melanoma and breast carcinoma. Since metastasis occurs to the inguinal and mesenteric lymph nodes in ARMM, SLNB is an applicable method (Tien et al., 2002). But the efficiency of the procedure is not known. SLNB can be performed in patients with ARMM in order to determine inguinal lymph nodes not detected clinically and then to perform curative resection and accurate staging of the tumour. However, studies conducted until now are insufficient to show meaningful results. When the nodal disease is identified, complete lymphadenectomy is frequently recommended, but a significant survival difference was not determined between the patients with and without a complete lymph node dissection. The role of performing a regional lymph node dissection is controversial in the surgical treatment of ARMM. Prophylactic inguinal lymph node dissection in ARMM could not be shown to improve survival (Reid et al., 2011; Stefanou and Nalamati, 2011).

There is no established standard adjuvant chemotherapy regimen in ARMM and particularly in metastatic disease. Some agents used in malignant cutaneous

melanoma are considered to may have utility in the treatment. Although it may be stated that satisfactory results can be achieved with curative APR and adjuvant chemotherapy, there have been no randomized controlled studies performed specifically on this subject (Ishizone et al., 2008). However, administering chemotherapy alone without surgery has no benefit in the treatment (Yap and Neary, 2004). Although cytotoxic chemotherapeutic agents such as cisplatin, dacarbazine, vinblastine, vincristine, temozolomide, and interferon B, interleukin 2 are agents that can be used in adjuvant therapy, no benefit has been achieved in none of them regarding survival (Malik et al., 2002). Dacarbazine is the most frequently used agent and response to this medication is only about 20%. Adjuvant radiotherapy after surgical excision is another method that can be used in the treatment of ARMM. It has been shown that radiotherapy after local excision decreased local recurrence from 50% to 17% compared to WLE alone (Kelly et al., 2011). No benefit of radiotherapy could be demonstrated other than decreasing local recurrence. Recently, use of immunomodulatory agents in cancer treatment is increasing. Immunotherapy supports anticancer immune response. Immunochemotherapy including systemic chemotherapeutic agents and immunomodulators (IL-2) has been shown to provide partial benefit in the treatment of ARMM in some studies (Ballo et al., 2002). In our series, dacarbazine, temozolomide + ipilimumab + RT, temozolomide + ipilimumab + interferon, and temozolomide + RT were administered in 2, 1, 1 and 2 patients; respectively.

Despite all treatment methods, the prognosis of the disease is significantly poorer compared to adenocarcinoma and cutaneous melanoma located in the same region. The 5-year survival rate is less than 20% (Weinstock, 1993; Brady et al., 1995; Chang et al., 1998). Survival of recurrent or metastatic disease is less than 10 months (Weinstock, 1993; Brady et al., 1995; Thibault et al., 1997). Survival is primarily dependent on locoregional lymph nodes and distant metastasis and it is irrespective of surgical treatment method performed. The depth of tumour infiltration, the presence of perineural invasion, age greater than 60 years and a tumour size of more than 1 cm in diameter are prognostic factors (Brady et al., 1995; Cagir et al., 1999; Yeh et al., 2006; Ishizone et al., 2008). In our series, 4 patients died due to the widespread metastatic disease at a mean of 13 months. Remaining 2 patients remain disease-free at postoperative 6th and 26th months.

In conclusion, ARMMs are rare but aggressive tumours. There is no specific symptom of the disease. It should be kept in mind particularly in the patients with rectal bleeding. All available possibilities should be used for preoperative staging. Since the tumour stage is among the most important prognostic factors, early diagnosis of the disease is of vital importance. It should be focused on minimizing morbidity and maximizing the quality of life and function while removing the gross tumour in the treatment.

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Minimally Invasive Fibrin Sealant Application in Pilonidal Sinus: A Comparative Study

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Abstract: The aim of this study was to compare the filling of the pilonidal sinus tract with fibrin sealant (FS) against tract excision and primary closure (PC) as the primary procedure. Details of all patients who underwent treatment for a symptomatic first episode of pilonidal sinus disease between January 2011 and December 2015 were prospectively recorded in a custom database. Patients underwent PC (n=17) or FS (n=17) according to patient preference. Prior surgical treatment and ongoing infection precluded entry. Patients were treated with antibiotics if presenting with infection. Outcomes measured were recurrence, further procedures, outpatient attendances and length of follow-up to resolution. 34 consecutive patients [FS vs. PC: male n=15 vs. 12 p=0.398; mean age 29 (SEM 12) vs. 30 (SEM 15) p=0.849] were included. Treated preoperative infections were similar FS (n=5) vs. PC (n=12) (p=0.038, chi-squared test). FS cohort had more sinuses FS median (range) 2 (1–4) vs. PC 1 (1–3) (p=0.046). Postoperative outcomes: recurrence rate FS (n=5) vs. PC (n=4) (p=0.629); infection rate FS (n=1) vs. PC (n=8) (p=0.045); total number of operations required FS 1 (1–2) vs. PC 1 (1–4) (p=0.19); total number of outpatient attendance FS 2 (1–7) vs. PC 3 (1–16) (p=0.629); follow-up FS 129 days ± 33 vs. PC 136 ± 51 (p=0.914). Fibrin sealant is not inferior to excision followed by primary closure.

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Introduction

Pilonidal sinus is a debilitating recurring benign condition that mainly affects young adults. Its formation arises from obstruction of hair follicles in natal cleft and subsequent rupture of follicles. The estimated prevalence is 26 over 100,000 (Sondenaa et al., 1995).

