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Victoria C. J. Wallace, Cathy M. Ellis, Rachel Burman, Catherine Knights, Christopher E. Shaw & Ammar Al-Chalabi

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ORIGINAL ARTICLE

The evaluation of pain in amyotrophic lateral sclerosis: A case controlled observational study

VICTORIA C. J. WALLACE¹, CATHY M. ELLIS², RACHEL BURMAN²,
CATHERINE KNIGHTS^{1,2}, CHRISTOPHER E. SHAW² & AMMAR AL-CHALABI^{1,2}

¹*Kings College London, Institute of Psychiatry, Department of Clinical Neurosciences, London, and*

²*The Motor Nerve Clinic, Academic Neurosciences Centre, Kings College Hospital, London, UK*

Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder leading to progressive paralysis. ALS is complicated by a number of non-motor symptoms including pain. Pain in ALS has been poorly studied and poorly managed. This study aimed to collate information regarding pain in ALS using standardized pain questionnaires. Forty-two patients with ALS participated in the study. Control subjects included 41 age-matched healthy volunteers and 42 age-matched patients with neurological conditions other than ALS. Data on pain were collected using the The Brief Pain Inventory and The painDetect Questionnaire. Eighty-five percent of subjects with ALS reported pain versus 50% of neurology clinic controls and 35% of healthy controls ($p < 0.01$). Pain in ALS included cramping, aching, tiring, sharp and tender, and was non-neuropathic. Pain impacted significantly on mood, general activity, relationships and general enjoyment of life. Fifty-four percent of people with painful ALS used regular analgesia and 29% regular opioids. Other non-motor symptoms suffered included tiredness, constipation, urinary problems, itching and drowsiness. In conclusion, these data support the fact that pain is a significant symptom in ALS which impacts on quality of life. These data can be used to educate clinicians and patients to promote better multidisciplinary management of ALS symptoms and a better quality of life.

Key words: *Amyotrophic lateral sclerosis, pain, non-motor symptoms*

Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative syndrome predominantly affecting the upper and lower motor neurons in adults, leading to progressive paralysis. Death, usually from respiratory failure, occurs within 2–5 years of symptom onset (1). The incidence increases with age, with the peak between 55 and 75 years (2).

As ALS progresses, secondary symptoms develop, further complicating the clinical condition. One such symptom is pain, which although generally not thought to be a consequence of ALS, has been reported to occur in 20–70% of people at some time during the course of the disease (3–6). Recent guidelines published by the European Federation of Neurological Societies acknowledge pain as a symptom that should be addressed in the management of ALS (7). Nevertheless, pain is poorly studied and poorly managed in ALS (4) and is often considered

a complication of the end-stages of the disease, being less well recognized in the earlier stages. There is a scarcity of up-to-date studies that explore the symptom and its implications to the patient in any depth and no randomized, controlled drug trials have been conducted to investigate the most effective analgesic therapies (1,8). Such information may not only aid better clinical recognition and therefore immediate management of pain, but in the longer term may help to drive research into pathophysiological mechanisms that underpin pain in ALS and the discovery of new and efficacious therapies.

Pain is defined as an unpleasant sensory and emotional experience in response to noxious stimuli, tissue injury, or trauma. It can be acute or chronic. Acute pain resolves with removal of the noxious stimulus. In contrast, chronic pain extends beyond the expected period of healing and therefore no longer serves a physiological purpose (9). Clinically,

the time-transition from acute to chronic pain is debatable and probably depends on the underlying pathophysiology, but is often taken as pain lasting longer than three to six months. Chronic pain may be divided into nociceptive and neuropathic. Nociceptive pain is that caused by direct activation of nociceptors, such as that associated with tissue injury and ensuing inflammation. Neuropathic pain follows injury or disease affecting peripheral nerves or sensory pathways within the spinal cord or brain (10), and can be the result of a variety of triggers including direct trauma as well as metabolic disorders such as diabetes mellitus, vitamin deficiencies, alcohol abuse, toxins and medication such as chemotherapeutics. Some chronic pain pathologies represent a mixture of nociceptive and neuropathic pain (9). It is likely that pain in ALS consists of nociceptive and neuropathic pain, but the balance may differ with disease stage.

Due to the variety of pathophysiological processes that underpin different presentations of chronic pain, medical therapies vary. For example, nociceptive types of pain tend to respond well to anti-inflammatory agents and opioids whereas neuropathic pain, which is harder to treat, responds in part to antidepressants and anticonvulsants that are currently recommended as first line treatment (9).

Therefore, in any condition or disease process that has pain as a symptom, it is important to understand the phenotype of pain as this can guide clinical management strategies. To gain such understanding, the study of pain in humans relies largely on clinical examination, which is open to objective and subjective variability. Additionally, validated questionnaires are used that not only aim to quantify pain as a symptom but, with reasonable sensitivity and specificity, can distinguish between nociceptive and neuropathic pain. For example, The Brief Pain Inventory (BPI) (11,12) is a qualitative and quantitative questionnaire that ascertains information regarding location, severity and type of pain experienced as well as the impact it has on activities of daily living (ADLs). In contrast, The painDetect Questionnaire (PDQ) (13) determines particular aspects of the nature of the pain experienced and is designed to ascertain the presence of neuropathic versus nociceptive pain.

This study employs the BPI and PDQ to estimate the prevalence of pain in ALS and collect information regarding the nature of pain experienced and its impact on quality of life.

Methods

Participants

The study was approved by the Research Ethics Committee of North West – Greater Manchester. Potentially suitable people with a known diagnosis of ALS attending a specialist multidisciplinary

clinic during a six-month period were identified from clinical notes and were sent a letter inviting them to participate. Inclusion and exclusion criteria are outlined below. A total of 80 people with ALS were contacted and 42 consented to be included, with the attrition rate largely due to time-resources on the day of the clinic. Relatives or friends of those attending were asked to participate as healthy control subjects. A further group of control subjects who did not have ALS or a primary presenting complaint of pain was selected from a general neurology outpatient clinic. This information was either determined at the time of interview or from clinic letters.

Inclusion criteria:

- 1a. Persons with a known diagnosis of ALS with a follow-up appointment to attend the specialist ALS clinic.
- 1b. Carers or friends of those attending, or people attending a general neurology clinic without ALS, and who did not present with pain as the main symptom.
2. Persons able to give informed consent to participate in the study.
3. Persons able to understand (either by reading or being asked) and answer (either verbally or in written form) the questionnaire alone or with the help of a carer or investigator.

Exclusion criteria:

1. Persons unable to give informed consent.
2. Persons lacking capacity to understand or answer the questionnaires.

Data collection

Details regarding diagnosis, including subtype of ALS, time since diagnosis, time since symptom onset and current stage of the disease (stages 1–4) (14) were obtained from clinic letters. Data regarding pain were obtained at the time of patient interview using The Brief Pain Inventory and The painDetect Questionnaire.

In brief, the BPI asks participants to identify the location of their pain on a diagram. They then rate their pain at its least, worst and on average on a scale of 0 (none) to 10 (as bad as you can imagine). Pain descriptors that represent the type of pain experienced are chosen from a list including: aching, cramping, tiring, sharp, tender, exhausting, shooting, nagging, miserable, throbbing, unbearable, penetrating, gnawing, burning, numb, radiating and squeezing. The impact of pain on daily activities including: general activity, mood, walking ability, normal work, relationships with other people, sleep and enjoyment of life is rated using the scale: 0 = no impact and 10 = completely interferes. Finally, participants describe what makes the pain worse or

better and what effects analgesic medications have (on a 0–100% relief scale).

The PDQ provides a visual representation of the course of pain that is used to describe either persistent pain with slight fluctuations, persistent pain with pain attacks, pain attacks without pain between them or pain attacks with pain between them. Questions specific to the presence of symptoms of neuropathic pain (burning, prickling, stinging, electric shocks, allodynia and numbness) are rated on a scale of 'never' to 'very strongly'. The responses are converted into a numerical score out of 38 which correlates to a diagnosis of nociceptive (0–12) versus neuropathic (>18). A score of 13–18 correlates to an unclear cause for pain.

Every participant was interviewed by the same investigator, and given time to read the questionnaires and consider their answers. For those who found communication difficult, for example due to dysarthria, alternative communication methods were employed including translation by their relative/carer, blinking and light writers.