There is no consensus on optimal management. Classically, treatment is by surgical excision of sinus tract. This is followed by either primary closure or leaving wound open for healing by secondary intention; neither option has been shown to be superior. It has a significant impact on patients as the traditional techniques are associated with prolonged recovery time and delay in returning to daily life (Al-Khamis et al., 2010).

Fibrin sealant has been described as an alternative to surgical techniques (Patti et al., 2006). It consists of human fibrinogen and bovine thrombin, when combined, results in a space filling clot. The sinus is curetted, and the sealant is introduced into the cavity. The resulting reduction in dead space promotes healing, negating the need for more extensive surgical procedure and its associated complications (Kayaalp et al., 2016). Recent studies have described the use of fibrin sealant resulting with improvement in recurrent rate, early return to normal activities and high level of patient satisfaction (Lund and Leveson, 2005; Patti et al., 2006; Handmer, 2012; Elsey and Lund, 2013; Lund et al., 2017).

To date, there is no data on outcomes of comparing fibrin sealant against the conventional primary closure technique in treating pilonidal sinus disease.

The aim of this study was to compare the minimally invasive filling of the pilonidal sinus tract with fibrin sealant (FS) against tract excision with primary closure (PC), as the primary procedure for patients who presented with uncomplicated pilonidal sinus disease.

Material and Methods

The study is a retrospective analysis of a prospectively maintained database.

Inclusion criteria

All patients with symptomatic pilonidal sinus disease who underwent surgical intervention between January 2011 and December 2015. Patients with associated infection received antibiotic treatment prior to procedure. Our patients were counselled regarding the treatment options, and were given the choice of either fibrin glue or primary closure. Patients' preference determined treatment modality.

Exclusion criteria

Patients who have had previous surgery for pilonidal sinus disease, or had ongoing associated infection.

Control treatment arm
Patients who underwent sinus tract excision followed by primary closure (PC) as the definitive and sole procedure, under general anaesthesia.

Fibrin sealant treatment arm
Patients who underwent sinus tract cleaning followed by filling of the pilonidal sinus tract with fibrin sealant (FS) as the definitive and sole procedure, under general anaesthesia.

Outcomes
Our primary outcomes were recurrences, total number of procedures required, number of outpatient attendances, and total length of follow-up until resolution.

Data collection procedure
All qualifying patients since 2011 were logged prospectively into department database. The database recorded procedures and outcomes. The data were retrieved and analysed retrospectively.

Statistics
Statistical analyses were conducted using SPSS® version 21 (Chicago, Illinois, USA).

Parametric data are expressed as mean and standard error of the mean (SEM). Non-parametric data are expressed as median and inter quartile range (IQR). Non-parametric unpaired data were analysed using the Mann-Whitney U test for two group comparisons. Categorical variables were analysed using the chi-squared test or Fisher's exact test. A p-value of less than 0.05 was considered significant.

Ethics
Research Ethics Committee review was not required under the harmonised GAfREC for research limited to the use of previously collected information non-identifiable by researchers outside the usual care team. This exception also applies to research undertaken by staff within the care team using information previously collected in the course of care for the team's own patients, with the proviso that data is anonymised or pseudoanonymised in conducting the research, as such research involves no breach of the duty of confidentiality owed by care professionals. (http://www.publichealth.hscni.net/sites/default/files/directorates/files/GAfREC_changes_Remit_REC_2011_08.pdf)

Results

Baseline characteristics
In total, 34 consecutive patients were included in this study. In each treatment arm, there were 17 patients. Cohorts were similar in terms of age and sex. The mean

Table 1 – Demographic

	FS (n=17)	PC (n=17)	P-value
Age (mean ± SEM)	29 ± 12	30 ± 15	0.849
Gender (male), n (%)	15 (88)	12 (71)	0.398

FS – fibrin sealant; PC – primary closure; SEM – standard error of the mean

Table 2 – Preoperative clinical profiles

	FS (n=17)	PC (n=17)	Chi-squared test
Infection, n (%)	5 (29)	12 (71)	0.038
Number of sinuses (median ± range)	2 (1–4)	1 (1–3)	0.046

FS – fibrin sealant; PC – primary closure

age was 29 (SEM 12) in the FS arm, and 30 (SEM 15) in the PC arm. Men made up 88% of patients (n=15) in the FS arm, and 71% (n=12) in the PC arm (Table 1).

The PC cohort had a higher preoperative infection rate than FS cohort (71% vs. 29%, $p<0.05$). All were treated prior to surgery. The FS cohort had more number of sinuses to be treated than PC cohort (median 2 vs. 1, $p<0.05$) (Table 2).

Outcomes

Postoperatively both cohorts had similar recurrence rate (FS 29% vs. PC 24%), but the postoperative infection rate was higher in PC cohort (FS 6% vs. PC 47%, $p<0.05$) (Table 3). All recurrent disease following fibrin sealant application were treated by lay open technique.

Table 3 – Postoperative complications

	FS (n=17)	PC (n=17)	Chi-squared test
Recurrence, n (%)	5 (29)	4 (24)	0.629
Infections, n (%)	1 (6)	8 (47)	0.045

FS – fibrin sealant; PC – primary closure

Table 4 – Postoperative follow-up

	FS (n=17)	PC (n=17)	Chi-squared test
Follow-up, days (mean ± SEM)	129 ± 33	136 ± 51	0.914
Outpatient visits (median ± IQR)	2 (1–7)	3 (1–16)	0.629
Operations needed (median ± IQR)	1 (1–2)	1 (1–4)	0.190

FS – fibrin sealant; PC – primary closure; SEM – standard error of the mean; IQR – inter quartile range

There was no significant difference in follow-up requirements. The total number of procedures, the number of outpatient attendances, and the total length of follow-up were similar in both arms (Table 4).

Discussion

Fibrin sealant application in pilonidal sinus can be used in three settings; to obliterate the dead space following primary closure; to cover open wounds following lay-open technique; and as primary treatment of sinus tracts by direct filling of sinus with sealant. In our unit, we have adopted the latter as a minimally invasive approach for uncomplicated pilonidal disease.

This study suggests that the recurrence rate between primary closure and use of fibrin sealant in patients with uncomplicated sinus disease, are comparable. In addition, the use of FS neither increases the need for further procedures and outpatient attendances, nor make follow-up longer.

A recent systematic review which included 113 patients from four studies using the same sealant technique found a recurrence rate of 20%, which is less than the current study (29%) (Kayaalp et al., 2016). However, the results of this review may not be comparable. One study recruited patients with single, noncomplicated sinus tract only (Isik et al., 2014), and another was limited by a high survey non-responder rate (Elsey and Lund, 2013). All procedures in this study were performed under general anaesthesia, whereas in the review, thirty-nine percent were performed under local anaesthesia (Kayaalp et al., 2016).

We treated all recurrent disease following fibrin sealant application with a lay-open technique. Previous studies on fibrin sealant were conducted with a small number of patients and there was no information regarding the effect of repetitive application of sealant or subsequent procedures (Kayaalp et al., 2016).

A recent Cochrane review which looked into 4 RCTs (randomized controlled trials) on the use of fibrin sealant as either a monotherapy or adjunct suggested that the benefits remains unclear (Lund et al., 2017). However, the studies included had dissimilar cohorts of patients, whereas our study was specific with standardized comparative interventions. This is an observational study looking specifically into the use of monotherapy against the traditional method. Our study did not address patients with complex pilonidal sinus disease. The key aim of our study was to explore whether fibrin sealant is suitable as the first line treatment for non-complicated pilonidal sinus disease. Even though the sample size is small in the groups, the demographics in the form of age and gender are similar and this provides a good direct comparison of both treatment options.

Conclusion

There is lack of comprehensive evidence on the use of fibrin sealant. The results from this study has shown that it is not inferior to excision followed by primary

closure. The treatment should be made available to selected groups of patients with a suitable pre-surgical profile to fully benefit from it.

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The Effect of Concurrent Tetanus-diphtheria Vaccination on the Antibody Response to Rabies Vaccine: A Preliminary Study

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Abstract: The number of studies in the literature investigating the effect of tetanus vaccination on rabies prophylaxis is rather limited. In this study, we aimed to investigate the effect of concurrent tetanus-diphtheria (Td) vaccination on the antibody response to rabies vaccine. The data of consecutive 80 patients who presented to Sakarya University Training and Research Hospital, Department of Emergency due to rabies suspected exposure between 15 October 2012 and 12 June 2013 were enrolled to this study. Postexposure rabies prophylaxis had been given to all cases, however concurrent tetanus vaccination had been administered to some of them according to their need. Cases were divided into two parts according to their receipt of tetanus prophylaxis as rabies only group (group R, n=37), and rabies and tetanus-diphtheria group (group R+Td, n=43). Rabies antibody levels were tested in sera of the cases at first and postvaccination 21st day. The median antibody levels of each group were measured and compared with each other statistically. In our study, postvaccination 21st day antibody level of

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group R was 0.68 IU/ml (IQR: 0.79), while the same for group R+Td was 0.52 IU/ml (IQR: 0.48) (p=0.022). Concurrent administration of Td vaccine was found to have a significant negative effect on the antibody response to rabies vaccine. Our results should be confirmed with further studies including more cases.

Introduction

According to the World Health Organization (WHO) data, about 60,000 people die due to rabies and more than 10 million people expose to rabies-suspected bites annually worldwide. Prophylaxis is the major priority due to the fatal outcome of the disease. Post-exposure prophylaxis (PEP) has a very important place due to life saving effect (Coleman, 2004; Shead et al., 2009; World Health Organization, 2013). In post-exposure rabies prophylaxis (PERP), four doses of vaccination administered on day 0, 3, 7 and 14 is known to provide adequate seroprotection against rabies (Manning et al., 2008; http://www.cdc.gov/rabies/resources/acip_recommendations.html).

Antibody response to rabies vaccine can be influenced by many factors such as individual's age, immunologic condition and body mass index (BMI) (Johnson et al., 2010; Banga et al., 2014). To our knowledge, there are a limited number of studies regarding the effect of simultaneous tetanus-diphtheria (Td) vaccination on rabies prophylaxis. The aim of the present study was to investigate the effect of simultaneous Td vaccination on the antibody response to rabies vaccine.

Material and Methods

In this study, retrospective data records of 80 consecutive patients who were admitted to the Department of Emergency of 400-bed tertiary care hospital of Sakarya University and given PEP between 15 October 2012 and 12 June 2013 were analysed and rabies antibody levels in previously stored serum samples were studied.

Ethical consent

Ethical consent was obtained from the Ethics Committee of Sakarya University Faculty of Medicine. Ethics committee approval number: B.30.2.SAÜ.0.20.05.04.050.01.04/41.

Inclusion and exclusion criteria

The inclusion criteria:

- Having a record in the Department of Emergency because of rabies suspected exposure in the study period and vaccinated with at least three doses of rabies vaccine

The exclusion criteria:

- Receiving immunosuppressive therapy
- Having immunosuppressive disease (e.g. AIDS)

- Being pregnant
- Having incomplete data record

Although 92 patients were included in our study initially, 12 patients were excluded due to various reasons after applying the exclusion criteria. The study was completed with the remaining 80 patients (Figure 1).