Statistical analysis

Data are reported as frequencies (%) or as mean score with standard deviation (SD). Comparison between means was performed using ANOVA. Frequencies were compared using a χ^2 test. Correlations were calculated using Pearson's coefficients. All tests were two-tailed. $p < 0.05$ was considered significant. Analyses were performed in SPSS v17.0 (SPSS Inc., Chicago, IL, USA).

Results

Group characteristics

The study group included 42 people with ALS (31 male, 11 female). Twenty-four had a diagnosis of ALS, 12 had primary lateral sclerosis (PLS), three had progressive muscular atrophy (PMA) and three had a flail limb syndrome (FLS). Five were classified as stage 1 disease, 16 were at stage 2, 12 were at stage 3 and nine were at stage 4. The mean age at the time of interview was 60 years (range 28–80; median 63) and the mean disease duration from diagnosis was 25 months (range 2–90 months; SD 25.8) and 45 months (range 8–146 months; SD 32.9) from symptom onset. There were 42 healthy controls (14 male) with a mean age of 56.7 years (range 26–78 years) and 42 controls from the general neurology clinic (25 male) with a mean age of 56 years (range 23–80 years). There was no significant difference between the ages of the subjects in each group. An overview of ALS patient characteristics is detailed in Appendix 1.

Control subjects attending neurology clinic presented with a range of diagnoses including Parkinson's disease, epilepsy, multiple sclerosis, dystonia,

post stroke syndrome, brain tumour, essential tremor, nerve entrapment and spinal degeneration.

Pain

Pain frequency. Pain was reported by a significantly greater proportion of people with ALS (85%) than healthy controls (35%, $p < 0.01$) and neurology clinic controls (53%, $p < 0.01$). All ALS participants reporting pain had experienced symptoms for at least one month prior to the study, with 97% reporting pain for at least six months. Twenty-five percent of those with painful ALS said they had pain prior to ALS symptom onset and reported that this pain had worsened with the onset of ALS symptoms. Pain was reported in all subtypes of ALS (21 of 24 with ALS, 10 of 12 with PLS, three of three with PMA and two of three with FLS). Further subgroup analysis is limited by sample size. Pain occurred at all stages of ALS (13) with a range of 8–146 months after onset of ALS symptoms. There was no significant difference in the age of those with ALS with or without pain (60.1 years (SD 13.7) vs. 65.8 years (SD 10.1)) or in time since symptom onset in those with or without pain (42.5 months (SD 32.5) vs. 59.5 months (SD 34)).

Pain intensity. Those with ALS scored their maximum pain as 6.5 (SD 1.8), minimum pain as 0.9 (SD 1.3) and average pain as 3.7 (SD 1.9). This did not differ significantly from the control subjects with pain (Table I). Interestingly, and in contrast to previous studies, there was no significant correlation between the number of months since onset of ALS symptoms, or the stage of the disease and the average or maximum pain scores reported.

Location and type of pain. The most common locations for pain in people with ALS were, in order of frequency, legs, arms, shoulders, neck, back, feet, abdomen and hands (see Figure 1). The most common types of pain reported were, in order of frequency, cramping, aching, tiring, sharp and tender (see Figure 2). Significantly more people with ALS reported cramping pain (60%) than did either control group (healthy = 24%, neurology clinic = 28%, $p < 0.01$). Furthermore, those with painful ALS reported a significantly greater number of concomitant types of pain (average number of descriptors of pain used = 5.9 (SD 3.6)) than did healthy control

Table I. Pain severity score (0–10) displayed as mean score $\pm$ standard deviation.

	MND	Healthy control	Neurology clinic control
Pain at worst	6.5 $\pm$ 1.9	5.1 $\pm$ 1.7	6.5 $\pm$ 2.7
Pain at least	0.9 $\pm$ 1.3	1.8 $\pm$ 1.5	1.8 $\pm$ 1.7
Average pain	3.7 $\pm$ 2.0	3.4 $\pm$ 1.3	4.7 $\pm$ 2.2
Pain in clinic	1.8 $\pm$ 2.2	3.2 $\pm$ 2.4	3.3 $\pm$ 2.6

Figure 1. Type of pain reported by participants represented as % of subjects reporting each type of pain.

subjects (3.7 (SD 2.5)) but at a level comparable to those with other neurological presentations and pain (6.1 (SD 4.8)).