Study design

In this retrospective study, rabies suspected bites were considered as dirty wounds. Patients who received PERP were also screened for tetanus prophylaxis, so they were divided into two groups according to the simultaneous administration of tetanus prophylaxis. These groups were called as the rabies only group (group R, n=37), and the rabies and tetanus-diphtheria group (group R+Td, n=43). At the beginning of the study, it was planned to test rabies antibodies at admission and day 21. So, serum collection was prospectively done for rabies PEP cases and then these samples were retrospectively analysed for the effect of Td vaccine.

Administration of vaccines

- Purified inactivated rabies vaccine prepared on Vero cells had been administered intramuscularly to both group R and group R+Td (Abhayrab 2.5 IU/0.5 ml containing human serum albumin, maltose, thiomersal and phosphate buffer).
- Adsorbed diphtheria-tetanus vaccine with aluminium adjuvant was administered intramuscularly to group R+Td simultaneously from the opposite upper limb than that of the rabies vaccine (Td-VAC 0.5 ml including aluminium phosphate, thiomersal, sodium acetate and sodium chloride). Diphtheria-tetanus vaccine had not been administered to some of the patients who had received tetanus prophylaxis within the last five years (Advisory Committee on Immunization Practices, 2012).

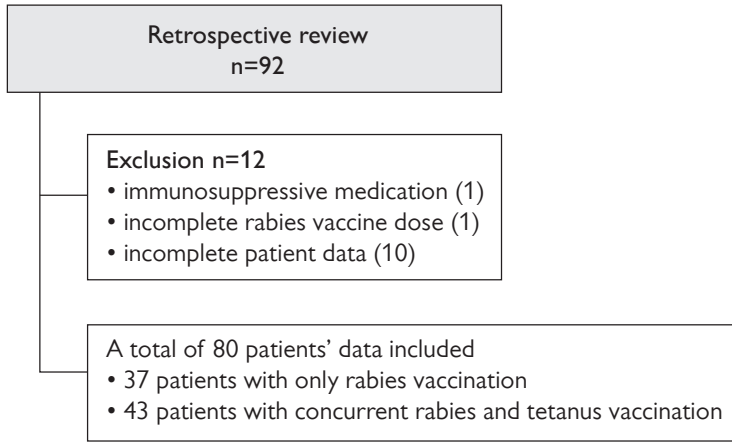

Figure 1 – Flow chart of the study.

- Additionally, immunoglobulin had been administered into and around the wounds to the patients as necessary according to the guidelines (Talan et al., 1999).
- Rabies prophylaxis had been administered by Department of Emergency nurses after skin disinfection with 70% alcohol.

Recording patient data
Demographic characteristics of the patients, locations and sizes of the bites, category of exposure, number of rabies vaccine dose, whether simultaneous tetanus prophylaxis was administered or not, BMI, smoking, comorbid diseases, species of the biting animal, vaccination status of the biting animal, post-exposure admission period, whether there was a history of rabies or tetanus prophylaxis within the last five years or not and allergy history were obtained from patient data.

Blood sampling and storage
Five ml of patient serum obtained at admission and day 21 had been stored in a freezer (–20 °C) until the study day. On the study day, serum samples were thawed at room temperature. Rabies antibody levels in these samples were measured quantitatively by microELISA method using Platelia Rabies II kit (Biorad, France) in a full automatic microELISA device (Triturus, Grifols, Spain).

Statistical methods
When continuous variables showing normal distributions were compared between the two groups, independent two sample *t*-test was used and when continuous variables not showing normal distribution was compared within the same group, Mann-Whitney U test was used. Continuous variables were shown with mean value and standard error, otherwise median value and interquartile range (IQR = third quartile – first quartile). When categorical variables were compared between the two groups, Pearson's chi-square test was used. Categorical variables were shown with number and percent. Multiple linear regression analysis was performed to determine the factors affecting postvaccination 21st day rabies antibody level. A p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed by a statistics software (IBM SPSS Statistics 20, SPSS Inc., IBM Co., Somers, NY).

Results

Patients
In our study, group R consisted of 37 patients (26 males, 11 females) and the median age in this group was 13 (IQR: 37). Group R+Td consisted of 43 patients (24 males, 19 females) and the median age in this group was 37 (IQR: 37). 53 (66.3%) patients had category II exposure, 27 patients (33.8%) had category III exposure.

Demographic characteristics

50 patients (62.5%) were male and 30 patients (37.5%) were female. The mean age was 32.9 ± 21.9. The average surface area of the bite was 5.3 ± 11.7 cm^2. Mean body weight was 61.7 ± 21.9 kg, the mean height was 1.6 ± 0.2 m and the mean BMI was 23.5 ± 5.7 kg/m^2. In total, 53 cases had category II exposure and 27 patients had category III exposure. So, 52 patients in our study had received 3 doses (0, 3, 7) and 28 patients had received 4 doses of rabies vaccine (0, 3, 7, 14).

In group R, average surface area of the bite was 6.3 ± 3.15 cm^2. The mean body weight was 51 ± 23 kg, the mean height was 1.49 ± 0.22 m, and the mean BMI was 21.52 ± 5.71 kg/m^2. Although eight patients (21.6%) in group R had comorbid disease, no patient had diabetes mellitus (DM). In this group, 25 (67.6%) patients had category II exposure and 12 (32.4%) had category III exposure. So, 26 patients had received 3 doses and 11 patients had received 4 doses of rabies vaccine.

In group R+Td, average surface area of the bite was 4.37 ± 7.33 cm^2, and the mean body weight was 71 ± 15 kg, mean height was 1.7 ± 0.1 m and the mean BMI was 25.2 ± 5.2 kg/m^2. Eight patients in this group (18.6%) had comorbid disease and three of them had DM. In this group, 28 (65.1%) patients had category II exposure, 15 (34.9%) had category III exposure. So, 26 patients received 3 doses and 17 patients received 4 doses of rabies vaccine.

In our study, the lower limit of the detection of rabies antibody level was 0.12 IU/ml and the upper limit for the same was 4 IU/ml. Values below and above these could not be determined. When the median antibody levels of the groups were measured, it was seen that postvaccination 21st day antibody level of group R was 0.68 IU/ml (IQR: 0.79), while the same for group R+Td was 0.52 IU/ml (IQR: 0.48) (p=0.022).

For defining obesity, a BMI z-score of ≥ 2 was used for patients under 18 years of age (Inokuchi et al., 2011) and a BMI of ≥ 30 kg/m^2 was used for patients over 18 years of age (World Health Organization, 2006). According to this definition, four patients in group R and eight patients in group R+Td were defined as obese.

Table 1 – Comparison of each group in itself according to seroconvertion rate

	Group R			Group R+Td		
	<0.5 (n=9)	≥0.5 (n=28)	p-value	<0.5 (n=21)	≥0.5 (n=22)	p-value
Age	10 (11.5)	18.5 (39.25)	0.065	37 (40)	38.5 (31.5)	0.855
Rabies vaccine dose	3 (1)	3 (2)	0.576	3 (2)	3 (2)	0.422
Obesity	0	4 (14.3)	0.230	3 (14.3)	5 (22.7)	0.477

Group R – rabies only group; Group R+Td – rabies and tetanus-diphtheria group

Table 2 – Factors affecting postvaccination 21st day rabies antibody level

	β	SE	95% CI	P-value
Concurrent tetanus-diphtheria vaccination	–0.255	0.103	–0.460 to –0.049	0.016
Rabies vaccine dose (three vs. four)	–0.016	0.053	–0.122 to 0.091	0.766
Gender	–0.010	0.109	–0.208 to 0.228	0.927
Obesity	0.088	0.145	–0.202 to 0.378	0.546
Smoking	0.048	0.125	–0.201 to 0.296	0.704
Comorbidity	0.025	0.100	–0.174 to 0.224	0.804
Age	0.001	0.003	–0.004 to 0.006	0.564

β – regression coefficient; SE – standard error; CI – confidence interval

Each group was separated in itself into two parts based on seroconvertion rate and comparison of the groups was shown in Table 1.

The values equal to or above 0.5 IU/ml are universally considered as protective antibody response to rabies vaccination (World Health Organization, 2013). Hence, the critical limit of protective antibody level was accepted to be ≥ 0.5 IU/ml at day 21 postvaccination. Based on the multiple linear regression analysis, factors which can affect the logarithm of postvaccination 21st day rabies antibody titers were presented in Table 2. According to this, simultaneous Td vaccination was determined as an independent factor which inversely affects rabies antibody response.

Discussion

Rabies and tetanus (in some countries Td) vaccines are often administered together. These different immunological products may have various effects on each other when administered simultaneously (Léry et al., 1986; Phanuphak et al., 1989; Moore et al., 2006). Effects of the tetanus vaccine on rabies vaccination have not been studied enough up to date. In a previous study investigating this interaction, rabies antibody response was found significantly higher when rabies vaccine was given in the same syringe with tetanus toxoid (Phanuphak et al., 1989). This was linked with the aluminium hydroxide in the tetanus vaccine which served as adjuvant for the rabies vaccine. In that study, purified Vero cell rabies vaccine and pure tetanus toxoid containing aluminium adjuvant were used. We used the same rabies vaccine [purified Vero cell rabies vaccine (Abhayrab 2.5 IU/0.5 ml)], but a different tetanus vaccine [adsorbed diphtheria-tetanus vaccine with aluminium adjuvant (Td-VAC 0.5 ml)] in our study. According to our results, simultaneous Td vaccination decreases the logarithm of postvaccination 21st day rabies antibody levels. We concluded that simultaneously administered Td vaccine had a significant negative effect on the rabies antibody response (p=0.016, 95% CI = from –0.460 to –0.049). Another important result was the fact that there was no significant difference between antibody levels obtained with three or four doses of rabies vaccine (p=0.766, 95% CI = from –0.122 to 0.091).

Immunologically, vaccines are classified as T-cell-dependent (e.g. rabies, tetanus, diphtheria, hepatitis B) and T-cell-independent (e.g. typhoid and pneumococcus) (Lang et al., 1997). Evaluating Td vaccine as an inversely affecting factor of rabies antibody levels, we believe that there may be a competitive inhibition between rabies antigens and Td toxoids since both stimulate T-dependent antibody response. Therefore, it can be possible that Td vaccine might have a negative effect on rabies antibody level. In a study conducted on infants by Lang et al. (1997), effects of simultaneous DTP-IPV (combined diphtheria, pertussis, diphtheria-tetanus, and inactivated polio vaccine) and PVRV (purified Vero cell rabies vaccine) vaccines were investigated. Eighty four infants of two-month-old were included in that study. Diphtheria immunogenicity at first month was found lower in simultaneously PVRV and DTP-IPV administered group than that of only DTP-IPV administered group. This was linked with the competition between rabies antigens and other antigens. Similarly, we believe that competitive inhibition might have affected our results.