Impact of pain on measures of daily living. Table II shows the data for the impact of pain on ADLs measured in the BPI. As the majority of people with ALS cannot work and have difficulty walking due to muscular weakness, these measures were excluded from the analysis. Those with ALS reported that pain significantly interfered with activity levels, mood, sleep, relationships, and general enjoyment of life to a similar extent. There was a significant correlation

between the average pain score reported by those with ALS and the interference with activity levels ($R = 0.44$, $p < 0.01$), mood ($R = 0.35$, $p = 0.04$), sleep ($R = 0.40$, $p = 0.02$), enjoyment of life ($R = 0.53$, $p = 0.01$) and relationships ($R = 0.34$, $p = 0.05$). These correlations were also reflected in maximum pain scores.

Exacerbating and relieving factors. Forty-two percent of people with painful ALS reported movement to be the main pain exacerbating factor closely followed by immobility in 37%. Only 8% reported both as exacerbating factors. However, the average time

Figure 2. Locations of pain reported by participants represented as % of subjects reporting each location of pain.

Table II. Pain interference score (0–10) displayed as mean score $\pm$ standard deviation.

	MND	Healthy control	Neurology clinic control
General activity	3.1 $\pm$ 3.4	2.5 $\pm$ 2.8	6.1 $\pm$ 2.8
Mood	2.9 $\pm$ 3.2	2.3 $\pm$ 2.5	5.0 $\pm$ 3.0
Relationships	2.1 $\pm$ 3.2	0.8 $\pm$ 1.1	4.1 $\pm$ 3.9
Sleep	3.2 $\pm$ 3.7	2.6 $\pm$ 2.3	3.6 $\pm$ 3.5
Enjoyment of life	3.5 $\pm$ 3.3	1.8 $\pm$ 1.9	5.2 $\pm$ 3.6

since disease onset was not significantly different between those reporting movement (average months since ALS symptom onset = 42.9 (SD 37.8)) and those reporting immobility (average months since ALS symptom onset = 42.2 (SD 29.8)) as making their pain worse.

The most commonly reported pain relieving factor in those with painful ALS was movement and exercise, which subjectively improved pain in 40% of people. Medication was reported as a relieving factor by 28% of those with painful ALS. Other relieving factors included heat (20%), massage (17%), and rest (14%). This highlights that the needs and management of pain in people with ALS varies and a multidisciplinary approach especially involving physiotherapy is important.

Analgesia. A comparable number of subjects with painful ALS and control subjects with pain reported taking analgesia (ALS = 54%, healthy control = 43%, neurology clinic control = 43%). However, significantly more subjects with painful ALS (29%) and pain associated with other neurological conditions (33%) were taking regular opioids than were healthy controls (14.2%, $p < 0.01$). Those with painful ALS reported on average 64% (SD 30%) relief from analgesia, which was equivalent to that reported by the control patients.

Associated symptoms. Apart from weakness, which is inherent to ALS, those with painful ALS reported the most common other associated symptoms, in order of frequency, as: tiredness, difficulty sleeping, constipation, itching, drowsiness, sweating, headaches, urinary problems, nightmares and diarrhoea (see Figure 3 for full list and comparisons to controls). Most of these symptoms were reported at similar frequencies by neurology clinic control participants with pain. However, all occurred at significantly greater frequencies than in healthy controls reporting pain. In accordance, the average number of symptoms reported was significantly less ($p = 0.016$) in healthy controls with pain (1.6 (SD 1.9)) than subjects with ALS and pain (4.9 (SD 2.8)) or neurology clinic subjects with pain (4.1 (SD 3.3)). The number of associated symptoms was significantly correlated with maximum pain score reported by those with ALS ($R = 0.36$, $p = 0.04$).

Neuropathic pain is not associated with ALS. Sixty-three percent of those with painful ALS reported their pain as ‘pain attacks with no pain in between’. Fourteen percent reported their pain as ‘persistent pain with fluctuations’ and 23% as ‘persistent pain with painful attacks’. The average overall painDetect score was 5.4 (SD 0.9, range 0–17). None of those reporting pain in ALS scored high enough to reach the neuropathic threshold. Eighty percent of people with ALS scored $< 12/38$ suggesting their pain was nociceptive in nature.