Antibody response against vaccination may be influenced by many factors. Age, smoking and obesity are the best known factors. In vaccine antibody studies related to hepatitis B vaccination, the effects of these factors have been clearly demonstrated. Age, smoking and obesity negatively affect antibody response to hepatitis B vaccination (Ingardia et al., 1999; Sunbul et al., 2000; Mast and Ward, 2008). Age and genetic factors were previously reported to have a negative effect on the antibody response to rabies vaccination (Ceddia et al., 1982; Mastroeni et al., 1994; Kennedy et al., 2007).

Age may affect rabies vaccine antibody response. Some studies have reported a relationship between age and efficacy of rabies vaccine (Mastroeni et al., 1994; Kennedy et al., 2007; Morris et al., 2007; Robertson et al., 2010). However, age had no effect in our study (p=0.564, 95% CI = from –0.004 to 0.006). This might be caused by the fact that most of our cases composed of young population. The mean age of our patients was 32.9 ± 21.9. It is well known that immune response decreases with advanced age. Indeed, many studies have reported the inverse effect between age and vaccine response (Mastroeni et al., 1994; Kennedy et al., 2007; Morris et al., 2007). We think, our results need to be confirmed with further studies including older age groups.

In our study, rabies antibody levels were only tested at day 21 after vaccination. Of our patients, 52 (65%) had received three doses of rabies vaccine, while 28 (35%) had four doses of rabies vaccine. In a previous study, all of the subjects receiving either three or four doses of rabies vaccine were found to have adequate seroconvertion (Robertson et al., 2010). Similarly, no significant effect of rabies vaccine dose (either three or four) on the antibody response was detected in our study (p=–0.016, 95% CI = from –0.122 to 0.091). We think, this finding is valuable. If this result that we have found with a limited number of patients can be confirmed with larger study samples and if it could be possible to show that three doses of rabies vaccine was as effective as four doses by prospective studies,

then it will be possible to increase the vaccine adherence and decrease vaccination outcomes. Therefore, we suggest that further studies need to be conducted to compare the efficacy of three and four doses of rabies vaccination.

Before concluding, we need to discuss the limitations of our study. The major limitation in this study is the low number of patients. In our study, one of the groups consisted of 37 patients while the other group consisted of 43 patients. In addition, a large portion of group R+Td consisted of pediatric patients who had received Td prophylaxis within the last five years. The median age of this group was lower than that of group R. Groups would be more homogenous if we had more patients. Another important limitation was the single measurement of antibody level after vaccination. Our patients' rabies antibody levels were tested postvaccination only at day 21. It could be possible to show that the antibody levels rise above 0.5 IU/ml in more patients if it would be measured at a later date.

Conclusion

In this study on 80 patients who received PERP, we found that rabies antibody levels measured postvaccination at day 21 was not affected from age, gender, obesity, smoking, comorbid disease and number of rabies vaccine doses, but affected from simultaneously administered Td vaccine. In addition, there was no significant difference among antibody titres obtained with three or four doses of rabies vaccine. The results of our study should be confirmed with further studies including more cases.

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Cervicomedullary Ganglioglioma in a Child – A Case Report

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Key words: Ganglioglioma – Intractable seizure – Posterior fossa – Cervicomedullary junction – Spinal cord

Abstract: Ganglioglioma is a benign slow-growing neoplasm that most frequently occurs at the supratentorial region. Nevertheless, there are occasional reports of ganglioglioma occurring in the brainstem and spinal cord. Here we report a rare case of the craniocervical ganglioglioma. A 3.5-year-old male, presented with severe progressive quadriparesis, gait disturbance, and sphincter deficit. Physical examination demonstrated the quadriparesis, associated with positive Hoffman, Babinski, and clonus signs, and increased respond of deep tendon reflexes. Magnetic resonance imaging (MRI) demonstrated an ill-defined mass within medulla and upper cervical spinal cord, which was hypo to iso signal on T1, heterogeneous iso to hypersignal on T2 and demonstrated marked bright enhancement on T1 with gadolinium (Gad) injection. On surgery, the mass had a soft texture, ill-defined border, and grey to brown appearance. According to the frozen section report, and due to the absence of the tumour-neural parenchymal interference, only decompression of the tumour and expansile duraplasty were performed. The histopathology revealed ganglioglioma. On last follow-up 14 months after surgery, the patient was asymptomatic and neurological status was improved. The craniocervical MRI demonstrated the tumour that did not grow. Although it is rare, the ganglioglioma should be in the differentiated diagnoses of tumours with compatible clinical and radiologic features even in the unusual locations, especially in the pediatric and young patients. Safety surgical resection should be considered in these patients, whenever possible. In the case of partial resection, that is common in the tumours located within functionally critical structures, long close follow-up rather than radiation therapy is required.

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Introduction

Ganglioglioma (GG) is usually a benign slow-growing neoplasm that mainly affects older children and young adults (Mpairamidis et al., 2008; Park et al., 2008). GG contains both glial and differentiated ganglion cells and accounts for approximately 0.4% of all central nervous system (CNS) tumours and 1–4% of pediatric CNS neoplasms (Mpairamidis et al., 2008; Park et al., 2008). It occurs most commonly in the supratentorial region; mostly in the temporal lobe (up to 85%) and presents with a long-standing intractable seizures (Mpairamidis et al., 2008; Park et al., 2008). Nevertheless, there are occasional reports of ganglioglioma occurring in the brainstem, cerebellopontine angle (CPA), thalamus, optic nerve, and spinal cord (Shin et al., 2002; Westwood and MacFarlane, 2009). The tumour size is variable, typically between 2–3 cm in adults, and larger (typically more than 4 cm) in children (Davis and Joglekar, 1981).

Here we report a rare case of the craniocervical ganglioglioma in a child and our experience in its management.

Case report

A 3.5-year-old male, presented with severe progressive quadriparesis, gait disturbance and sphincter deficit (urine and fecal incontinence) from about 1 month ago. At first, symptoms began with paraparesis, and gradually upper limbs weakness and gait disturbance added to the initial complaint. Past medical, drug and present patient history demonstrated no positive findings. On physical examination, the muscle strength force of upper limb was 4/5 on proximal and 3/5 on distal muscles on both sides. Lower limbs demonstrated the muscle strength force of 3/5 in the proximal and 2/5 in the distal. The upper motor signs such as

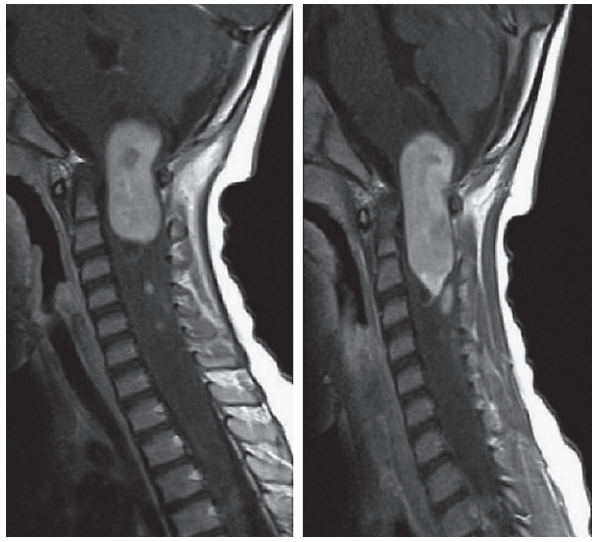

Figure 1 – The T1 with gadolinium injection image sequence demonstrates the tumour in cervicomedullary region.

Hoffman and Babinski sign, increased deep tendon reflexes (DTR), and clonus were positive on both sides. Moreover, the examination demonstrated the increased muscular tone and generalized spasticity. Magnetic resonance imaging (MRI) demonstrated an ill-defined mass within medulla and upper cervical spinal cord, which was hypo to iso signal on T1, heterogeneous iso to hypersignal on T2 and demonstrated marked bright enhancement on T1 with gadolinium (Gad) injection (Figure 1).

After whole spine and brain MRI evaluation, surgical intervention was planned. On Concord position, the head fixed on the Mayfield head holder. Suboccipital

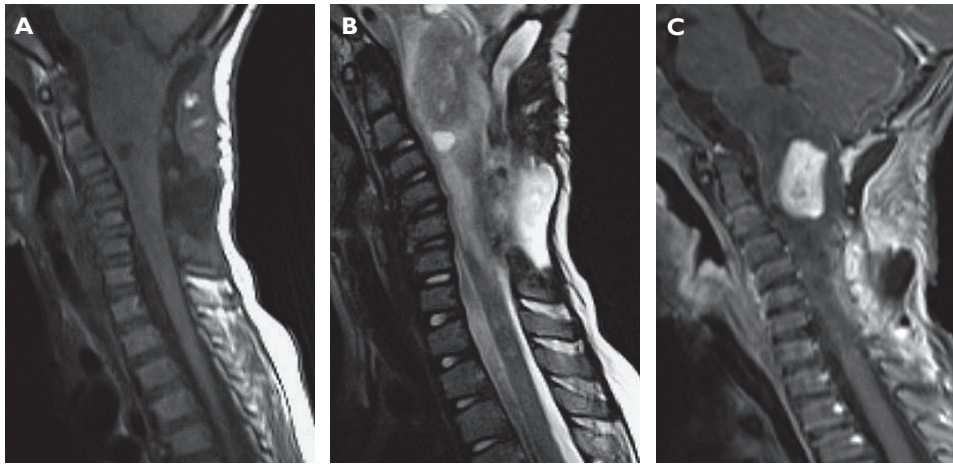

Figure 2 – The just postoperative magnetic resonance imaging demonstrates the tumour, which had only been decompressed (A – T1; B – T2; C – T1 after gadolinium injection).

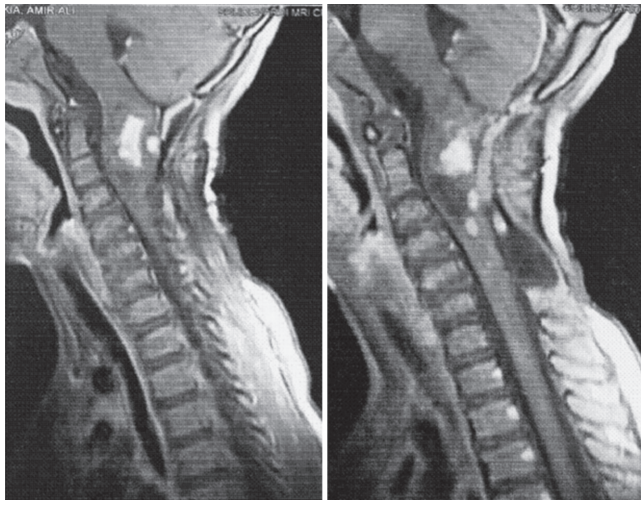

Figure 3 – The postoperative craniocervical magnetic resonance imaging fourteen months after surgery demonstrates no growth of the tumour.

craniectomy, C1 posterior arc laminectomy, and laminectomy of C2 to C6 performed. After opening the dura, posterior midline myelotomy performed. The mass had a soft texture, ill-defined border, and grey to brown appearance. A biopsy specimen sent for frozen section and reported a high-grade undifferentiated tumour. According to the frozen section report, and due to the absence of the tumour-neural parenchymal interference, only decompression of the tumour performed. Moreover, the dura was expanded via synthetic dural graft. The definite histopathologic examination was in favour of ganglioglioma (Figure 2).