Discussion

We have shown that pain is a significant symptom associated with ALS and confers a significant amount of morbidity. Moreover, pain can be present at any stage or in various clinical subtypes of the disease.

Figure 3. Associated symptoms reported by participants represented as % of subjects reporting each symptom.

The incidence of pain reported here is at the higher end of the range demonstrated by previous studies (3,4,6). This may be a reflection of the fact that our study is of a clinic based sample and, therefore, may not be as generalizable as a larger population based study. However, this does make our results and conclusions directly relevant to clinical practice. Additionally, in contrast to previous studies (4,6), the intensity of pain did not correlate with the time-course of disease. It may be the case that a larger study would reveal a true correlation and we acknowledge that one caveat of this study is the relatively small sample size. Moreover, our sample group has a relatively long mean disease duration that may have affected this measure and a more in-depth study of the very early stages of disease may be required. However, our sample includes a wide range of disease duration and stage, with half of the sample being at clinical stages 1 or 2 by the King's staging system. This demonstrates that pain is a prevalent symptom in ALS that is not just a feature of late stage disease. We have also shown for the first time that neuropathic pain is not a component of ALS pain. Therefore, it is important that clinicians are aware of pain as a symptom of ALS that needs to be identified early and managed effectively throughout the course of the disease and that analgesics used for neuropathic pain may be of less use clinically.

Despite the relatively small size, our patient group is representative of the ALS population in which males are more at risk than females with a ratio of about 3:2 and the peak age of onset is between 56 and 70 years (2). Another caveat of our study is that the healthy control subjects were not gender-matched. However, previous studies have shown that females report pain more frequently than males (15) and therefore correction for any gender effect would be expected to increase the significance of our results. There was no correlation between pain and gender or age in this study.

That people experience pain at early stages of ALS may represent a complex underlying pathophysiology of pain in addition to purely mechanical changes related to spasticity, stiffness and immobility. Undoubtedly, prolonged immobility and postural changes are a cause of pain in ALS especially in the latter stages of the disease with spasticity leading to contractures, cramps and pressure related pain (1). This is reflected here by the fact that immobility was a significant pain exacerbating factor in this study, with movement and exercise reported as the most common pain relieving factors. This highlights the importance of physiotherapy and the promotion of exercise techniques in the multidisciplinary management of those with ALS. However, our data also suggest that pain is an issue for many before the onset of immobility, with movement being the most significant exacerbating factor throughout the course of the disease including in those where immobility

was yet to be an issue. The description of the pattern of pain experienced (as explored in painDetect), implies that a mixture of acute (pain attacks with no pain in between) and chronic (persistent) pain is being experienced. Moreover, the fact that multiple pain descriptors were selected by those with ALS implies that a range of painful symptoms are experienced representing a combination of underlying pathological processes.

Theories of the complexity of muscle dysfunction in ALS and the long-term effects on the nociceptive cascade are emerging that may in part explain this complex pattern of painful phenotypes (1). One such proposes that in addition to acute pain caused by immobility and the effects of direct pressure on skin and joints, motor neuronal death, muscle wasting and denervation (as occurs early in the disease) results in axonal sprouting and reorganization of the motor end-plate. As a result there is a mechanical and electrical dissociation of the muscle (16) on ligaments, tendons, and joints resulting in micro trauma and low levels of inflammation. Continual muscle wasting with decreased strength and tone leads to repetitive bouts of inflammatory injury (1) throughout the course of the disease. Constant inflammatory input in other conditions is known to lead to sensitization and damage of nociceptive pathways both peripherally and centrally resulting in chronic pain (17). In support of this, peripheral nerve electrophysiological studies in people with ALS provide some evidence for such generalized sensory system abnormalities that may be consistent with degeneration of motor neurons and dorsal root ganglion cells (18). Moreover, glial cell changes are related to motor neuron apoptosis in the spinal cord and brain (19) and the activation of glial cells has been identified as a key process in the development of many chronic pain states (20). These processes deserve further investigation in ALS with a view to the development of potential novel and efficacious therapeutic targets.

Pain significantly interferes with the quality of life of people with ALS as demonstrated by its impact on activity levels, mood, sleep, relationships, and general enjoyment of life at a level comparable to chronic pain conditions suffered in the general population. The level of interference positively correlated with severity of pain, suggesting a causal relationship. Moreover, the types and severity of pain reported were comparable to pain associated with a number of neurological conditions that are more widely recognized to be associated with pain such as Parkinson's disease, post stroke, multiple sclerosis, spinal cord injury and neuropathy (21). This was reflected in the number of patients requiring regular opioids highlighting the chronicity and impact of the pain in ALS. The use of morphine in the treatment of pain in ALS has been explored in a number of studies (22,23), particularly in relation to the late stages of the disease and end-of-life care. However,

opioids confer a large side-effect profile that often impacts on quality of life. Our findings emphasize the importance of the early recognition of pain as a significant influential factor on quality of life as well as the need for clinical trials into alternative analgesic compounds that may confer a lower side-effect profile and greater pain relieving potential than opioids.

Finally, we have demonstrated that in addition to movement problems and pain, people with ALS experience a range of less well recognized symptoms that further complicate the course and management of the disease including: tiredness, difficulty sleeping, constipation, itching, drowsiness, sweating, headaches, urinary problems, nightmares and diarrhoea. The number of these symptoms was positively correlated with the severity of pain suggesting that there may be a causal relationship between pain and some non-motor ALS symptoms. This may be as a direct consequence of pain or due to side-effects of pain medication. Further studies are required to explore these symptoms in more depth. However, these data highlight the importance that clinicians are educated to be aware of the complex nature of ALS and plethora of potential symptoms which can greatly impact on the patient's quality of life.

In conclusion, pain is a significant symptom associated with ALS that is present throughout the course of the disease and confers significant morbidity. This highlights the need for early pain assessment and a multidisciplinary approach to the management of this disease including neurology and palliative care physicians, physiotherapists, occupational therapists, and psychologists. Clinicians therefore need to be educated regarding the importance of pain and other non-motor symptoms of this disease and clinical trials are required to optimize future management of this devastating symptom.

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Appendix 1. Clinical characteristics of participants with ALS. The presence of pain is indicated Y = yes, N = no. Subtype of ALS is indicated including primary lateral sclerosis (PLS), amyotrophic lateral sclerosis (ALS), progressive muscular atrophy (PMA) and flail limb syndrome.

Age	M/F	Pain?	Diagnosis	Time since diagnosis (months)	Time since symptom onset (months)	Stage
74	F	Y	PLS	6	24	2
65	M	Y	ALS	20	46	3
78	M	N	PLS	47	78	2
28	M	Y	ALS	30	50	1
44	F	Y	ALS	38	48	1
80	M	Y	PMA	42	90	4
59	M	Y	ALS	21	30	4
62	M	Y	ALS	2	23	3
52	F	Y	ALS	7	18	2
45	F	Y	ALS	8	24	2
79	M	Y	PMA	28	44	4
74	F	Y	ALS	18	36	2
69	M	Y	PLS	90	120	4
65	M	Y	ALS	6	8	1
56	M	Y	Flail Arm	5	13	2
60	M	Y	PLS	22	54	4
67	M	Y	PLS	29	45	2
69	M	Y	PLS	38	48	3
38	M	Y	ALS	22	26	3
38	F	Y	ALS	22	38	3
53	M	Y	ALS	14	32	3
65	M	Y	PLS	10	26	2
63	M	Y	PMA	74	146	2
78	F	Y	ALS	2	24	3
60	F	Y	Flail leg	86	120	2
66	F	Y	ALS	4	15	3
57	M	Y	ALS	16	30	2
59	M	Y	PLS	3	30	2
72	M	Y	ALS	3	12	1
47	M	Y	ALS	18	31	2
78	M	Y	ALS	17	34	4
66	M	Y	ALS	6	31	4
34	M	Y	ALS	42	49	2
42	M	Y	PLS	1	20	2
77	F	Y	PLS	62	89	3
63	M	Y	ALS	6	14	4
78	M	N	PLS	47	78	2
63	M	N	Flail Arm	3	14	1
73	M	N	ALS	34	70	3
69	M	N	ALS	3	20	3
49	M	N	ALS	90	96	4
68	F	N	PLS	63	79	3