After surgery, the neurological status partially improved, and the patient discharged, while he demonstrated a muscle strength force of 4/5 on all the limbs, he could to walk and showed improved sphincter control.

Due to benign nature of GG, and despite low volume surgical resection, the patient candidate for follow-up observation. On the last follow-up visit, 14 months after surgery, the patent has no complaint and neurological status improved. The craniocervical MRI demonstrated the tumour that did not grow (Figure 3).

Discussion

GG is a rare mixed glioneural tumour originating from neoplastic glial and neural cells. It consists 0.5–1.7% of all CNS neuroepithelial tumours, but up to 4% of CNS tumour in pediatrics. It is the most common tumour related to the intractable focal seizures (Mpairamidis et al., 2008; Park et al., 2008).

It has been seen throughout the CNS, but the majority of them occurred at supratentorial location (Gupta et al., 2014). At supratentorial location, the most common site is temporal, followed by frontal and medial parietal (I-Hao et al., 2003; Gupta et al., 2014). The posterior fossa is an uncommon site for GG, and brain stem and spinal cord are rare sites (I-Hao et al., 2003; Gupta et al., 2014).

GG of the brain stem is rare, is more common in pediatrics and young adult, and has an affinity to the medullary region. If it is diagnosed early, it has a more favourable prognosis than the cases with delay diagnosis (Blatt et al., 1995).

In the supratentorial location, the long-term intractable seizure is the most common symptom, but in the case of posterior fossa GG, symptoms include focal neurologic deficits (FND), cranial nerve (CN) deficits, and gait and speech disturbance (Kim et al., 2014).

GG located within cerebral lobe is well circumscribed, so it can be totally resected. Nevertheless, GG located in cerebellum and spinal cord has a poorer outcome, probably due to the site of the tumour or perhaps innate variance in biologic behaviour of the tumour (Gupta et al., 2014). Five-year event-free survival (EFS) for brainstem GG is five times lower than from supratentorial cases (Pan et al., 2016).

GG has a benign course with minimal malignant transformation potential, but in the cases with midline tumour, the prognosis is poorer. Despite this, it has a more indolent course in compared to the other brain stem intrinsic tumours (Blatt et al.,

1995). Because this, the differentiation from other tumours is important (Kim et al., 2014). Although, the malignant transformation potential is low, it is related to the glial component (Mpairamidis et al., 2008).

Most tumours are cystic (70%) associated with mural nodules (Davis and Joglekar, 1981). Clinical, radiological, and even surgical findings cannot easily differentiate ganglioglioma from other differential diagnoses. The most important differential diagnosis includes dysembryoplastic neuroepithelial tumour (DNET), oligodendroglioma, low-grade glioma, pleomorphic xanthoastrocytoma (PXA), astrocytoma, ependymoma, low-grade astrocytoma (grade II), oligodendroglioma, medulloblastoma, choroid plexus papilloma, and neurocysticercosis (I-Hao et al., 2003; Mpairamidis et al., 2008).

Posterior fossa GG demonstrated iso to hypo signal intensity on T1, hypersignal on T2, and a range of no enhancement to marked enhancement on T1 with Gad injection. Moreover, malignant GG demonstrated more enhancement (Kim et al., 2014).

Surgery in cases with GG of brainstem and spinal cord is restricted, because total resection is impossible (Davis and Joglekar, 1981). GG of the brainstem has a shorter duration of symptoms, higher mortality, and shorter progression free survival (PFS) in compare to supratentorial or cerebellum GG (Janjua et al., 2017).

Whenever possible, gross total resection should be tried in the case of GG, as it is possible in supratentorial location, it is less problematic in the cerebellum, but it is challenging in the case of brainstem GG (Janjua et al., 2017). The prognosis relates to the extent of resection (EOR) and more EOR caused to more survival (Pan et al., 2016).

The GG is not radiosensitive and role of radiotherapy is controversial, it can be even harmful. Despite increased local tumour control, some authors suggested that it can cause malignant transformation of GG, especially when the patient is young (Si et al., 2013). Moreover, chemotherapy has a little effect to control tumour progression and has more complications (Si et al., 2013). But chemoradiation is reserved for the cases with recurrence after surgery or suspicious to the adjacent parenchymal infiltration (Mpairamidis et al., 2008).

Janjua and the others surveyed 142 cases with brainstem GG within five years. The mean age was 11.4 years with a range of 1 day to 59 years old. The most majority of patients were below 20 years old. The most common symptoms include dysesthesia, motor weakness, and lower cranial nerves deficits. The severity of enhancement decreased with increased age but without any relation to the sex. In this study, all of the medullary tumours had contrast enhancement. The majority of tumours occurred in pons/medulla, followed by medulla and then the only pons tumours. The midbrain was the less common site of involvement. About one-third of the patients had cervicomedullary junction involvement (Janjua et al., 2017).

Our patient demonstrated an intraaxial mass within the cervicomedullary junction that showed marked enhancement. Although this case demonstrated the

typical imaging features of GG, the preoperative definite diagnosis was impossible. The follow-up demonstrated the indolent nature of GG in our case, although, the duration of follow-up is too short for the conclusion.

Conclusion

Although it is rare, the GG should be considered in the differential diagnoses of tumours with compatible clinical and radiologic features even in the unusual locations, especially in the pediatric and young patients. Whenever possible, safety surgical resection should be considered in those patients. In the case of partial resection, that is common in the tumours located within functionally critical structures, long close follow-up rather than radiation therapy is required.

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